June 2012 Epidemics and AIDS Update

1. Battling the virus
2. Chagas Disease and HIV Are Killers With Very Different M.O.’s
4. Senate Passes Preventing Child Marriage Act
5. How infectious disease may have shaped human origins
6. Immune System Glitch Tied to Fourfold Higher Likelihood of Death Identified
7. Shape-Shifting Shell of Retroviruses Detailed ****
8. Fifty-Year Cholera Mystery Solved ****
9. All Proteins That Bind to RNA, Including 300 New Ones, Catalogued
10. Titan Cells Protect Cryptococcus
11. Tanzania: HIV Testing for All 'Touches Raw Nerves'
12. Doctors With Gay Bias Denied Meds, Man Says
14. Global Cancer Cases Could Rise 75 Percent by 2030
15. Guardian Examines High Incidence Of Drowning Deaths Among Children In Bangladesh
16. Growing Obesity In Developing Countries A Sign Of Historic Global Tipping Point
17. Short-term risk of shingles recurrence low
18. ASCO: Breast Cancer Outcomes among HIV Positive Women
19. MALAWI: Where Is HIV/AIDS on Banda's to-do list?
20. Iatrogenic Creutzfeldt-Jakob Disease, Final Assessment
21. Dengue Fever Vaccine 'May Be In Sight,' Reuters Reports
22. WHO Warns Of Drug-Resistant Strains Of Gonorrhea
23. Cedars-Sinai researchers explore role of fungus in digestive disorders
24. Study predicts imminent irreversible planetary collapse
25. Complex World of Gut Microbes Fine-Tune Body Weight
26. Protein Knots Gain New Evolutionary Significance
27. Can HIV Infection Be Cured?
28. Hepatitis B is a major health issue for migrants in the US
29. Colombian court rules that blood donors cannot be turned down for sexual orientation
30. TowelTalk: Inside Toronto’s Bathhouses
31. Nobel winning Barre-Sinoussi optimistic about HIV cure
32. Pre-existing mutations can lead to drug resistance in HIV virus
33. Alzheimer's vaccine trial a success
34. HIV Superinfection Rate Comparable to Initial HIV Infection
35. Mystery to the Origin of Long-Lived, Skin-Deep Immune Cells Uncovered
36. Health educators should work with the inner contradictions that 'barebackers' express
37. HIV-positive saliva not a 'deadly weapon'—NY court
38. Are HIV Non-Progressors Really Very Slow Progressors?
39. HIV Gene Therapy Shows Long-term Safety and Activity after 11 Years
40. Pregnancy: Why Mother’s Immune System Does Not Reject Developing Fetus as Foreign Tissue
41. The So Called HIV Cured "Berlin" Patient Still Has Detectable HIV In His Body
42. African HIV Activists Want a New Model for Prevention
43. Health Class May Be Waived
44. African Cholera Vaccine Trial
45. DNA Methylation Declines with Age
46. The Fungus Among Us
47. Naturally Resistant HIV Foils Therapy
48. Study shows that use of darunavir/ritonavir and etravirine in HIV treatment as a prevention method is biologically plausible
49. Latest Effort to End Ban on Gays Donating Blood
50. Census of microbes in healthy humans reported ****
51. Scripps research scientists show lack of single protein results in persistent viral infection
52. Novel Mechanism Involved in Key Immune Response
53. Early Gut Bacteria Regulate Happiness
54. Protein Residues Kiss, Don't Tell: Genomes Reveal Contacts, Scientists Refine Methods for Protein-Folding Prediction
55. **U.S. Africa Command Establishes Regional Task Forces To Combat Malaria In Africa**
56. Childhood virus infection linked to prolonged seizures with fever
57. The Battle Against HIV
58. Atomic-resolution view of a receptor reveals how stomach bacterium avoids acid
59. Oregon man contracts plague saving mouse from cat
60. Judge Dismisses Lawsuit on ‘40s US STD Experiments
61. High School Sex Numbers Rising: Schools Get ‘F,’ Says Planned Parenthood
62. Microbiome analysis helps understand cause of chronic sinus condition, suggests cure
63. Brothers in arms: Commensal bacteria help fight viruses
64. Immune System May Protect Against Alzheimer’s Changes in Humans
65. Normal Bacterial Makeup Has Huge Implications for Health
66. Tending the Body’s Microbial Garden
67. Teacher With HIV Sues Calif. School for Wrongful Termination
68. HIV Superinfections Appear Common
69. Trainer’s Secret Is Too Big a Weight to Bear
70. ‘Breast Best’ Policy Challenged in South Africa
71. Low-cost Australian HIV test to reach poor
72. **HIV Frontlines: The Doctor Who Cured HIV**
73. Zimbabwe Lawmakers Volunteer for Public HIV Testing, Circumcision
74. Haley Vetoes Bill Providing Access to HPV Vaccine
75. Drug combo much better than AZT alone at preventing mother-to-infant HIV transmission
76. Children Exposed to HIV in the Womb at Increased Risk for Hearing Loss
77. Chicago Woman Cured of Sickle Cell Disease ****
78. Crucial Immune Fighter Role of STING Protein Revealed
79. Factors Associated with Uptake of Infant Male Circumcision for HIV Prevention in Western Kenya
80. Boulder Firm Giving Condoms to Haitians
81. **U.S. Senate Foreign Relations Committee Passes Senator Paul Simon Water For The World Act**
82. Avian Flu Viruses Which Are Transmissible Between Humans Could Evolve in Nature
83. Immune System Molecule Weaves Cobweb-Like Nanonets to Snag Salmonella, Other Intestinal Microbes
84. Our Microbes, Ourselves: Billions of Bacteria Within, Essential for Immune Function, Are Ours Alone
85. Prions and cancer: A story unfolding
86. Gut Microbes Battle a Common Set of Viruses Shared by Global Populations
87. Bacterial vaginosis is associated with higher risk of female-to-male transmission of HIV
88. Take the Test and Risk Arrest?
89. 'War on Drugs' Is Fueling HIV Epidemic: Report
90. Calgary Doctors and Parents Want Catholic School Board to Revisit HPV Vaccine
91. Immune response to heart attack worsens atherosclerosis, increases future risk
92. New mechanism of bacterial pathogenesis discovered
93. Dietary fiber alters gut bacteria, supports gastrointestinal health
94. New Role for RNAi Discovered: Epigenetic Memory May Pass RNA Silencing from One Generation to the Next
95. Scientists Detect New Immune Alert Signal
96. S.C. House Upholds Haley Veto on HPV Vaccine
97. Disparities in Sexually Transmitted Disease Rates Across the ‘Eight Americas’
98. Lymph node roundabout
99. Both innate and adaptive immune responses are critical to the control of influenza
100. Gene discovery helps explain how flu can cause severe infections
101. Flu immunity is affected by how many viruses actually cause the infection
102. Programmable DNA Scissors Found for Bacterial Immune System
103. New Mechanism of Bacterial Pathogenesis Discovered
104. Broad Spectrum Pro-Quorum-Sensing Molecules as Inhibitors of Virulence in Vibrios
105. Abstract
106. Could Stem Cells Cure MS?
107. Jumping Genes a Cause of Cancer?
108. Literature Review Examines Incidence of MRSA Infections Among HIV-Infected People
109. Four-in-one AIDS Drug Gets the OK in Clinical Trial
Battling the virus
A huge, strange drug market
Jun 2nd 2012 | NEW YORK | from the print edition

THE coming weeks may bring a victory in the long war against the human immunodeficiency virus (HIV), which causes AIDS. A drug called Truvada already treats the disease. By June 15th American regulators are expected to approve its use to prevent the transmission of HIV, too.

The past 30 years have produced several triumphs. A flood of money has helped scientists to invent new drugs and health workers to deliver them to those in need (see chart 1). These drugs have transformed a fatal disease into a chronic one. They have also made HIV a big business.

Sales of antiretroviral drugs in America and the five biggest European markets reached $13.3 billion in 2011, according to Datamonitor, a research outfit (see chart 2). The market is as unusual as it is large, both buoyed by government support and worryingly dependent on it. The past decade has brought fancier medicine in rich countries and copious aid for poor ones. But the war is far from won.

Publicly funded research has played a larger role in developing drugs for HIV than for other diseases. A study published last year in Health Affairs found that HIV drugs were three times as likely to involve a patent from the public sector. HIV also has special status among regulators. America’s Food and Drug Administration (FDA) created a faster way to review HIV drugs, allowing them on the market before the most expensive stage of clinical trials.
Convenient cocktails
In total, public and private investment has yielded more than two dozen HIV drugs. In 1987 Burroughs-Wellcome (now part of GlaxoSmithKline) introduced the first one, tackling an enzyme that helps the virus progress inside human cells. In 1995 Hoffmann-La Roche, a Swiss drug firm, launched the first protease inhibitor, which interrupts the virus at a later stage of replication. Today different medicines are combined to suppress resistance or reduce side-effects. The rise of combination therapy has brought a flurry of cross-licensing: companies strike deals to sell each other’s drugs in carefully calibrated cocktails.

One company stands out: Gilead, of California. A late entrant to the HIV race, Gilead quickly took the lead. Its strategy was simple: the more convenient the treatment, the better. In 2004 Gilead launched Truvada, a once-a-day, one-pill combination of two drugs. In 2006 it introduced Atripla, a once-a-day, one-pill combination of Truvada and another treatment. Atripla’s average wholesale price in America is nearly $25,000 per patient, per year. In 2011 its global sales reached $3.2 billion.

More good news for Gilead has come in recent weeks. An FDA panel recommended Truvada for preventive use: ie, to protect healthy people from contracting the virus. Another FDA panel endorsed Gilead’s new Quad pill, which is the simplest, most effective combination drug to date.

If the process for developing HIV drugs has been unusual, selling them has been even more so. America is the rich world’s biggest market, with 841,000 patients diagnosed—ten times as many as in Britain. More than 60% of HIV drugs in America are bought with public money. Insurers give HIV special treatment: patients are rarely pressed to buy the cheapest pills, as they might be if they had another disease.

Distributing drugs in poor countries is harder. A decade ago, hardly any poor people could afford them. At first, drugs firms handled this badly. In 1998, 39 big Western firms sued South Africa to protect their HIV patents. Global uproar ensued; the firms backed down in 2001.

Then two things changed. First, rich countries started donating vast sums to fight AIDS in poor ones. In 2000 there was less than $2 billion for HIV programmes each year; by 2010 there was $15 billion, thanks to the Global Fund to Fight AIDS, Tuberculosis and Malaria and George Bush junior’s President’s Emergency Plan for AIDS Relief (PEPFAR).

Second, the price of AIDS drugs plunged. In May 2000 a year’s “triple cocktail” therapy cost $10,000 or so. By 2011 the same pills sold for $62 in poor countries. PEPFAR cash buys generic versions of patented drugs, which may be supplied only to poor countries. Last year two drugmakers won most of PEPFAR’s contracts: Aurobindo, an Indian firm, and Matrix, an Indian firm acquired in 2007 by Mylan, an American one. PEPFAR’s bidding system keeps margins slim even by the standards of the generics industry, says Rajiv Malik, the president of Mylan. But volumes are huge.

Can treatment expand further? Despite the subsidies and the plunge in prices, less than half of those infected with HIV take HIV drugs. Those who do, however, live a long time, and they have to keep taking the pills. What’s more, new studies show that it helps to start treating patients early, so demand is sure to rise.

Alas, aid dipped in 2009 and 2010, thanks to the financial crisis. To make matters more complicated, there is a trade-off between more drugs and better ones. Most patients in poor countries get outdated pills, according to Médecins Sans Frontières. Allowing generics firms to copy yet more patented drugs might help. Since 2006 Gilead has licensed drugs to generics firms for 5% royalties. Last year it went further, agreeing to license drugs to a “patent pool” to centralise royalty deals for a range of firms. So far, however, Gilead is the only Western company to join.

Even in rich countries, public willingness to pay for the best drugs may be waning. Express Scripts manages drug costs for American employers. With Gilead’s expensive Quad poised to enter the market, employers have started asking Steve Miller, the chief medical officer, to contain HIV costs, possibly by nudging patients towards cheaper drugs.
There are two distinct HIV markets. In rich countries, many good treatments jostle for market share. The best will generate fat profits, since patients have to take their pills every day. But Datamonitor predicts that growth will slow after 2017, as many drugs lose patent protection and prices crash. In poor countries, by contrast, Big Pharma makes very little money but the most efficient copycats thrive. Meanwhile, the world still waits for a cure.

Chagas Disease and HIV Are Killers With Very Different M.O.’s
Deadly Chagas affects millions and needs attention, but calling it new HIV is a publicity stunt
By Jason Koebler
June 1, 2012 RSS Feed Print
Earlier this week, the medical community was rocked with the release of an editorial that called Chagas disease “The New HIV/AIDS of the Americas.” But is that true?
Chagas disease—considered a "neglected tropical disease"—is estimated to affect about 10 million people in Latin America—most of them living in poverty. After contracting the disease, victims experience mild fevers, fatigue, and swelling at the site of infection.

The disease then goes dormant, sometimes forever, sometimes for many years. When it resurfaces, it causes heart, digestive, and nervous system problems, eventually killing many of those infected.

While Chagas is no small problem, it’s no HIV, according to experts who study both diseases—and even the editorial’s author says he wrote the essay to cause a stir.

"I wrote it purposefully to have a provocative title ... there's no attention at all [on Chagas]. I didn't write this in any way to diminish the importance of HIV/AIDS,” says Peter Hotez, who is currently working on a vaccine for Chagas.

He certainly got what he wanted—his editorial has been covered far and wide. "When you work on something called neglected tropical diseases, it's amazing to see this kind of press. It's more than I can ever remember," he says.

Hotez was well placed to write the editorial. He was (and still is) the founding editor of PLoS Neglected Tropical Diseases, the journal that published his piece.

Comparing a disease to HIV has become a common tactic used to call attention to a disease. In the past couple years, scientists have called leishmaniasis the "parasitic version of HIV," while others have said hepatitis C and cancer are "the new AIDS."

"As an organization working to develop new and improved medicines for both diseases, we would not compare the two for various reasons, both scientific and otherwise," says Rachel Cohen, executive director of the North American branch of the Drugs for Neglected Diseases initiative.

Cohen says she's glad someone has pointed a spotlight on Chagas, "but [she's] not going to make a judgment about whether the ends justify the means."

"I think the only thing we have to be concerned about is this leading to misleading information. That's where you'd have concerns," she adds. "There's no question [Chagas] is a terribly neglected disease and we need a huge amount of increased attention on it, but I wouldn't make the comparison from any scientific standpoint."

Chagas and HIV do have similarities—they disproportionately affect poverty-stricken populations, can be passed from mothers to their offspring, and often have a long dormant period before causing severe complications—but there are many important differences, Cohen says.

HIV eventually kills nearly everyone it affects; Chagas kills between 20 percent and 30 percent. If treated during its acute stage, Chagas is curable in one to three months, while managing an HIV infection requires a lifetime of antiviral drugs. And Chagas is almost always caused by a protozoan parasite passed through the feces of the kissing bug, native to Latin America, while HIV is a virus spread from person to person, most often through sexual activity or intravenous drug use.
In his editorial, Hotez writes that Chagas and other neglected diseases "cause a burden of disease in the Latin American and Caribbean region that closely approximates or even exceeds that resulting from HIV/AIDS," but then later writes that although Chagas affects more than five times as many Latin Americans as HIV, the number of "attributed deaths are about five times higher for HIV/AIDS."

No expert denies that Chagas is a growing problem in Latin America, and it is becoming increasingly prevalent in Texas and other parts of the United States.

Mario Grijalva, director of the Tropical Disease Institute at Ohio University who takes frequent trips to study Chagas in Ecuador, says "the problem of Chagas is directly related to socioeconomic conditions." Poorer houses in Latin America are often easily penetrable by the bugs, where they live on boxes, the floors, and walls. Kissing bugs feed on human flesh for up to 20 minutes at a time, then defecate.

"That's how it's transmitted. Luckily for all of us, it's not an effective method of transmission," he says. "It's not like malaria, where a single bite can do it—but for poor people who are constantly exposed to thousands of bugs, it's a cumulative risk."

The Chagas problem is one of poverty and ignorance—current drugs are expensive and fairly toxic, and a doctor has to be specifically looking for the disease in order to diagnose it. As a result, millions of people are living with Chagas without knowing it, Grijalva says.

"It's a very hidden disease. If you look for it, you'll find it. If you don't look for it, you won't find it," he says. "If the system is not primed to look at it, it's invisible. It's absolutely a disease of the neglected ... we call Chagas an umbrella disease because the very basic problem is not the disease itself, but the causes that allow the disease to happen."

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Experts Respond To PLoS Editorial Comparing Chagas Disease To HIV/AIDS
"Chagas disease, a parasitic infection spread to humans by insects, is not the new HIV/AIDS of the Americas, according to infectious disease experts who called the comparison," made in an editorial published in PLoS Neglected Tropical Diseases last week, "'unrealistic' and 'unfortunate,'" ABC News' "Medical Unit" blog reports. "Rick Tarleton, president of the Chagas Disease Foundation, said the diseases have little in common beyond disproportionately affecting poor people," the blog notes (Moiisse, 6/1).

According to U.S. News & World Report, "the editorial's author [Peter Hotez, founding editor of PLoS Neglected Tropical Disease], says he wrote the essay to cause a stir." "I wrote it purposefully to have a provocative title. ... I didn't write this in any way to diminish the importance of HIV/AIDS," says Hotez, the news service writes (Koebler, 6/1). "It's difficult to say whether the type of attention this is generating is going to be good or bad for people with the disease,' said Tarleton, describing how many people with Chagas disease face obstacles in getting care," the ABC News blog adds (6/1).

Bangladesh Braces for HIV Epidemic
By Naimul Haq
DHAKA, Jun 3, 2012 (IPS)—Bangladesh has shown low HIV prevalence rates so far but may be silently moving towards an epidemic, say experts pointing to underreporting and poor monitoring for the virus in the general population.

Just 2,533 people are presently known to be carrying HIV—which causes acquired immune deficiency syndrome (AIDS)—within a population of 160 million people.

The last sero-surveillance report, published in June 2011, showed the virus confined to sections categorised as 'high risk', including injecting drug users (IDUs), commercial sex workers (CSWs), men having sex with men and returning migrant workers.

While the report, based on a sampling of 2,894 individuals from 36 geographical areas, showed overall prevalence of HIV at 0.7 percent, there was a three percent prevalence of active syphilis, suggesting high rates of sexually transmitted diseases (STDs).

Active syphilis rates were as high as 12.5 percent among street sex workers of Hili town, 10.3 percent in Chittagong and 9.3 percent among hotel sex workers in Sylhet.

However, low HIV prevalence, even among sex workers, has kept Bangladesh on track to achieving the United Nations millennium development goal that calls for halting of HIV transmission by 2015.

Professionals and volunteers working in the HIV/AIDS field say there is no room for complacency and that Bangladesh may well be on the brink of an epidemic, going by continuing high levels of STDs alone.
Other worrisome factors include increasing numbers of IDUs, floating CSWs, low condom use, large numbers of young migrant workers and a porous border with India, a country with 2.4 million of HIV carriers.

Bangladesh is also situated in close proximity to Myanmar (or Burma) which has high HIV prevalence, and Nepal which has a concentrated HIV epidemic among its IDUs.

Iqbal Ahammed, executive director of ‘Padakhep’, a leading non-government organisation (NGO) working in the field, told IPS: "Bangladesh enjoys low HIV status due to many factors, including religious values, coordination among programme implementing agencies and political will."

The United Nations agency (UNAIDS) responsible for supporting Bangladesh’s efforts in combating HIV/AIDS programmes believes that timely interventions by the government have helped the nation maintain low HIV prevalence rates.

Leo Kenny, UNAIDS coordinator in Bangladesh, told IPS, "We believe that the low prevalence in Bangladesh is largely due to early and timely intervention. For instance, the government managed to restrict transmission of HIV from an epidemic among the IDUs."

Mohammad Abdul Waheed, chief of Bangladesh’s national programme on HIV/AIDS, known as NASP, told IPS: "Factors contributing to Bangladesh’s low HIV prevalence include early intervention – we moved to address HIV transmission four years before actually detecting the first HIV case (1989)."

"We started early, forming the National AIDS Committee (NAC) which quickly engaged NGOs and media at the grassroots in late 1990s which apparently helped build an understanding of HIV/AIDS," Waheed said.

Other experts, however, argue that there is significant underreporting of cases because of the country's limited voluntary testing and counselling capacity and because of social stigma surrounding HIV/AIDS.

"Low prevalence or low detection is a dilemma and shall remain a dilemma until it turns into an epidemic," says Dr. Halida Khandaker, chief of Confidential Approach to AIDS Prevention (CAAP), a leading NGO. She believes that high STD rates are a warning that cannot be ignored.

Dr. Amzad Ali, executive director of the HIV/AIDS and STD Alliance Bangladesh or HASAB, told IPS, "The low figures that NASP tells everyone are from incidental, voluntarily reported cases. Many cases are actually not reported."

Pointing to Bangladesh’s porous border with India and the movement of large numbers of young migrant workers across it, Ali said there is "every possibility that HIV transmission in the general population is higher than reported."

Habiba Akhter, executive director of the Ashar Alo Society, a leading NGO that offers care and support for people living with HIV/AIDS, told IPS that she "strongly believes that the virus has already found a significant number of hosts in the general population.

"The intervention they talk about is confined to high risk groups. What about the housewives? What about school children? Returning migrant workers and the brothel-based sex workers (across the borders in India) are completely ignored," she said.

Akhter said many countries believed the virus was confined to high risk groups only to discover that it had sneaked into the general population. "Look at India, South Africa and Thailand. All these countries initially denied having the virus in the general population."

In central Dhaka, HIV prevalence rates among IDUs jumped from 1.4 percent to 4 percent, then to 8.9 percent over a period of three years. The June 2011 sero-surveillance report said: "Dhaka in general appears to be vulnerable to an HIV epidemic as most cases were detected here."

One concern is the significant number of IDUs in the country who sell their blood in private clinics and district hospitals. There is no monitoring on the illegal blood-transfusion trade.

The Christian Commission for Development in Bangladesh (CCDB), an NGO that has been working on social aspects of HIV/AIDS, believes that social and religious values can no longer protect Bangladesh from HIV transmission in the general population.

Imran Kibria, coordinator of CCDB, told IPS, "We believe that social and cultural behaviours, religious norms and practices are not static; these have been changing over time and highly influenced by intrusion of alien cultures.

"Movement of people in and out of the country has increased significantly; conservative values that people once practiced are now weakening. All these factors point to a highly vulnerable situation which cannot be controlled by the government."

High rates of STDs, including syphilis, suggest risky sexual behaviour that can facilitate the spread of the HIV infection, experts say.
A national baseline survey conducted among young people aged 15-24 years and published in 2006, suggested that STD burden could be as high as 25 percent among males and 21 percent among females in that age group.

The same survey, conducted by the International Centre for Diarrhoeal Disease Research, Bangladesh, showed higher prevalence of STDs among married women in comparison with unmarried women, due to risky behaviour of their spouses.

**Senate Passes Preventing Child Marriage Act**

In this post in Management Sciences For Health’s (MSH) "Global Health Impact" blog, Chanell Hasty, policy and advocacy coordinator of MSH’s Office of Strategic Development and Communications, reports on the International Protecting Girls by Preventing Child Marriage Act (S. 414), writing, "Key tenets of the Senate bill include expanding investments at the community level to empower girls, promoting community understanding about the harmful impact of marriage, and requiring the U.S. government to develop a strategy to prevent child marriage.” Noting the bill passed on the Senate floor by way of voice vote on May 24, Hasty adds, "If passed by both chambers of Congress, the U.S. government will be committed to policy that protects girls from marriage on a global scale” (6/1).

**How infectious disease may have shaped human origins**

Inactivation of 2 genes may have allowed escape from bacterial pathogens, researchers say

Roughly 100,000 years ago, human evolution reached a mysterious bottleneck: Our ancestors had been reduced to perhaps five to ten thousand individuals living in Africa. In time, “behaviorally modern” humans would emerge from this population, expanding dramatically in both number and range, and replacing all other co-existing evolutionary cousins, such as the Neanderthals.

The cause of the bottleneck remains unsolved, with proposed answers ranging from gene mutations to cultural developments like language to climate-altering events, among them a massive volcanic eruption.

Add another possible factor: infectious disease.

In a paper published in the June 4, 2012 online Early Edition of The Proceedings of the National Academy of Sciences, an international team of researchers, led by scientists at the University of California, San Diego School of Medicine, suggest that inactivation of two specific genes related to the immune system may have conferred selected ancestors of modern humans with improved protection from some pathogenic bacterial strains, such as Escherichia coli K1 and Group B Streptococci, the leading causes of sepsis and meningitis in human fetuses, newborns and infants.

"In a small, restricted population, a single mutation can have a big effect, a rare allele can get to high frequency,” said senior author Ajit Varki, MD, professor of medicine and cellular and molecular medicine and co-director of the Center for Academic Research and Training in Anthropogeny at UC San Diego. "We've found two genes that are non-functional in humans, but not in related primates, which could have been targets for bacterial pathogens particularly lethal to newborns and infants. Killing the very young can have a major impact upon reproductive fitness. Species survival can then depend upon either resisting the pathogen or on eliminating the target proteins it uses to gain the upper hand.”
In this case, Varki, who is also director of the UC San Diego Glycbiology Research and Training Center, and colleagues in the United States, Japan and Italy, propose that the latter occurred. Specifically, they point to inactivation of two sialic acid-recognized signaling receptors (siglecs) that modulate immune responses and are part of a larger family of genes believed to have been very active in human evolution.

Working with Victor Nizet, MD, professor of pediatrics and pharmacy, Varki's group had previously shown that some pathogens can exploit siglecs to alter the host immune responses in favor of the microbe. In the latest study, the scientists found that the gene for Siglec-13 was no longer part of the modern human genome, though it remains intact and functional in chimpanzees, our closest evolutionary cousins. The other siglec gene – for Siglec-17 – was still expressed in humans, but it had been slightly tweaked to make a short, inactive protein of no use to invasive pathogens.

"Genome sequencing can provide powerful insights into how organisms evolve, including humans," said co-author Eric D. Green, MD, PhD, director of the National Human Genome Research Institute at the National Institutes of Health.

In a novel experiment, the scientists "resurrected" these "molecular fossils" and found that the proteins were recognized by current pathogenic strains of E. coli and Group B Streptococci. "The modern bugs can still bind and could potentially have altered immune reactions," Varki said.

Though it is impossible to discern exactly what happened during evolution, the investigators studied molecular signatures surrounding these genes to hypothesize that predecessors of modern humans grappled with a massive pathogenic menace between 100,000 and 200,000 years ago. This presumed "selective sweep" would have devastated their numbers. Only individuals with certain gene mutations survived – the tiny, emergent population of anatomically modern humans that would result in everyone alive today possessing a non-functional Siglec-17 gene and a missing Siglec-13 gene.

Varki said it's probable that humanity's evolutionary bottleneck was the complex result of multiple, interacting factors. "Speciation (the process of evolving new species from existing ones) is driven by many things," he said. "We think infectious agents are one of them."

### Immune System Glitch Tied to Fourfold Higher Likelihood of Death Identified

ScienceDaily (June 4, 2012) — Mayo Clinic researchers have identified an immune system deficiency whose presence shows someone is up to four times likelier to die than a person without it. The glitch involves an antibody molecule called a free light chain; people whose immune systems produce too much of the molecule are far more likely to die of a life-threatening illness such as cancer, diabetes and cardiac and respiratory disease than those whose bodies make normal levels.

The study is published in the June issue of Mayo Clinic Proceedings.

Researchers studied blood samples from nearly 16,000 people 50 and older enrolled in a population-based study of plasma cell disorders in Olmsted County, Minn. They found that those who had the highest level of free light chains—the top 10 percent—were about four times more at risk of dying than those with lower levels. Even after accounting for differences in age, gender and kidney function, the risk of death was roughly twice as high.

The study suggests that high levels of free light chains are markers of increased immune system response to infection, inflammation or some other serious disorders, says lead researcher Vincent Rajkumar, M.D., a Mayo Clinic hematologist.

Researchers have known that high levels of free light chains are associated with increased risk of death among patients with plasma disorders, such as lymphomas and other blood cancers, but this is the first study to find that high levels of light chains are associated with increased mortality in the general population. Free light chain levels can be measured by using a serum free light chain assay, a simple blood test. This test is often used to monitor light chain levels in patients with plasma disorders such as myeloma to gauge how well they are responding to treatment.

However, Dr. Rajkumar cautions against administering this test with the intent of gauging one's risk of death.

"We do not recommend this test as a screening test, because it will only cause alarm," Dr. Rajkumar says. "We do not know why this marker is associated with higher rates of death. We do not have a way of turning things around. Therefore, I would urge caution in using this test until we figure out what to do about it and what these results mean."

Plasma cells are white blood cells that produce large amounts of antibodies and are key to fighting off infection. The antibodies are composed of two different types of molecules tightly joined to each other: heavy chains and light chains. Most people produce at least a slightly excess amount of light chains that
can be detected in the blood in the "free" state, unbound to heavy chains. Free light chains are not usually a threat to health, but excess levels serve as a marker of underlying immune system stimulation, kidney failure or plasma cell disorders such as myeloma.

Next steps for researchers include identifying the precise mechanisms by which excess free light chains are associated with a higher likelihood of death and determining if specific diagnostic or treatment options need to be pursued.

Journal Reference:

Shape-Shifting Shell of Retroviruses Detailed ****

ScienceDaily (June 4, 2012) — Scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, have for the first time uncovered the detailed structure of the shell that surrounds the genetic material of retroviruses, such as HIV, at a crucial and potentially vulnerable stage in their life cycle: when they are still being formed. The study, published online today in Nature, provides information on a part of the virus that may be a potential future drug target.

Retroviruses essentially consist of genetic material encased in a protein shell, which is in turn surrounded by a membrane. After entering a target cell – in the case of HIV, one of the cells in our immune system – the virus replicates, producing more copies of itself, each of which has to be assembled from a medley of viral and cellular components into an immature virus.

“All the necessary components are brought together within the host cell to form the immature virus, which then has to mature into a particle that’s able to infect other cells” says John Briggs, who led the research at EMBL. “We found that when it does, the changes to the virus’ shell are more dramatic than expected.”

Both the mature and immature virus shells are honeycomb-like lattices of hexagon-shaped units. Using a combination of electron microscopy and computer-based methods, Briggs and colleagues investigated which parts of the key proteins stick together to build the honeycomb of the immature shell. These turned out to be very different from the parts that build the mature shell. This knowledge will help scientists to unravel how the immature virus is assembled in the cell and how the shell proteins rearrange themselves to go from one form to the other.

Findings such as these may one day prove valuable to those wanting to design new types of anti-retroviral therapies. Many anti-retroviral drugs already block the enzyme that would normally separate components of the immature shell to allow it to mature. But there are currently no approved drugs that act on that shell itself and prevent the enzyme from locking on.

Although the virus shells imaged in this study were derived from the Mason-Pfizer monkey virus and made artificially in the laboratory, they closely resemble those of both this virus and HIV – which are very similar – in their natural forms.
“We still need a lot more detailed information before drug design can really be contemplated,” Briggs concludes, “but finally being able to compare mature and immature structures is a step forwards.”

Fifty-Year Cholera Mystery Solved ****
ScienceDaily (May 29, 2012) — For 50 years scientists have been unsure how the bacteria that gives humans cholera manages to resist one of our basic innate immune responses. That mystery has now been solved, thanks to research from biologists at The University of Texas at Austin.

The answers may help clear the way for a new class of antibiotics that don’t directly shut down pathogenic bacteria such as V. cholerae, but instead disable their defenses so that our own immune systems can do the killing.

Every year cholera afflicts millions of people and kills hundreds of thousands, predominantly in the developing world. The infection causes profuse diarrhea and vomiting. Death comes from severe dehydration.

"If you understand the mechanism, the bacterial target, you’re more likely to be able to design an effective antibiotic," says Stephen Trent, associate professor of molecular genetics and microbiology and lead researcher on the study.

The bacterium's defense, which was unmasked this month in the Proceedings of the National Academy of Sciences, involves attaching one or two small amino acids to the large molecules, known as endotoxins, that cover about 75 percent of the bacterium's outer surface.

"It's like it's hardening its armor so that our defenses can't get through," says Trent.

Trent says these tiny amino acids simply change the electrical charge on that outer surface of the bacteria. It goes from negative to neutral.

That’s important because the molecules we rely on to fight off such bacteria, which are called cationic antimicrobial peptides (CAMPs), are positively charged. They can bind to the negatively charged surface of bacteria, and when they do so, they insert themselves into the bacterial membrane and form a pore. Water then flows through the pore into the bacterium and pops it open from the inside, killing the harmful bacteria.

It's an effective defense, which is why these CAMPs are ubiquitous in nature (as well as one of the main ingredients in over-the-counter antibacterial ointments such as Neosporin).

However, when the positively charged CAMPs come up against the neutral V. cholerae bacteria, they can't bind. They bounce away, and we’re left vulnerable.

V. cholerae can then invade our intestines and turn them into a kind of factory for producing more cholera, in the process rendering us incapable of holding onto fluids or extracting sufficient nutrients from what we eat and drink.

"It pretty much takes over your normal flora," says Trent.

Trent says that scientists have known for some time that the strain of V. cholerae responsible for the current pandemic in Haiti and elsewhere is resistant to these CAMPs. It's that resistance that is likely responsible, in part, for why the current strain displaced the strain that was responsible for previous pandemics.

"It's orders of magnitude more resistant," says Trent.

Now that Trent and his colleagues understand the mechanism behind this resistance, they hope to use that knowledge to help develop antibiotics that can disable the defense, perhaps by preventing the cholera bacteria from hardening their armor. If that happened, our CAMPs could do the rest of the work.

Trent says the benefits of such an antibiotic would be considerable. It might be effective against not just cholera but a range of dangerous bacteria that use similar defenses. And because it disarms but doesn’t kill the bacteria outright, as traditional antibiotics do, it might take longer for the bacteria to mutate and evolve resistance in response to it.

"If we can go directly at these amino acids that it uses to protect against us, and then allow our own innate immune system to kill the bug, there could be less selection pressure," he says.

Trent’s lab is now screening for compounds that would do precisely that.

Journal Reference:
All Proteins That Bind to RNA, Including 300 New Ones, Catalogued
ScienceDaily (June 1, 2012) — In one of the most famous faux pas of exploration, Columbus set sail for India and instead 'discovered' America. Similarly, when scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, set out to find enzymes—the proteins that carry out chemical reactions inside cells—that bind to RNA, they too found more than they expected: 300 proteins previously unknown to bind to RNA—more than half as many as were already known to do so.

The study, published online June 1 in Cell, could help to explain the role of genes that have been linked to diseases like diabetes and glaucoma.

"We are very excited that, unlike Columbus, we found what we were looking for: well-known enzymes that bind to RNA," says Matthias Hentze, who led the study at EMBL with Jeroen Krijgsfeld. "But we never thought there was still so much unexplored territory, so many of these RNA-binding proteins to be discovered."

Almost 50 of the new proteins Hentze and Krijgsfeld found are encoded by genes known to be mutated in patients suffering from a variety of diseases, from diabetes and glaucoma to prostate and pancreatic cancers. This finding opens new avenues for researchers studying these disorders. It raises the possibility that such conditions could be caused by a malfunction not in the protein’s previously established function, but in its potential role in RNA control.

The idea that enzymes might also function as genetic regulators, by binding to RNA and controlling its function, had already been raised by previous work in the Hentze lab. To investigate further, Alfredo Castello, Bernd Fischer at EMBL and colleagues developed a new method for identifying and isolating all proteins that bind to RNA in living cells. The new approach will have many further uses, as it can be applied to other cell types and conditions, to explore which proteins bind to RNA under different circumstances. This will enable scientists to study how the cell’s machinery adapts to stressful situations, responds to drugs or to changes in metabolism, or is altered in disease.

Journal Reference:

Titan Cells Protect Cryptococcus
ScienceDaily (May 28, 2012) — Giant cells called "titan cells" protect the fungus Cryptococcus neoformans during infection, according to two University of Minnesota researchers. Kirsten Nielsen, Ph.D., an assistant professor in the department of microbiology, and recent Ph.D. recipient Laura Okagaki believe their discovery could help develop new ways to fight infections caused by Cryptococcus.

The findings will be published in the June issue of the journal Eukaryotic Cell.

Cryptococcus, a fungus frequently found in dust and dirt, is responsible for the deaths of more than 650,000 AIDS patients worldwide each year. It is also a potentially deadly concern among chemotherapy and organ transplant patients. Currently, Cryptococcus causes more annual deaths in sub-Saharan Africa than tuberculosis.

"While most healthy individuals are resistant to Cryptococcus infections, the fungus can cause deadly disease for those with already weak immune systems," said Dr. Nielsen.

When inhaled, Cryptococcus can cause an infection in the lungs. This infection can spread to the brain and result in meningitis, an often-deadly inflammation of the brain and spine.

Nielsen and Okagaki found that titan cells, or Cryptococcus cells ten to twenty times the size of a normal cell, are too large to be destroyed by the body's immune system.

Researchers also found the presence of titan cells can protect all Cryptococcus cells in the area, even the normal sized Cryptococcus cells.

"This tells us that titan cell formation is an important aspect of the interaction between the human/host and the organism that allows Cryptococcus to cause disease," said Nielsen. "This information will help us find new ways to treat Cryptococcus infections that are very difficult to treat with currently available drugs."

Journal Reference:
Tanzania: HIV Testing for All 'Touches Raw Nerves'
By Alvar Mwakyusa, 4 June 2012

PEOPLE living with HIV/AIDS (PLHAs) and a section of lawmakers have proposed that every person living in the country be subjected to compulsory HIV testing in a bid to promote the fight against the disease.

However, not everyone supports the idea. Some of the people interviewed by the 'Daily News' are against the idea. Many point out that it is against human rights to compel someone to undergo a HIV test or any other medical tests.

Speaking in Dar es Salaam recently, the board chairperson of the National Council of People Living with HIV/AIDS (NACOPHA), Mr Vitalis Makayula, was of a view that if the fight against the disease was to be won, then all people must be aware of their HIV status.

He also said that those found to be positive must disclose their status. Mr Makayula made these remarks at a seminar organized by the Association of Journalists Against AIDS in Tanzania (AJAAT), to sensitize journalists on the HIV and AIDS Prevention and Control Act (HAPCA) of 2008.

"Tackling HIV/AIDS would be more effective if everyone tested for HIV and disclose his/her status. Otherwise it is like fighting an enemy you don't know," he stressed.

Mr Makayula was also optimistic that if everyone knew their HIV status stigma against those found to be positive would be reduced. When contacted for comment, the Deputy Minister for Health and Social Welfare, Dr Seif Suleiman Rashid, said that there are factors that must be considered before deciding if testing should be compulsory or not.

"Before deciding on the matter we should consider revising the current legislation, human rights and availability of resources, among others. It is an issue which requires discussion among experts and stakeholders," he explained in a telephone interview.

The government’s position was supported by the Vice-Chairperson of the Parliamentary Committee on HIV/AIDS, Ms Rosweeter Kasikila, who was against compulsory testing. She said that people should be encouraged to test voluntarily.

"People must be educated that once they test and found to be positive then they would have to go through CD4 count. If their CD4 counts is low they should be administered with ARVs (anti-retroviral drugs)," the MP noted.

The Member of Parliament for Mtambile, Mr Masoud Abdallah Salim (CUF), suggested that the government should introduce incentives for people who test for HIV. "The incentives are likely to encourage people to test for HIV," the MP, who is also a committee member, said.

For his part, Mr Titus Kamani (Busega-CCM) did not mince words in noting that everyone should be subjected to compulsory HIV testing. Section 15 of HAPCA, sub-section (1), states that every person living in Tanzania may on his/her own motion volunteer to undergo HIV testing.

It adds in sub-section (5) that: "Every pregnant woman and the man responsible for the pregnancy or spouse and every person attending health care facility shall be counseled and offered voluntary HIV testing."

However, some expectant mothers who undergo health check-ups in medical centres complain that they are forced to test for HIV against their will through the prevention of mother to Child transmission (PMCT) initiative.

This is against sub-section (7) which stipulates that: "Any health practitioner who compels any person to undergo HIV testing or procures HIV testing to another person without the knowledge of that other person commits an offence."

A section of dispute according to the NACOPHA boss, is Section 47 of HAPCA which states that: "Any person who intentionally transmits HIV to another person commits an offence and on conviction shall be liable to imprisonment to a term of not less than five years and not exceeding ten years."

"You can clearly see that this section targets people who have tested positive and have disclosed their status. Otherwise this section should be removed from the legislation," he said.

However, the Business Coalition on HIV AIDS (ABCT)'s Chief Executive Officer, Mr Richard Kasesela, said it was against United Nations (UN) standards to conduct compulsory testing. "Compulsory testing is done on all diseases and not HIV/AIDS alone, it is against human rights to compel people to test for HIV," Mr Kasesela said.

He was of a view that even if the compulsory testing was to be introduced today, the country lacks adequate resources in terms of human and financial resources.
"The main cost is on counting on CD4s and not just the testing for HIV. We do not have enough personnel for the exercise. Even if we did, would we be in a position to provide anti-retroviral (ARVs)," he queried. Reached for comment, Muhimbili University of Health and Allied Sciences (MUHAS)'s Head of Preventive and Community Dentistry, Dr Emeria Mugonzibwa-Mwanga, said she supported compulsory testing.

"Personally, I think everyone should be obliged to test for HIV/AIDS. Those saying it would be against human rights should state how they want the rights of other people to be protected.

"This should be debated. We should not talk of protecting rights of people while there are innocent people whose lives are put at risk. We should shun being selfish. The rights of innocent people also need to be protected," she maintained.

She expressed concern that only pregnant women were subjected to obligatory testing whilst other groups of people were not required to check their HIV status.

Efforts to get comment from Tanzania Commission for AIDS (TACAIDS) were not successful as of yesterday. It is estimated that Tanzania has roughly two million people infected by HIV/AIDS. The transmission rate stands at 5.7 per cent, down from 18 per cent in the 1990s.

And since President Jakaya Kikwete and his wife, Mama Salma Kikwete, launched a nation-wide voluntary counseling and testing campaign in July 2007, some 14 million people of the 40 million plus population has tested for HIV.

**Doctors With Gay Bias Denied Meds, Man Says**

By CHRIS FRY

ELIZABETH, N.J. (CN)—A gay HIV-positive man says in court that a hospital denied him treatment and visitors, as the doctor remarked, "This is what he gets for going against God’s will."

Joao Simoes sued Trinitas Regional Medical Center in Union County Superior Court. He says that the hospital admitted him in August 2011, but that "requests for his lifesaving medication were not honored," and his sister was denied visitation rights.

Susan V. Borga, M.D., from the Department of Behavioral Health and Psychiatry, allegedly approached Simoes while he was confined to the hospital's mental health wing. Borga is not named as a defendant.

Simoes says Borga was unfazed when another patient told her that he had just gotten out of prison, where he served time for murder. But her reaction was allegedly different when Simoes said that he did not work because he planned to go back to school and because of his HIV status.

Borga then allegedly asked Simoes how he got HIV, to which he responded, "I got it from unprotected sex."

The complaint then says that "Dr. Borga closed the plaintiff's file, put it down and looked at plaintiff with disgust on her face and asked, "Is that from sex with men?"

Simoes says he responded affirmatively and that, "immediately after hearing this, Dr. Borga proceeded to exit the room."

After this consultation, no nurse or doctor came to see Simoes, even though he told them that he needed to take his HIV medication, according to the complaint.

When the hospital finally permitted Simoes to call his personal physician on the third day of his stay, he learned that the doctor had already spoken with Borga about Simoes' medication, according to the complaint.

Borga allegedly responded: "You must be gay, too, if you're his doctor."

"Additionally, apparently realizing that plaintiff's doctor had an accent, Dr. Borga exclaimed, 'What, do you need a translator?' to which plaintiff's doctor had again responded that Dr. Borga needed to give plaintiff his HIV medication," the complaint states.

"Dr. Borga responded to plaintiff's doctor by stating, 'This is what he gets for going against God’s will,' and hung up the phone on plaintiff's doctor."

Simoes says his sister had been at the hospital when he checked in, but the hospital refused to let her visit.

When the sister came to the hospital again on the day Simoes spoke with his personal physician, she brought her brother’s medication.

"Plaintiff witnessed his sister leave his medication with the nurses' station and it was not until this time that the nurses, seeing that the plaintiff had witnessed his sister give his medication to the nurses, that the nurses eventually gave plaintiff his medication," the complaint states.

The hospital's conduct allegedly caused Simoes to miss five doses of his medication.
Simoes seeks punitive damages for discrimination. He is represented by Kevin Costello with Costello & Mains of Mount Laurel, N.J.

**Fighting US’s Worst Teen Pregnancy Rate in Miss.**
*Associated Press*, (05.29.2012) Laura Tillman
A new state law requires schools in Mississippi to teach sex education starting next year, with districts selecting either an abstinence-only or abstinence-plus curriculum. The goal, according to officials, is to reduce the state’s teen pregnancy rate by dismantling the culture of silence around the issue.

Though Mississippi has seen teen births decline over the past decade, mirroring a trend nationwide, its rate of 55 births per 1,000 girls ages 15-19 is well above the national average of 34.3, data from the National Center for Health Statistics show.

Programs like the “Delta Health Partners Healthy Start Initiative” are seeking to make a lasting impact on teen pregnancy. Run through Tougaloo College since 1999, DHPHSI explores the relationship between poverty and teen motherhood. It works out of one of the poorest areas of the poorest state, addressing in frank terms issues surrounding parenting skills, career goals, and contraception.

DHPHSI helps girls in 17 Delta high schools and at their homes. Jodi Bailey, a nurse and case manager for the program, said providing support is key to boosting participants’ self-confidence and motivation. “We want to keep you in high school, we want you to graduate and say ‘I did it,’” she tells the girls.

**Global Cancer Cases Could Rise 75 Percent by 2030**
*Associated Press*, (05.31.2012) Maria Cheng
A team of international researchers projects that cancer cases could increase 75 percent by 2030 on account of population growth, aging, and more developing countries adopting Western lifestyles linked to the disease.

While infection-caused cancers—such as those of the cervix, liver, and stomach—are declining, those linked to bad diet and exercise habits, drinking, and smoking are rising. Poor countries could see the number of people with cancer rise by more than 90 percent, said scientists at the American Cancer Society and the International Agency for Research on Cancer in Lyon, France. Cancer is a “byproduct” of increasing education, income, and longevity, said Freddie Bray, an IARC researcher.

The team used recent cancer trends and demographic projections from the UN to estimate 22.2 million new cases of cancer in 184 countries by 2030. In 2008, an estimated 12.7 million cancer cases were seen globally. However, the data are limited by the fact that cancer registries in Africa, Asia, and Latin America report on less than 10 percent of the population, said Bray. Most cancers in developing countries are linked to infections, but lifestyle-related cancers are expected to increase there.

However, “It’s a misconception that nothing can be done,” said John Groopman of the Johns Hopkins Bloomberg School of Public Health, who was not a study author. For example, he said, “If we employed cervical cancer screening and the vaccine [to prevent the cancer], we could eliminate cervical cancer in this century.”

[PU editor’s note: The study, “Global Cancer Transitions According to the Human Development Index (2008-2030): a Population-Based Study,” was published early online in The Lancet Oncology (2012;doi:10.1016/S1470-2045(12)70211-5).]

**Guardian Examines High Incidence Of Drowning Deaths Among Children In Bangladesh**
"Bangladesh, a country crisscrossed with rivers and canals, has one of the highest drowning rates in the world," the Guardian reports. "More than 17,000 Bangladeshi children drown every year—nearly 50 a day, according to the Bangladesh health and injury survey [pdf], conducted in 2003," the news service writes.

"A report by UNICEF and the Alliance for Safe Children (Tasc) has found that the cause of death in roughly one in four children who die between one and 10 years of age is drowning," making "drowning the leading killer of children in Bangladesh, overtaking diseases such as diarrhea and pneumonia," the Guardian adds.

"It’s a hidden epidemic,’ said Dr. Jahangir Hossain, program coordinator for the Centre for Injury Prevention and Research, Bangladesh (CIPRB)," the Guardian writes. "Proportionate to population, more children die from drowning in Bangladesh than in any other country. But most of the programs combating child mortality are focused on infectious diseases. Drowning hardly gets a mention in national policy circles," Hossain said, according to the newspaper. The article highlights the SwimSafe initiative, which
"has trained more than 200,000 children" since its inception in 2006, noting, "SwimSafe is one component of a larger child injury prevention project, explains Amy Delneuville, child protection specialist with UNICEF in Bangladesh" (Al-Mahmood, 6/1).

**Growing Obesity In Developing Countries A Sign Of Historic Global Tipping Point**

In this Bloomberg Businessweek opinion piece, Charles Kenny, a fellow at the Center for Global Development and the New America Foundation, examines the global obesity epidemic, writing, "It may seem strange to be worried about too much food when the United Nations suggests that, as the planet's population continues to expand, about one billion people may still be undernourished," but "[growing obesity in poorer countries is a sign of a historic global tipping point." He continues, "After millennia when the biggest food-related threat to humanity was the risk of having too little, the 21st century is one where the fear is having too much."

"The issue isn't so much that we can't grow enough," he states, adding, "Rather, existing food supplies are so poorly distributed that those hundreds of millions have too little for their own health, while two billion-plus have too much." He writes that "the global obesity epidemic is a more complex problem than the conditions that felled most poor people in the past," and notes it "has a whole range of different causes and no simple public health solution." He concludes, "The problem of global plenty is a real one. But for all of [the world's] challenges with excess, it is still considerably better than the reverse" (6/4).

**Short-term risk of shingles recurrence low**

No urgent need to get vaccinated to prevent a second shingles episode

PASADENA, Calif., June 5, 2012 — People who have had an episode of herpes zoster, also known as shingles, face a relatively low short-term risk of developing shingles, according to a Kaiser Permanente Southern California study published online in the *Journal of Infectious Diseases*. These findings suggest that among people with immune systems that have not been compromised, the risk of a second shingles episode is low.

Researchers reviewed electronic health records and monitored recurrence of shingles for more than 6,000 individuals. They found fewer than 30 cases of recurrent shingles in an average of two years of follow-up and little difference in the rate of recurrence between the vaccinated and unvaccinated population.

"This study's findings are important because we found that the risk of having a recurrent shingles episode is not as high as previous research indicates," said Hung-Fu Tseng, PhD, MPH, study lead author with the Kaiser Permanente Southern California Department of Research & Evaluation in Pasadena, Calif. "We now have empirical data that show the risk of recurrence is low among an elderly population who did not have compromised immune systems, regardless of their vaccination status."

More than 1 million people develop shingles every year in the United States. Shingles is a painful contagious rash caused by the dormant chickenpox virus which can reactivate and replicate, damaging the nerve system. The elderly are especially vulnerable because immunity against the virus that causes shingles declines with age.

When the Food and Drug Administration approved the shingles vaccine in 2006, the agency said that having an episode of shingles boosts immunity and suggested it was unlikely that people would experience a recurrence. It further stated that the effectiveness of the vaccine in preventing repeat episodes had not been proven in clinical trials because trials have not been conducted.

By contrast, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recommended the herpes zoster vaccine for people ages 60 and older, including those who reported a previous episode.

"While this latest study adds to the growing evidence base of emerging knowledge about the shingles vaccine, more research is needed. Our findings need to be replicated by studies with larger populations. Kaiser Permanente Southern California researchers will continue to follow this population of vaccinated people in order to determine the long term preventative efficacy," said Dr. Tseng.

Researchers studied electronic health records for 1,036 vaccinated and 5,180 unvaccinated Kaiser Permanente members aged 60 and older. The vaccinated population included members who received vaccines between 2007 and 2010. The zoster vaccine is not recommended for patients with immune systems that have been compromised as a result of cancer or other medical conditions, so they were excluded from this study.
Based on the clinically confirmed cases, researchers found the risk of the recurrence of shingles after a recent episode is fairly low regardless of vaccination status. Each year, on average, 19 persons per 10,000 in the vaccinated cohort experienced a recurrence of shingles. The rate was only slightly higher for the unvaccinated population, at approximately 24 persons per 10,000 per year.

This is the latest in a series of published Kaiser Permanente studies conducted to better understand vaccine effectiveness and safety. Among these studies were:

- In 2011, Dr. Tseng was a lead researcher in a Vaccine Safety Datalink study published in the *Journal of Internal Medicine* that found the herpes zoster vaccine to be safe.
- Also last year, Dr. Tseng published a study in the journal *Vaccine* that found that administering the pneumococcal and the herpes zoster vaccines at the same time is as beneficial as if they are administered separately.
- On top of that study, Dr. Tseng published a study in 2011 in the *Journal of the American Medical Association* that found that the shingles vaccine is associated with a 55 percent reduced risk of developing the disease.
- In 2010, another study by Dr. Tseng in *JAMA* found the pneumococcal pneumonia vaccination is not associated with a reduced risk of heart attacks or strokes in men.
- Two Kaiser Permanente studies found that the combination vaccine for measles, mumps, rubella, and chickenpox is associated with double the risk of febrile seizures for 1- to 2-year-old children, compared to same-day administration of the separate vaccine for MMR (measles, mumps, rubella) and the varicella vaccine for chickenpox.
- Other Kaiser Permanente studies found that children of parents who refuse vaccines are nine times more likely to get chickenpox and 23 times more likely to get pertussis (commonly known as whooping cough), compared to fully immunized children.
- Another study found that herpes zoster is very rare among children who have been vaccinated against chickenpox.

**ASCO: Breast Cancer Outcomes among HIV Positive Women**

Published on Tuesday, 05 June 2012 00:00

Written by Liz Highleyman

Women with HIV can do well on a variety of different types of treatment for breast cancer, but they are prone to infections and blood cell deficiencies and may benefit from adjunct therapies, researchers reported at the American Society of Clinical Oncology Annual Meeting (ASCO 2012) taking place this week in Chicago.

As people with HIV live longer thanks to effective antiretroviral therapy (ART), they have more time to develop malignancies. Breast cancer is generally not one of the non-AIDS cancers that have been found to occur more frequently among HIV positive compared with HIV negative people, but HIV positive women share the high risk of the population at large.

Roberto Enrique Ochoa and colleagues performed a retrospective review of breast cancer cases in HIV positive patients seen at the University of Miami Sylvester Comprehensive Cancer Center/Jackson Memorial Hospital between January 1999 and June 2011.

The review identified 46 women and 1 man with breast cancer and HIV. The average patient age was 46 years (range 31-65 years), 79% were African-American, 21% were white, and 14% were Hispanic. Two-thirds of the women were pre-menopausal.

**Results**

- 36 patients had HIV before or were diagnosed at the same time with HIV and breast cancer, while 6 were diagnosed with HIV within 1 year after breast cancer diagnosis (5 had unavailable HIV diagnosis dates).
- 23% of patients had CD4 T-cell counts > 500 cells/mm³, 37% had 201-500 cells/mm³, 20% had 51-200 cells/mm³, and 20% had < 50 cells/mm³; 27% had received an AIDS diagnosis.
- 15 people had been diagnosed with breast cancer before the advent of effective combination ART; among those diagnosed after 1996, 60% were on ART.
- Most patients had moderate to advanced breast cancer:
  - Stage 0 — tumor in situ, or non-invasive cancer: 4%;
  - Stage 1 — cancer invading normal breast tissue or lymph nodes, with tumors smaller than 2 mm: 6%;
  - Stage 2 — cancer that has spread to underarm lymph nodes, with tumors smaller than 5 mm: 38%;
  - Stage 3 — cancer that forms clumps and may have spread further into the chest: 38%;
Stage 4 – invasive cancer that has spread to other organs: 9%.

- Half of patients had estrogen receptor (ER) positive breast cancer, 15% had HER-2 positive cancer, and 21% had triple negative cancer.
- 43 patients had localized disease, 32 underwent modified radical mastectomy, 8 had breast-conserving surgery, and 3 refused surgery.
- 26 people received either curative or palliative chemotherapy.
- 11 treated patients reported serious side effects of treatment, including 10 who developed neutropenia with fever or sepsis – that is, infections related to immune cell deficiency – including 6 with herpes zoster.
- 1 person experienced acute respiratory distress syndrome (ARDS).
- 3 developed rapidly progressive and fatal AIDS within 6 months of completing chemotherapy.
- Survival rates over the study period were 100% for people with Stage 1 breast cancer, 50% for those with Stage 2, 28% for those with Stage 3, and 0% for those with Stage 4.
- Stage 2 patients were more likely to die of HIV/AIDS than breast cancer, while the reverse was true for Stage 3 and 4 patients.

Based on these findings, the researchers concluded, "Breast cancer in patients with HIV infection spans the spectrum of breast cancer presentations."

"Hormonal therapy, surgery, and radiation therapy were well tolerated," they continued. "Infectious complications were common in patients treated with chemotherapy and routine use of growth factors [for blood cell deficiencies] and prophylactic acyclovir [to prevent herpesvirus infections] should be considered."

**Reference**

**MALAWI: Where Is HIV/AIDS on Banda's to-do list?**

JOHANNESBURG, 6 June 2012 (PlusNews) – Malawi’s new president, Joyce Banda, has inherited an unenviable to-do list from former president Bingu wa Mutharika, and AIDS activists are hoping that bolstering the donor-dependent AIDS response will be one of her most urgent priorities.

A lot is at stake. An estimated 10 percent of the adult population is HIV-positive, with about 70,000 Malawians newly infected with HIV every year. Yet the country is almost entirely dependent on external funding for its AIDS programmes, and ambitious plans to scale up treatment have been derailed after the Global Fund to fight AIDS, Tuberculosis and Malaria rejected a succession of funding proposals.

To make matters worse, under former president Bingu wa Mutharika, who died suddenly in April 2012, Malawi had fallen out of favour with Western donors as a result of concerns about human rights and poor governance, leading to a significant loss of donor support.

Banda has been working to restore relations with donors, and it seems to be paying off. Britain has agreed to unlock aid frozen in 2011 after a diplomatic spat with Mutharika. The UK’s International Department for International Development (DFID) pledged to release an initial £30 million (US$47.3 million) tranche of urgent funding, €10 million ($15.8 million) of which will be used to support Malawi’s ailing healthcare system, while the remainder will go towards stabilizing the economy.

"We are hopeful that since more donors are now coming forward, such aid will trickle down to funding HIV/AIDS programmes that have been hit by lack of funds," said Norman Mwambakulu, deputy secretary of the Department of Nutrition and HIV/AIDS. He is optimistic that the steps taken by the new administration to regain donor confidence will put the government’s efforts back on track, and that Malawi could still reach its target of having zero new HIV infections by 2015.

But Gift Trapence, executive director of the Centre for Development of People (CEDEP), a rights NGO, warned that the money may have come too late for smaller AIDS organizations. "Malawi has been struggling with AIDS funding for some time. The window of hope that the new administration has provided may not be enough," he told IRIN/PlusNews.

**Progressive position**

Banda has also pledged to repeal some of the repressive laws passed by Mutharika, among them the Indecent and Unnatural Acts, which criminalizes homosexuality. Human rights activists noted that the legislation heightened anxiety in Malawi’s underground lesbian, gay, bisexual, transgender (LGBT) community, and compromised HIV prevention efforts among men who have sex with men (MSM).
The move has been welcomed by activists who have been living in fear in the shadow of the controversial trial in 2010 of two Malawian men charged with sodomy and indecency after they became engaged to be married in December 2009. The couple were found guilty but later released on condition that they have no further contact.

According to Trapence, the "progressive" stance taken by Banda has also been adopted by other government officials, such as the Minister of Justice and Constitutional Affairs, who recently spoke out against gays being arrested.

Although president Banda did not specify when the proposal to repeal the laws will come before parliament, Trapence said her statement gave activists a chance to increase awareness of the rights of homosexuals.

"The President has created a space to debate this issue. This is a very good opportunity for us to challenge misconceptions and bring the facts to legislators, the media and traditional leaders."

Medscape CME Activity

**Iatrogenic Creutzfeldt-Jakob Disease, Final Assessment**

P. Brown et al.
The book on iatrogenic Creutzfeldt-Jakob disease (CJD) in humans is almost closed. This form of CJD transmission via medical misadventures was first detected in 1974. Today, only occasional CJD cases with exceptionally long incubation periods still appear. The main sources of the largest outbreaks were tissues from human cadavers with unsuspected CJD that were used for dura mater grafts and growth hormone extracts. A few additional cases resulted from neurosurgical instrument contamination, corneal grafts, gonadotrophic hormone, and secondary infections from blood transfusions. Although the final solution to the problem of iatrogenic CJD is still not available (a laboratory test to identify potential donors who harbor the infectious agent), certain other measures have worked well: applying special sterilization of penetrating surgical instruments, reducing the infectious potential of donor blood and tissue, and excluding donors known to have higher than normal risk for CJD.

**Dengue Fever Vaccine 'May Be In Sight,' Reuters Reports**

*Reuters* reports on efforts to develop a vaccine for dengue fever, writing that "victory over ... the intensely painful 'breakbone fever' ... may be in sight." Paris-based firm Sanofi "hopes for positive results in September from a key trial among children in Thailand that would set it on course to market a shot in 2015, which would prevent an estimated 100 million cases of dengue infection each year," the news service writes, noting, "Of 20,000 annual deaths, many are of children." According to Reuters, "Results from that clinical study, in what is known as the Phase IIb of the international standard three-stage process of assessment, are expected in the third quarter" and "will also be presented for scientific scrutiny at the annual meeting of the American Society of Tropical Medicine and Hygiene in Atlanta in November."

The news service recounts a history of the disease, noting it "was spread to global pandemic proportions in part due to the massive movements of armies through the Pacific theatre in World War II," which "prompted the first efforts to develop a vaccine, as U.S. and Japanese scientists isolated the virus spread by the bite of the Aedes aegypti mosquito." Reuters writes, "The U.S. Army's quest for a vaccine had most recently been pursued in partnership with GlaxoSmithKline," but "Sanofi now seems closest to offering a viable treatment," adding, "Orin Levine, executive director of the International Vaccine Access Center (IVAC) at the Johns Hopkins Bloomberg School of Public Health, says the new vaccine is a potential breakthrough but warned its roll-out may not be straightforward" (Hirschler, 6/5).

**WHO Warns Of Drug-Resistant Strains Of Gonorrhea**

"Drug-resistant strains of gonorrhea have spread to countries across the world, the U.N. health agency said on Wednesday, and millions of patients may run out of treatment options unless doctors catch and treat cases earlier,"*Reuters* reports (Kelland, 6/6). "Already several countries, including Australia, France, Japan, Norway, Sweden and the United Kingdom are reporting cases of resistance to cephalosporin antibiotics—the last treatment option against gonorrhea," a WHO press release states (6/6).

"'This organism has basically been developing resistance against every medication we've thrown at it,' said Dr. Manjula Lusti-Narasimhan, a scientist in the agency's department of sexually transmitted diseases," according to the *Associated Press*. "In a couple of years it will have become resistant to every treatment option we have available now," she added, the news service notes. The WHO "is urging
governments and doctors to step up surveillance of antibiotic-resistant gonorrhea, a bacterial infection that can cause inflammation, infertility, pregnancy complications and, in extreme cases, lead to maternal death,” the AP writes (6/6).

Cedars-Sinai researchers explore role of fungus in digestive disorders

Study published in Science indicates that fungus plays a role in inflammatory bowel disease

LOS ANGELES (Emargoed until Wednesday, June 6, 2012 at 2 p.m. Eastern) – Cedars-Sinai researchers say their examination of the fungi in the intestines suggests an important link between these microbes and inflammatory diseases such as ulcerative colitis.

In the new study, published in the June 8 issue of Science, researchers at Cedars-Sinai’s Inflammatory Bowel and Immunobiology Research Institute identified and characterized the large community of fungi inhabiting the large intestine in a model of the disease.

The digestive tract is home to a large number of micro-organisms. In fact, with an estimated 100 trillion bacteria residing in the gut, microbes outnumber human cells in the body. Some are necessary to aid in digesting food, producing necessary vitamins and suppressing the growth of harmful microbes. Others are harmful to the body, contributing to illnesses such as Crohn’s disease, ulcerative colitis and obesity.

Modern DNA-sequencing technology has revolutionized the study of these microbes in the last decade, allowing the role of bacteria in disease to be understood more clearly, as is shown in the Cedars-Science research published in Science.

"It's long been recognized that fungi must also exist in the gut, but we’re among the first to investigate what types, how many, and whether they’re important in disease,” said David Underhill, PhD, associate professor and director of the Graduate Program in Biomedical Science and Translational Medicine, who led the study. "We were truly stunned to see just how common fungi are, identifying more than 100 different types" and seeing linkages to digestive disorders.

An estimated 1.4 million Americans have Inflammatory Bowel Disease, or IBD, a chronic digestive disorder, and about 30,000 new cases are diagnosed annually. Ulcerative colitis, one of the most common types of IBD, causes inflammation and ulcers in the top layers of the lining of the large intestine. Common symptoms include abdominal pain, diarrhea, bleeding, fatigue, weight loss and loss of appetite. Ulcerative colitis patients can be at increased risk of developing colorectal cancer.

"This study takes us an important step closer to understanding how fungi contribute to disease, as well as significantly expanding our understanding of what types of fungi are living in our bodies,” said Iliyan Iliev, PhD, a Cedars-Sinai research scientist and lead author on the study.

To determine fungi contribute to inflammatory disease, the study homed in on a protein called Dectin-1, produced by white blood cells and used by the immune system to detect and kill fungi. In an animal model of the disease, researchers found that the protein is important in protecting against inflammation caused by indigenous fungi. The finding has significant implications for human disease, as scientists at the Cedars-Sinai Medical Genetics Institute found a variant of the gene for Dectin-1 that is strongly associated with severe forms of ulcerative colitis.

Study predicts imminent irreversible planetary collapse

Using scientific theories, toy ecosystem modeling and paleontological evidence as a crystal ball, 18 scientists, including one from Simon Fraser University, predict we're on a much worse collision course with Mother Nature than currently thought.

In approaching a state-shift in Earth’s biosphere, a paper just published in Nature, the authors, whose expertise span a multitude of disciplines, suggest our planet’s ecosystems are careening towards an imminent, irreversible collapse.

Earth’s accelerating loss of biodiversity, its climates' increasingly extreme fluctuations, its ecosystems' growing connectedness and its radically changing total energy budget are precursors to reaching a planetary state threshold or tipping point.

Once that happens, which the authors predict could be reached this century, the planet’s ecosystems, as we know them, could irreversibly collapse in the proverbial blink of an eye.

"The last tipping point in Earth's history occurred about 12,000 years ago when the planet went from being in the age of glaciers, which previously lasted 100,000 years, to being in its current interglacial state. Once that tipping point was reached, the most extreme biological changes leading to our current
state occurred within only 1,000 years. That’s like going from a baby to an adult state in less than a year," explains Arne Mooers. "Importantly, the planet is changing even faster now."

The SFU professor of biodiversity is one of this paper’s authors. He stresses, "The odds are very high that the next global state change will be extremely disruptive to our civilizations. Remember, we went from being hunter-gathers to being moon-walkers during one of the most stable and benign periods in all of Earth’s history.

"Once a threshold-induced planetary state shift occurs, there’s no going back. So, if a system switches to a new state because you’ve added lots of energy, even if you take out the new energy, it won’t revert back to the old system. The planet doesn’t have any memory of the old state."

These projections contradict the popularly held belief that the extent to which human-induced pressures, such as climate change, are destroying our planet is still debatable, and any collapse would be both gradual and centuries away.

This study concludes we better not exceed the 50 per cent mark of wholesale transformation of Earth’s surface or we won’t be able to delay, never mind avert, a planetary collapse.

We’ve already reached the 43 per cent mark through our conversion of landscapes into agricultural and urban areas, making Earth increasingly susceptible to an environmental epidemic.

"In a nutshell, humans have not done anything really important to stave off the worst because the social structures for doing something just aren’t there," says Mooers. "My colleagues who study climate-induced changes through the earth’s history are more than pretty worried. In fact, some are terrified."

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**Complex World of Gut Microbes Fine-Tune Body Weight**

ScienceDaily (June 6, 2012) — Microorganisms in the human gastrointestinal tract form an intricate, living fabric made up of some 500 to 1000 distinct bacterial species, (in addition to other microbes). Recently, researchers have begun to untangle the subtle role these diverse life forms play in maintaining health and regulating weight.

In a new study appearing in the journal *Nutrition in Clinical Practice*, researcher Rosa Krajmalnik-Brown and her colleagues at the Swette Center for Environmental Biotechnology at Arizona State University’s Biosdesign Institute in collaboration with John DiBaise from the Division of Gastroenterology at the Mayo Clinic, review the role of gut microbes in nutrient absorption and energy regulation.

According to Krajmalnik-Brown, "Malnutrition may manifest as either obesity or undernutrition, problems of epidemic proportion worldwide. Microorganisms have been shown to play an important role in nutrient and energy extraction and energy regulation although the specific roles that individual and groups/teams of gut microbes play remain uncertain."

The study outlines the growth of varied microbial populations—from birth onwards—highlighting their role in extracting energy from the diet. The composition of microbial communities is shown to vary with age, body weight, and variety of food ingested; as well as in response to bariatric surgery for obesity, use of antibiotics and many other factors.

Based on current findings, the authors suggest that therapeutic modification of the gut microbiome may offer an attractive approach to future treatment of nutrition-related maladies, including obesity and a range of serious health consequences linked to under-nutrition.

**Micromanagers**

The microbes in the human gut belong to three broad domains, defined by their molecular phylogeny: Eukarya, Bacteria, and Achaea. Of these, bacteria reign supreme, with two dominant divisions—known as **Bacteroidetes and Firmicutes—making up over 90 percent of the gut’s microbial population.** In contrast, the Achaea that exist in the gut are mostly composed of methanogens (producers of methane) and specifically by Methanobrevibacter smithii—a hydrogen-consumer.

Within the bacterial categories however, enormous diversity exists. Each individual’s community of gut microbes is unique and profoundly sensitive to environmental conditions, beginning at birth. Indeed, the mode of delivery during the birthing process has been shown to affect an infant’s microbial profile.

Communities of vaginal microbes change during pregnancy in preparation for birth, delivering beneficial microbes to the newborn. **At the time of delivery, the vagina is dominated by a pair of bacterial species, Lactobacillus and Prevotella.** In contrast, infants delivered by caesarean section typically show microbial communities associated with the skin, including **Staphylococcus, Corynebacterium, and Propionibacterium.** While the full implications of these distinctions are still murky, evidence suggests they may affect an infant’s subsequent development and health, particularly in terms of susceptibility to pathogens.
Diet and destiny

After birth, diet becomes a critical determinant in microbial diversity within the gut. Recent research indicates that microbial populations vary geographically in a manner consistent with regional differences in diet. Children in rural areas of Burkina Faso for example showed much more abundant concentrations of Bacteroidetes compared with their cohorts in Italy, a finding consistent with the African children's plant-rich diet.

While microbiomes appear to have adapted to local diets, changes in eating habits significantly alter composition of gut microbes. Variations in macronutrient composition can modify the structure of gut microbiota in a few days—in some cases, a single day. Studies in mice show that changing from a low fat, plant polysaccharide diet to a Western diet high in sugar and fat rapidly and profoundly reconfigures the composition of microbes in the gut.

Another modifier of gut microbe composition is gastric bypass surgery, used in certain cases to alleviate conditions of serious obesity. In earlier work, the authors found that the post-surgical microbial composition of patients who underwent so-called Roux-en-Y gastric bypass was distinct from both obese and normal weight individuals.

"Obesity affects more than a third of adults in the U.S. and is associated with a raft of health conditions including heart disease, stroke, type 2 diabetes and certain forms of cancer," says Dr. John DiBaise. The authors further note that concentrations in the blood of lipopolysaccharides derived from gut bacteria increase in obese individuals, producing a condition known as metabolic endotoxemia. The disorder has been linked with chronic, systemic, low-level inflammation as well as insulin resistance.

Energy harvest

In the current review, the cycle of microbial energy extraction from food, involving hydrogen-producing and consuming reactions in the human intestine, is described in detail. Short chain fatty acids (SCFAs) are a critical component in this system. During the digestive process, fermentation in the gut breaks down complex organic compounds, producing SCFA and hydrogen. The hydrogen is either excreted in breath or consumed by 3 groups of microorganisms inhabiting the colon: methanogens, acetogens and sulfate reducers.

Research conducted by the authors and others has demonstrated that hydrogen-consuming methanogens appear in greater abundance in obese as opposed to normal weight individuals. Further, the Firmicutes—a form of acetogen—also seem to be linked with obesity. Following fermentation, SCFAs persist in the colon. Greater concentration of SCFAs, especially propionate, were observed in fecal samples from obese as opposed to normal weight children. (SCFAs also behave as signaling molecules, triggering the expression of leptin, which acts as an appetite suppressor.)

While it now seems clear that certain microbial populations help the body process otherwise indigestible carbohydrates and proteins, leading to greater energy extraction and associated weight gain, experimental results have shown some inconsistency. For example, while a number of studies have indicated a greater prevalence of Bacteroidetes in lean individuals and have linked the prevalence of Firmicutes with obesity, the authors stress that many questions remain.

Alterations in gut microbiota are also of crucial concern for the one billion people worldwide who suffer from undernutrition. Illnesses resulting from undernutrition contribute to over half of the global fatalities in children under age 5. Those who do survive undernutrition often experience a range of serious, long-term mental and physical effects. The role of gut microbial diversity among the undernourished has yet to receive the kind of concentrated research effort applied to obesity—a disease which has reached epidemic proportions in the developed world.

Exploiting microbes affecting energy extraction may prove a useful tool for non-surgically addressing obesity as well as treating undernutrition, though more research is needed for a full understanding of regulatory mechanisms governing the delicate interplay between intestinal microbes and their human hosts.

Dr. Krajmalnik-Brown and colleagues at the Biodesign Institute and Mayo Clinic are currently in the second year of an NIH-funded study to better understand the role of the gut microbiome in the success or failure of surgical procedures performed to treat obesity including the Roux-en-Y gastric bypass, adjustable gastric band and vertical sleeve gastrectomy.

Journal Reference:
Protein Knots Gain New Evolutionary Significance

Molecular structures and matrix presentation for ubiquitin C-terminal hydrolases from (A) human, (B) yeast, and (C) P. falciparum plasmodium cells form the same knotting motif. (Credit: Image courtesy of University of California—Santa Barbara)

ScienceDaily (June 5, 2012) — A new study suggests that protein knots, a structure whose formation remains a mystery, may have specific functional advantages that depend on the nature of the protein’s architecture.

"The presence of a knotted or slipknotted structure in a protein is relatively rare but really is very interesting," said Kenneth Millett, a professor of mathematics at UC Santa Barbara and a co-author of the paper, "Conservation of complex knotting and slipknotting patterns in proteins," published in the Proceedings of the National Academy of Sciences.

Relatively little is known about protein folding, the process by which a polypeptide chain with a specific sequence of amino acid chains forms the three-dimensional structures—their "native states"—required to become functional. How this process reproducibly achieves the required structure is the subject of intensive study. Even harder is understanding how this is accomplished for knotted proteins, where the chain loops around itself in entanglements of varying complexity; or the even rarer slipknotted proteins, where a loop is bound by another segment of the protein chain, similar to a shoelace bow.

What intrigued the scientists about the protein knots is that the folding process resulting in the formation of knots is intrinsically more difficult than the process producing unknotted proteins. The protein has to avoid not only energetic traps but also topological barriers. If an amino acid chain takes too
much time to find its native state or if it is stuck in a misfolded or partially unfolded state, the result may be a useless protein or one that produces harm by causing protein aggregation which is known to cause neurodegenerative disorders.

"From an evolutionary point of view, knotting might seem unlikely to occur but, in fact, it does occur," said Millett, who, along with co-first authors Joanna Sulkowska from UC San Diego and Eric J. Rawdon from the University of Saint Thomas and with Jose N. Onuchic from Rice University and Andrzej Stasiak from the University of Lausanne, examined, analyzed, and classified 74,223 protein structures submitted to the Protein Data Bank for the location and formation of knots. Millett worked on the development of the mathematical theory and the computer implementation needed to identify the location and type of knots in the proteins studied in the paper.

What they found was that protein knots and slipknots, instead of being discarded through the process of evolution, are often strongly conserved. This suggests that, despite their reduced efficiency of folding, the knots are somehow advantageous and important to the function of the protein.

Additionally, the researchers found that the location of these knots and slipknots is highly conserved, marked by points of flexibility—"hinges"—in the chain that may have properties necessary for more efficient folding.

Knots and slipknots could contribute to the stability of the protein, as shown by the similar slipknot loops observed in several families of proteins that form transmembrane channels—the ducts through membranes of a cell, that allow certain materials to pass through. The slipknot, according to the authors, seems to strap together several transmembrane structures giving stability and forming the channel needed to allow passage through cell membranes.

The researchers will continue their study of the little-understood process of protein folding and knotting, said Millett.

"These knots may help to identify features that turn out to be important, and aspects of the structure that are more generalizable. We need to clearly understand how these things come to be, what are the implications of their structure, and how might one be able to somehow guide them," said Millett.

**Can HIV Infection Be Cured?**

May 7, 2012

**What Have We Learned About HIV?**

In 1981, several cases of rare pneumonia (PCP, see Fact Sheet 515) and skin cancer called Kaposi’s sarcoma (see Fact Sheet 511) were reported. These cases were in homosexual men in Los Angeles and New York City. This was a mystery to researchers.

The virus that causes AIDS was identified in 1983. No medications were available to treat this disease until 1987. In that year, a cancer drug called zidovudine (AZT) was found to slow down the multiplication of the Human Immunodeficiency Virus (HIV.)

By 2011, over 30 medications had been approved to fight HIV. None of these drugs kills the virus. Each of them slows down HIV at a specific point of its life cycle (see Fact Sheet 106.)

**Hope for a Cure**

In 1996, several research studies suggested that triple-drug combinations could drive HIV into remission or eradicate it. Many people taking combinations of antiretroviral medications have an undetectable viral load (see Fact Sheet 125.)

However, by some estimates, only 2% of the virus in the body is in the blood, where it can be measured by viral load tests. Even in patients taking potent triple medication combinations, HIV was not eradicated.

**Where Does the Virus Hide?**

Very early in HIV infection, the virus becomes part of the genetic code of millions of cells. Some of these cells are hidden from the immune system, and from antiviral medications. Areas where the virus is hiding are called reservoirs. These include the genital tract and the central nervous system. One researcher estimated that it might take 70 years of controlling HIV to eliminate these reservoirs.

**The Berlin Patient**

Another boost to hopes for an HIV cure came from the "Berlin patient." This was a person with HIV living in Berlin who also had leukemia. Standard leukemia treatment failed. He then received a bone marrow transplant. This wiped out his immune system. It was replaced from a donor with a rare genetic mutation that made him resistant to HIV infection. When the treatments were completed, the Berlin patient had no sign of HIV in his body.
Bone marrow transplants are dangerous. As many as 1/3 of patients who get them die from the procedure. Therefore, it is not clear that the success of the Berlin patient could or should be tried in anyone else. However, this case provides some clues about how HIV might be removed from a patient.

**Current Cure Research**

There are ongoing research efforts in several areas:

- Clearing out reservoirs of infection
- Vaccinations to help the immune system fight HIV (therapeutic vaccination)
- Making cells resistant to HIV
- Modifying stem cells

Many researchers believe that a cure will require a combination of approaches.

**Clearing Out Reservoirs**

During initial HIV infection, millions of cells are infected. The virus is latent. It does not produce new virus. It is invisible to the immune system and to antiretroviral medications.

Researchers are working with drugs that activate HIV in reservoirs. This might make it possible for existing antiretroviral medications to clear the virus. This approach could increase some cancers.

**Therapeutic Vaccinations**

Most vaccines are given to prevent infection. Therapeutic vaccinations are given to boost the body's ability to fight an existing infection. So far, studies of therapeutic vaccines for HIV have not shown strong results. One possible risk is that a therapeutic vaccination would increase immune activity and inflammation.

**Making Cells Resistant to HIV**

In this approach, CD4 cells are taken from the patient. They are modified to make them resistant to HIV. Then they are given back to the patient. The hope is that the modified cells will multiply in the patient.

This approach requires the patient to be connected to a machine for several hours while CD4 cells are removed from the blood. When the modified cells are given back to the patient, it can cause chills, fever, headache, sweating, dizziness and fatigue.

A new approach includes suppressing the immune system to "make room" for the new, modified cells. This might result in more modified cells in the body. However, this can leave patients temporarily at risk for serious infections.

**Modifying Stem Cells**

The Berlin Patient received transplants of stem cells that resisted HIV infection. Stem cells can grow into various types of cells in the body, and in some cases, act as a repair system.

There is significant risk in this approach. If the stem cells are not modified correctly, they could cause serious illness. Stem cell therapy may also require destroying part or all of a patient's immune system.

This approach might only make sense for people with HIV who need to "turn down" their immune systems as part of treatment for cancer.

**Treatment Interruptions**

Many cure research studies involve the patient stopping antiretroviral treatment. This allows researchers to see if the experimental treatment is helping the immune system fight HIV. There are many risks with treatment interruptions (see Fact Sheet 406). The interruptions in these studies currently do not exceed 12 weeks.

**The Bottom Line**

There have been ups and downs in the search for a cure for HIV. So far, it seems that the approaches all carry some risks. The benefits are not yet clear.

However, there is growing interest in cure research. It will continue, and probably increase, in the coming years.

**Hepatitis B is a major health issue for migrants in the US**

Michael Carter
Published: 07 June 2012
Between 1.04 million and 1.61 million migrants now resident in the US have chronic hepatitis B infection, investigators report in the online edition of *Hepatology*.

“The finding that as many as 1.6 million foreign born individuals in the United States may be living with chronic hepatitis B – nearly twice the number previously estimated – highlights the need for HBV [hepatitis B virus] screening in all foreign-born persons,” write the authors.
After adding the 300,000 to 600,000 chronic hepatitis B infections in US-born individuals, the investigators suggest that there could be as many as 2.2 million chronic hepatitis B infections in the United States, a far higher figure than any other current estimate.

Chronic hepatitis B is a major global health problem. It is thought that there are between 350 and 400 million infections worldwide. Up to a quarter of people with chronic hepatitis B infection have a significant risk of premature death because of complications related to the infection.

Despite the serious health implications of the infection, the epidemiology of chronic hepatitis B in the US is poorly understood. This is partly because testing for the infection is not part of routine health care. Moreover, surveillance activities for the infection have inadequate funding and are poorly developed. Estimates of the number of chronic hepatitis B infections in the US vary from a low of 500,000 to as high as two million.

It is well recognised that many of cases of chronic hepatitis B infection involve people who were born outside the US. Between 2006 and 2008, approximately 3% of refugees entering the US were found to have the infection – this is compared to a prevalence rate of between 0.1 and 0.2% in the US-born population.

Current hepatitis B surveillance data are likely to be inaccurate because vulnerable and marginalised individuals – including those born abroad – are under-represented.

A team of investigators therefore conducted a meta-analysis, surveying the prevalence of chronic hepatitis B in 102 countries and the rate of the infection in migrants.

Some 2053 prevalence surveys were included in the study. Of these, 256 involved emigrants and 1797 examined rates of chronic hepatitis B infection among individuals still living in the country studied.

Countries with the highest prevalence of chronic hepatitis B infection were Sudan (19%), Liberia (17%), Guinea (16%), Eritrea (16%) and Zimbabwe (14%).

Rates of the infection among migrants were highest among those who emigrated from Africa (10%), followed by Asia (7%), Oceania (5%) and the Caribbean (5%).

Overall, the prevalence of chronic hepatitis B among foreign-born individuals in the US was calculated at 3.45%.

The total number of infections among foreign-born individuals living in the US in 2009 was calculated to be 1.32 million. But estimates varied from a low of just over 1 million to a high of 1.61 million.

Approximately 58% of foreign-born people with chronic hepatitis B in the US had migrated from Asia and 11% were of African origin – the infection is endemic in both these regions.

The five countries from which the largest number of individuals with the infection had migrated were China (12% of migrants), Vietnam (13%), the Philippines (7%), the Dominican Republic (11%) and Mexico (0.5%).

“The number of foreign-born individuals living with chronic hepatitis B will continue to increase with ongoing migration from countries with intermediate and high HBV endemicity,” write the authors. “Primary care physicians and general internists have an opportunity to identify foreign-born persons living with chronic hepatitis B in the United States via screening and follow-up to ensure the benefit from monitoring and treatment.”

The authors of an editorial in the same edition of Hepatology praise the study’s “convincing data”. They believe these can “help public health officials identify at-risk populations and direct prevention to communities in need of culturally appropriate services. HBV testing, followed by linkage to care and treatment, can prevent new cases of HBV infection...and improve health outcomes for persons living with hepatitis B.”

Reference


Colombian court rules that blood donors cannot be turned down for sexual orientation

Tuesday, 29 May 2012 07:20 Sarah Kinosian

Colombia’s Constitutional Court ruled that an individual cannot be barred from giving blood based on their sexual orientation, reported local media Tuesday.
“The risk of contamination depends on risk behavior, not on the donor population. A heterosexual person that has sexual relations with strangers and without protection is mucho more likely to contract HIV than a gay man with a stable partner that uses protection,” said the ruling.

The court made the decision in response to an appeal from a man in Bucaramanga, capital of the eastern department of Santander, who was barred from donating blood after workers learned he was gay.

The nurses at the health center argued there was a government decree banning them from receiving blood donated by gay individuals.

The ruling ordered that the Ministry of Health design training guides, programs and plans for health professionals and laboratory workers on how to poll and interview potential donors without asking them their sexual orientation.

“Policy should focus on screening all donors for high-risk behavior, instead of excluding donors based on who they choose to have sex with,” according to the high court’s decision.

The judges noted as well that the exclusion and discrimination against the gay community in Colombia cannot continue, and called for a public health policy that eradicates this type of violation of individual freedoms.

Colombia’s Constitutional Court ruled Friday that the government cannot restrict gay couples’ freedom to express affection in public after two men were forced to leave a Cali mall after they were seen kissing.

TowelTalk: Inside Toronto’s Bathhouses
Author: John McCullagh — Publisher Categories: Gay Men, Mental Health, Sexual Health, Features and Interviews, Health, Population Specific, Sex and Sexuality, John McCullagh

John McCullagh talks with Marco Posadas about TowelTalk, a bathhouse counselling program that seeks to address the psychosocial issues that have an impact on HIV risk for gay and bisexual men and other men who have sex with men.

For many years, outreach workers and volunteers from community-based organizations have worked with bathhouses to provide HIV and STI awareness, prevention and education services to bathhouse patrons. ACT, a Toronto ASO, has augmented these sexual health promotion activities through TowelTalk. This innovative program offers brief, walk-in counselling sessions in the bathhouse by
professionally trained counsellors. The objective is to address the psychosocial issues that can have an impact on HIV risk for gay and bisexual men and other men who have sex with men.

I recently went to ACT to talk about TowelTalk with Marco Posadas, the program’s coordinator. He’s a registered social worker in Ontario and a licensed psychologist in his native Mexico. A psychotherapist for 13 years, with a private practice in Toronto, Marco has international clinical experience working with LGBT communities and with people living with HIV.

**John McCullagh: Marco, I’d like to start by asking you what exactly is TowelTalk.**

Marco Posadas: Towel Talk is a community-based mental health intervention program in three Toronto bathhouses, provided by professional counsellors.

**John: And what’s a bathhouse?**

Marco: It’s a place where men who are gay or bisexual or men who don’t identify as gay go to connect with one another, usually, but not necessarily, to have sex.

**John: So why was TowelTalk developed?**

Marco: ACT has been doing safer sex outreach in bathhouses for 15 or 18 years. The outreach workers identified that there was a need for a more in-depth intervention to help those men who want to talk about psychosocial issues but who would be unlikely to seek counselling from an ASO or other community-based organizations.

**John: Let’s talk a bit more about that. Why would some men be comfortable seeking out your help in a bathhouse yet wouldn’t readily make an appointment to see you in your office?**

Marco: For some men, going to a bathhouse can sometimes trigger a lot of anxiety. For example, if I’m married to a woman and I access bathhouses, I might be uncomfortable with what I’m doing there yet not have the language to talk about my feelings. So giving these men an opportunity to talk to a counsellor when they are perhaps feeling most anxious can be helpful. It provides an opportunity for these guys to talk in depth about sexual identity, about relationships, safer sex, anger management, childhood sexual abuse and other traumas, homelessness, immigration. All the social determinants of health basically that surround HIV transmission. Then maybe we can really hit back in the trenches at a decision-making moment.

**John: You just gave the example of a married man who goes to a bathhouse but who doesn’t necessarily identify as gay. Who are some of the other clients that bathhouse counsellors see?**

Marco: We are in three bathhouses out of the six or seven in Toronto so the population that we serve is really wide. What we’re noticing is that most of the men that talk to us are from racialized communities, newcomers to Canada, men who use substances and men who are married to women. The ages of the men is variable too. When I go to a bathhouse in the west end of the city, I might talk to men who are married, retired, older. If I go to a bathhouse here in the gay village, I might talk to younger men, newcomers.

**John: Tell me about the counselling sessions and how you connect with potential clients.**

Marco: Usually interactions happen as interactions in a bathhouse happen. Yet I’m not in a towel, I’m wearing a T-shirt that says “Want to talk?” on the front and “Counsellor” on the back. So guys are surprised, running into a counsellor in a bathhouse. They’re very curious, like, “What are you doing here?”, “Why are you dressed?”, “Are you here to have sex?” It’s often during those first interactions that there’s a comment that may lead to a counselling session.

**John: For example?**

Marco: Usually sessions start with somebody saying, “So why are you not wearing a towel?” “I’m here to talk”, I reply. “Oh, what do guys talk about here?” “Well, they talk about many things. They talk about guilt, about relationships.” And the guy might say, like, “Oh, I know all about that”. So I ask him if he wants to talk about it. And then, 25 minutes later, he’s disclosing some emotional part of his life that he needs support.
around. He might not have had this at the top of his brain when he came into the bathhouse but yet it’s
something that he’s been wanting to talk with someone about. So we provide him with that opportunity.

**John: So where does the talking take place, exactly?**

Marco: The bathhouse managers are very supportive of the program and they provide a room for the
counsellors to use.

**John: How long does a counselling session last?**

Marco: We differentiate between contacts and sessions. Contacts are any conversation that lasts under ten
minutes, while sessions are longer conversations that can last up to 45 minutes. So that gives us the
opportunity to have three full sessions during a three-hour shift.

**John: Do the clients have to identify who they are or can they remain anonymous?**

Marco: TowelTalk is an anonymous program. If you’ve ever been into a bathhouse you’ll know that the
walls don’t go all the way to the ceiling. So, in order to protect the client’s confidentiality as much as
possible, the session will be anonymous. If the client wants to provide his name, that’s awesome, but we
don’t keep track of those things. It’s completely anonymous.

**John: We’ve talked a little bit about this, but can you identify what are some of the most
common themes?**

Marco: Sure. Off the top of my head I think the most common themes are guilt and anxiety in connection
with a bathhouse. So whether I’m gay or straight, going to a bathhouse can be a very complicated
experience. I might not feel comfortable to disclose it to my gay friends or I cannot even talk about having
sex with other men if I’m married to a woman. Relationships? Whether I’m in an open relationship or a
closed monogamous relationship or single, divorced or in-between. These things can give rise to a lot of
anxiety as well. And sexual health. So, HIV transmission, syphilis transmission. Negotiating condom use,
negotiating sexual practices. Those are the main ones. But also we have sessions where we talk about
issues like housing and immigration. It’s very wide.

**John: It’s unlikely, isn’t it, that in 45 minutes you can do any more than just touch the
surface of these issues? So is there an opportunity for guys to see you in follow-up
sessions?**

Marco: Once there’s a need identified in a session, a guy can come and talk to me for up to eight sessions,
completely free, here at ACT. But you know what? You’d be surprised how powerful single conversations
in a bathhouse can be for someone who’s never talked before with another man about being gay. So, some
of the one-time sessions can be very transformative.

**John: I imagine that there are some issues where a client may benefit from a referral
to an agency outside of ACT. I’m thinking of issues like substance use or immigration. And
I know those outside agencies often have long waiting lists. So how do you avoid losing that
guy, because people often give up in the face of a long wait time?**

Marco: You’re right. Many of the clients we serve are part of a hard-to-reach population that would have a
lot of issues with a wait list, which is why they often don’t access mainstream services. That’s why we’ve
been able to negotiate some streamlined referral agreements with various community agencies. So, for
example, I can literally go with a client to, say, Rainbow Services at CAMH, where we have an agreement
that they would at least assess the person sooner than they might otherwise have been able to do. And, in
the meantime, they still get to work with me for up to eight sessions, or longer if it’s necessary. So we help
them in the transition.
John: Marco, I imagine many of the people in bathhouses are going to be high on substances, they’re going to be partying. How do you manage the challenge of engaging somebody and talking meaningfully with them when they are high?
Marco: We work from a harm-reduction perspective and a sex-positive perspective so that means that so long as you can engage in a conversation we’re more than happy to talk to you. And what we’ve learned is that some men use these substances to cope with feelings and that it can support, actually, their sense of comfort in talking with someone who’s open-minded enough to be in a session with them while they’re high. So we talk to a lot of guys while they’re high. They might not remember it afterwards. But if they run into the counsellor again, they might remember that sense of comfort they felt with him. And we’ve been able to refer people later for follow-up counselling when they’re not high and talk with them here at ACT. But as long as you’re able to talk, to speak, then we’re there for you.

John: I’d like to turn this conversation around and ask how you and your colleagues deal with working in such a sexually charged environment. You’ve got guys who are wearing towels or less, you’ve got loud music, you’ve got porn playing, you’ve got men having sex all around you. How easy or difficult is it for you to work in that kind of environment?
Marco: Like every other stressful job, it can be very challenging but at the same time it can be very rewarding. So having a healthy lifestyle, having friends and laughing and having outside interests help to balance working in a highly sexualized environment. We also have many supports in place. We can access a clinical consultant with whom we can talk about the clinical challenges and our personal experiences in providing these services. We can can talk with our manager. And there’s also myself, the coordinator of the program, with whom my two fellow counsellors can debrief. At the same time, bathhouses are kind of fun. After all, it’s a perk to have porn in your workplace!

John: Are bathhouse counsellors allowed to be bathhouse patrons as well, when they’re not working?
Marco: Yes. We’re working within a gay community to which we belong. And we believe that bathhouses are spaces that all gay men can access. But we have very clear boundaries. So, for example, we can’t go to a bathhouse as a patron 24 hours before and after a shift, to ensure that a client or potential client has left the premises.

John: So what would happen then if you were in a bathhouse counselling a guy and then you were there on another day as a patron yourself and you bump into this guy, a former client. Are there any issues that would come into play here that you’d be concerned about? Is that then an issue in terms of the client/counsellor relationship?
Marco: There’s nothing wrong with being in the same space, as long as the boundaries are clear. An issue would be if the patron wanted to have sex with the counsellor. As in any counselling relationship that would be inappropriate. A guy can be either a client or a possible sex partner, but not both.
John: There’s an evaluation component to TowelTalk, isn’t there? What does it consist of and who’s doing it?
Marco: Yes, TowelTalk is still a pilot project, so we have an evaluation committee to measure the program’s effectiveness. They analyze the feedback surveys each client is invited to fill out, other data we collect and the notes we make of individual sessions. They also interview the counsellors and bathhouse staff about their experiences with the program. And right now we’re in the second stage of the evaluation, where we are beginning to address the effectiveness of the follow-up counselling sessions.

John: What has the evaluation told you about what’s good about the program as well as some of the things that need improvement?
Marco: What works really well? The T-shirt, the branding, the collaboration, having several counsellors in order to attract different types of client, these are strengths of the program. It raises awareness, and guys actually access and know about TowelTalk.
We also learned that it didn’t work to be in a bathhouse past 11pm on weekends as it gets very sexualized then so you have to deal more with boundaries than having an actual session.
Some of the things that we can do better? Speaking more languages and having a greater ability to access more, faster mental health referrals for our clients. We could help address that by providing a longer-term intervention ourselves but we’re restricted by funding constraints. So that’s a challenge.

John: I’d like to finish with a more personal question. You’re a psychotherapist, an analyst, a social worker, you have a lot of qualifications, you have a private practice. So I’m wondering what motivates you to come out of your office and work in bathhouses. Why do you do that?
Marco: I love this program. It’s unique. There’s another bathhouse counselling program in the States but they only do HIV and sexual health counselling. So ours is the only one of its kind. I work from a psychoanalytic perspective in my private practice so that means that I’m used to long-term type of work.
So this is a very unique challenge for me that helps me to harness a different set of skills. Also, as a psychotherapist, it can be very isolating to work in a private practice on my own. TowelTalk allows me to work in the community, doing short-term counselling, project coordination, project management.

John: Marco, TowelTalk is an amazingly creative and innovative program and we’re lucky to have it here in Toronto. Thanks for taking the time to talk about it with PositiveLite.com.
Marco: Thank you very much, John, for giving me the opportunity to do so.

This interview has been edited and condensed.

TowelTalk is a collaborative project between ACT and the AIDS Bureau of the Ontario Ministry of Health and Long-Term Care.

**Nobel winning Barre-Sinoussi optimistic about HIV cure**
The scientist who won a Nobel prize for her work in first identifying HIV says she at last believes finding a cure for the virus which causes Aids might be possible.

French virologist Francoise Barre-Sinoussi said she could not put a timescale on when it might be found but scientists were developing promising new tools.

Over 30 million people have died from HIV/AIDS since it was first identified in 1981.

Since then there has been a number of prevention and treatment breakthroughs so that people with HIV can expect to live a relatively normal lifespan – providing they have access to the correct drugs.

"The reason why we are talking about a cure today is because we have some evidence that it might be possible," Professor Barre-Sinoussi told Tim Franks on the BBC's HARDtalk programme.

Until recently medical researchers had virtually given up the pursuit of a cure but the experiences of two patients now suggest to many scientists that it may be achievable.

*Proof of concept*

One man, the so-called Berlin patient, apparently has cleared his HIV infection, albeit by arduous bone marrow transplants.

More recently, a 50-year-old man in Trenton, New Jersey, underwent a far less difficult gene therapy procedure.

While he was not cured, his body was able to briefly control the virus after he stopped taking the usual antiviral drugs, something that is highly unusual.

Professor Barre-Sinoussi said of the Berlin patient case: "It turns out today that after two bone marrow transplants we can say we cannot detect the virus anymore in his body."
"It is a proof of concept somehow that we did not have before."

There are two main approaches to finding a cure. One is to seek the complete eradication of HIV from the body. The other, a functional cure, would not eliminate the virus but would allow a person to remain healthy without antiviral drugs.

Currently a patient is required to take antiviral drugs every day. This is costly and drugs are not so readily available in poorer countries.

New tools
"The reason why we are pushing for a cure is the fact that we know it is a life-long treatment. We know that it is of course very difficult for universal access, for treatment for all.

"We know as well that there is a small proportion of patients that on long-term treatment are developing complications so that means we need to have new tools for the future," she said.

In 2008 she was awarded the Nobel Prize in Physiology or Medicine, together with her former mentor, Luc Montagnier, for their discovery of HIV.

She will shortly take up the post of President of the International Aids Society.

In her new role she will continue to be a stoic defender of funding for research which in many countries is under threat because of the economic climate.

She has in the past spoken of being "upset and furious" about cuts to international funding for tackling HIV.

While it is hoped securing funding for research will bring a cure for HIV closer, Professor Barre-Sinoussi is reluctant to commit herself as to how close we are in time to that moment that scientists have waited so long to arrive.

"I cannot answer this question if I am honest. A scientist should be honest in my opinion. We don't know."

HARDtalk is broadcast on the BBC News Channel on Mondays, Tuesdays, Wednesdays and Fridays at 0030 and 0430 BST and on the BBC World News Channel on Monday to Thursday at 0330, 0830, 1530 and 2030 GMT.

Pre-existing mutations can lead to drug resistance in HIV virus
In a critical step that may lead to more effective HIV treatments, Harvard scientists have found pre-existing mutations in a small number of HIV patients.

In a critical step that may lead to more effective HIV treatments, Harvard scientists have found pre-existing mutations in a small number of HIV patients. These mutations can cause the virus to develop resistance to the drugs used to slow its progression.

The finding is particularly important because, while researchers have long known HIV can develop resistance to some drugs, it was not understood whether the virus relied on pre-existing mutations to develop resistance, or if it waits for those mutations to occur. By shedding new light on how resistance evolves, the study, reported in online journal PLoS Computational Biology opens the door to the development of new, more effective treatments.

Pennings collected her data from 26 clinical trials. Patients were treated with a typical combination of NNRTI drugs, which helps block the virus from multiplying. She found that the virus is more likely to develop resistance shortly after the start of treatment or when treatment is restarted following an interruption of a week or more. However, it is less likely to develop resistance later on and when patients do not interrupt treatment.

"In order to prevent the evolution of resistance, we need to know where the resistance mutations are coming from, it was exciting to realize data from clinical trials could help us solve this puzzle," Pennings said. "If we understand how the virus develops resistance, we can think of new ways to prevent it."

This finding suggests that pre-existing mutations are behind the virus’ drug resistance, and that resistance which develops early in treatment is likely the result of pre-existing mutations. Resistance that develops later is tied to mutations in the virus that occur after treatment began.

While the study holds out hope for the future development of more effective HIV treatments, Pennings emphasized that data used in the study came from trials, which exclusively included patients receiving NNRTI or unboosted protease inhibitor treatments. It is unclear whether the results can be generalized to other treatments and to patients who are not enrolled in clinical trials.

Alzheimer's vaccine trial a success
[NEWS 6 June] A study led by Karolinska Institutet reports for the first time the positive effects of an active vaccine against Alzheimer's disease. The new vaccine, CAD106, can prove a breakthrough in the
search for a cure for this seriously debilitating dementia disease. The study is published in the distinguished scientific journal Lancet Neurology.

Alzheimer’s disease is a complex neurological dementia disease that is the cause of much human suffering and a great cost to society. According to the World Health Organisation, dementia is the fastest growing global health epidemic of our age. The prevailing hypothesis about its cause involves APP (amyloid precursor protein), a protein that resides in the outer membrane of nerve cells and that, instead of being broken down, form a harmful substance called beta-amyloid, which accumulates as plaques and kills brain cells.

There is currently no cure for Alzheimer’s disease, and the medicines in use can only mitigate the symptoms. In the hunt for a cure, scientists are following several avenues of attack, of which vaccination is currently the most popular. The first human vaccination study, which was done almost a decade ago, revealed too many adverse reactions and was discontinued. The vaccine used in that study activated certain white blood cells (T cells), which started to attack the body’s own brain tissue.

The new treatment, which is presented in Lancet Neurology, involves active immunisation, using a type of vaccine designed to trigger the body’s immune defence against beta-amyloid. In this second clinical trial on humans, the vaccine was modified to affect only the harmful beta-amyloid. The researchers found that 80 per cent of the patients involved in the trials developed their own protective antibodies against beta-amyloid without suffering any side-effects over the three years of the study. The researchers believe that this suggests that the CAD106 vaccine is a tolerable treatment for patients with mild to moderate Alzheimer’s. Larger trials must now be conducted to confirm the CAD106 vaccine’s efficacy.

**Publication:**

**HIV Superinfection Rate Comparable to Initial HIV Infection**
ScienceDaily (June 7, 2012) — Human immunodeficiency virus (HIV) superinfection may be as common as initial HIV infection and is not limited to high risk-populations, according to a new study led by researchers at the Johns Hopkins Bloomberg School of Public Health and the National Institute of Allergy and Infectious Diseases (NIAID). In the first large-scale study of HIV superinfection in a general heterosexual population, researchers examined the rate of superinfection among a community of sub-Saharan adults. HIV superinfection occurs when an HIV-infected individual acquires a new viral strain that is phylogenetically different from all other detectable viral strains. Superinfection can have detrimental clinical effects as well as accelerated disease progression, and increased HIV drug resistance even among individuals who were previously controlling their HIV infection.

The results are featured online in of the Journal of Infectious Diseases.

"We found it remarkable that the rates of superinfection and underlying new HIV infections were equivalent. This raises many interesting questions about the natural immune response and its inability to generate resistance to HIV reinfection," said Thomas Quinn, MD, MS, co-author of the study, an NIAID senior investigator, a professor with the Bloomberg School’s Department of International Health and director of the Johns Hopkins Center for Global Health.

"For years there has been great debate regarding the rate of HIV superinfection among populations, and previous studies have focused on individuals exposed to the virus through high-risk sexual activity or intravenous drug use," said Andrew Redd, PhD, lead author of the study and a postdoctoral fellow at the Laboratory of Immunoregulation at NIAID. "We were looking to determine the rate of HIV superinfection among a broader, general population using a novel technique sensitive enough to detect even the lowest levels of circulating HIV strains."

Researchers, in collaboration with colleagues at the NIAID Rocky Mountain Laboratories, the Johns Hopkins Rakai Health Sciences Program in Kalisizo, Uganda, and Makerere University in Kampala, Uganda, used an ultra-deep sequencing technique to examine the blood samples of HIV-infected participants of the Rakai Community Cohort Study. Samples were tested at initial HIV diagnosis and at least one year later, prior to beginning antiretroviral therapy. The rate of superinfection was then compared to an estimated overall HIV incidence rate for HIV-negative individuals during this same time. Of the 149 individuals tested, Quinn and colleagues identified seven cases of HIV superinfection during follow-up and all were initially infected with some variant of HIV subtype D. In addition, the rate of
superinfection was 1.44 per 100 persons and consisted of both intersubtype and intrasubtype superinfections, comparable to primary HIV incidence in initially HIV-negative individuals in the general population in Rakai.

"These results also have significant implications for estimations of the age of the HIV epidemic and for phylogenetic modeling of viral evolution because many of these models assume that superinfection is not occurring," suggest the authors. "In addition, the finding that superinfection is common and occurs within and between HIV subtypes suggests that the immune response elicited by primary infection confers limited protection and raises concerns that vaccine strategies designed to replicate the natural anti-HIV immune response may have limited effectiveness."

Redd added, "Our findings suggest that HIV vaccine strategies designed to recreate the natural immune response to HIV may be insufficient to protect an individual from infection. However, the data also provide an interesting new population to explore since it is possible that some individuals will be protected from superinfection. Determining what controls this could lead to new avenues for vaccine research."

**Journal Reference**


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**Mystery to the Origin of Long-Lived, Skin-Deep Immune Cells Uncovered**

ScienceDaily (June 7, 2012) — Scientists at A*STAR's Singapore Immunology Network (SIgN) uncovered the origin of a group of skin-deep immune cells that act as the first line of defense against harmful germs and skin infections. SIgN scientists discovered that these sentry cells of the skin, called the Langerhans cells (LCs), originate from two distinct embryonic sites—the early yolk sac and the fetal liver.

LCs are dendritic cells (DCs) found in the outermost layer of the skin. DCs are a critical component of the immune system because they are the only cells able to 'see' and 'alert' other responding immune cells to initiate a protective response against harmful foreign invaders. Like sentries of the immune system, DCs are strategically positioned where they are likely to encounter harmful pathogens. Identifying the source of these specialized immune cells may hold exciting possibilities to novel strategies for vaccination and treatment of autoimmune diseases and inflammatory skin disorders.

In contrast to other DCs which are constantly replaced by a circulating pool of bone marrow-derived precursors, LCs has the interesting ability to maintain themselves throughout life. While it is established that these long-lived sentry cells of the skin arise from precursors that are recruited to the skin prior to birth, this is the first time that the exact origin of the precursors of LCs is revealed through advanced fate-mapping technique (a method of tracing cell lineages to their embryonic origin).

In this study, published in the June issue of *Journal of Experimental Medicine*, Dr Florent Ginhoux, and his team demonstrated that adult LCs originate from two distinct embryonic lineages in two succeeding waves. The first wave of precursor cells from the yolk sac 'seed' the skin before the onset of the fetal liver. Interestingly, the team discovered that at the later stage of development, the yolk-sac precursors are largely replaced by a type of white blood cells from the fetal liver.

Said Dr Ginhoux, Principal Investigator of SIgN, "Whether this unique dual origin of Langerhans cells influences their ability to maintain skin integrity or dictate their specialized immune functions in response to microbes and vaccines needs to be examined. But having identified their origin surely opens new possibilities of using them as novel vaccination strategies or as therapeutic tool for treating inflammatory skin diseases like psoriasis."

Scientific Director of SIgN, Professor Paola Castagnoli said, "This discovery sheds light on understanding the complexities of the immune system, in particular the relationship between immune responses and human diseases. It will bring us closer to our goal of discovering novel ways of treating and preventing a range of immune diseases that will impact healthcare."

**Journal Reference**


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**Health educators should work with the inner contradictions that 'barebackers' express**
When asked by researchers to talk about their practice of having ‘bareback’ sex (unprotected anal intercourse), HIV-negative gay and bisexual men express a contradiction between their concern to remain uninfected and their simultaneous awareness that their behaviour may expose them to infection, according to a study published in the July issue of *Qualitative Health Research*.

The research suggests that, rather than giving factual information about risks, health promoters should create spaces in which men who bareback can talk about their behaviour and its justification, in order to explore inner contradictions and reframe their behaviour.

This isn’t the first study to show that many HIV-negative gay men who bareback remain concerned about the prospect of acquiring HIV and want to avoid infection. However, previous studies have given little attention to how men understand and deal with this tension.

Researchers at Columbia University therefore recruited men who self-identified as a ‘barebacker’ or someone who ‘practices barebacking’ to take part in a two-hour, face-to-face, in-depth interview about their sexual behaviour. Men were recruited from dating web sites associated with bareback sex in New York. Interviews were conducted in 2005 and 2006.

Although HIV-positive men were also interviewed, this analysis covers the 89 HIV-negative men who took part. Their average age was 32, four-fifths were employed and they were broadly representative of the ethnic diversity of New York City.

**Findings**

Timothy Frasca and colleagues say that they “observed contradictions in some men’s narratives between their wishes to avoid HIV infection and their simultaneous acknowledgment of the risks involved in their barebacking practices”. The researchers identified a number of ways in which their respondents dealt with these contradictions during the interviews.

Some men said that, on occasion, intense sexual sensations could overwhelm their calculations about risk:

“Something happens. You know, you get to a point, it’s as if being sexually turned on – you know, they talk about how your judgment is impaired when you’re on drugs. I don’t need drugs. All I need is to be with a hot guy, and a good deal of my judgment gets put on hold.”

Men who said that they were powerless in the face of sexual desire did not try to explain such incidents away as not really being risky. Instead they admitted that they were unable to carry out their prior intentions.

However, the authors note that, like a number of others, this respondent used the present tense to describe this scenario. His language suggests a recurrent or habitual situation, rather than a specific and unusual incident.

Other men described sexual practices – such as withdrawing before ejaculation or not barebacking on a first meeting – which they thought could reduce the risk of infection. But at the same time, they often expressed doubt about the reliability of what they were doing.

“I know that precum has HIV in it too. So you really don’t protect somebody by pulling out. But it’s kind of a pretence toward that.”

“You know, if you do an enema, then that kind of washes everything around, so, um, [a doctor] said that’s not, not always, you know, a sure way to make sure that even if someone does come inside you, to get that out, so, you know [inaudible] risk is still high.”

Given interviewees’ lack of confidence in strategies such as these, the researchers suggest that the beliefs about sexual risk did not determine the limits of the men’s behaviour, but helped to reassure the men about the behaviour they were engaging in anyway.

A number of respondents employ a strategy that the researchers describe as ‘compartmentalisation’ – contradictory thoughts and ideas were separated out and dealt with at different times. Typically, men pushed their thoughts about HIV and risk aside for the duration of a sexual encounter.

“Sometimes I just try to push it out [of my mind] so I can enjoy the sex, because that’s what I’m there for. I’m not there to freak out about my status.”

“If someone doesn’t put [the condom] on, then I actually get a little more excited, that, oh my god, he’s actually going to fuck me without a condom. And at that time, it doesn’t really come in my mind that, oh, I should talk to him first if he’s negative, or ... like, the risks involved, or does he do this often? Like, any of that stuff. I’ll say, like, no, no, no, it will just kill the moment. Let’s just do all that later.”

Some interviewees struggled to resolve the contradictions in their reasoning:
“Now granted, if, you know, a guy comes, and he fucks me, and I don’t have any other previous experience with him, nor do I know whether or not he’s taken loads, then I don’t know. So I know I’m at equally high risk, but I don’t know that I’m at that risk. Does that make sense?”

Others acknowledged the existence of contradictions, while expressing discomfort in doing so:

“You know what? I usually assume everyone is positive. Which makes it seem even more stupid of me to fuck without a condom, but I do it.” Researcher: Does it trouble you? “Eh, I tend not to over-process that sort of part.”

“Life is filled with contradictions... I suppose I’m contradicting myself by saying that I’m super concerned. I am. Granted, I am very concerned. But then, if I’m so concerned, why do I have unprotected sex? I honestly don’t know.”

Finally, some men expressed confidence in their ability to remain uninfected based on their success in doing so until now. Some men felt ‘invincible’ or suggested that they had an approach that had worked for them so far:

“I mean, I always, always tended to go with the gut feeling. With the gut feeling. And in the twenty-five years I’ve been on this earth, it has never led me wrong.”

**Interpretation**

Timothy Frasca and colleagues believe that the theory of cognitive dissonance, developed by the social psychologist Leon Festinger in the 1950s, can be helpful in understanding these men’s accounts.

Festinger argued that conflicting cognitions about beliefs and behaviours (e.g., “I want to remain HIV negative” vs “I am engaging in risk that could result in HIV infection”) produce discomfort and motivate individuals to resolve the tension by bringing the two cognitions into agreement – especially when the contradiction threatens the individual’s understanding of himself as being a decent or rational person.

The tension often leads people to change their beliefs to fit their actual behaviour, rather than to change their behaviour (which may be more difficult). They may deny or distort certain understandings, or incorporate new beliefs to make their overall beliefs more consistent.

The researchers comment: “When questioned about barebacking in the research interview, many men who practice it offered a perception of their own risk that fit the behavior engaged in. That is, the barebacking behavior of men in our sample appears to have influenced their construction of risk-avoidance postures that are consistent with continuing the practice. This is quite different from the assumptions of behavior change models that address perceptions of risk as a precursor to risk modification.”

Other researchers have used cognitive dissonance theory to design interventions to reduce behaviours such as smoking and excessive online gaming. The interventions typically ask participants to describe and advocate behaviours they themselves do not practice, with the intention that this will help them re-examine their own behaviour and beliefs.

For example, in one study adolescent girls with body-image concerns (for example dissatisfaction with their own body, believing themselves to be too fat) were asked to write a letter to a hypothetical younger girl that discussed the costs of pursuing of the ‘thin-ideal’. In another session, they described incidents when they felt a pressure to be thin—and were then asked to think up verbal responses and challenges that could have been used.

The authors suggest that a similar approach with gay and bisexual men who bareback could be more helpful than giving men information about the dangers associated with their behaviour.

Indeed, many interviewees commented that taking part in the study had provided a rare and welcome opportunity to consider and reflect on their sexual behaviours, attitudes, and needs. The authors note that gay and bisexual men currently lack social spaces in which collective discussion of sexual choices can take place.

“As opportunities for the shared processing of decisions about sexual risk and satisfaction decline, individuals relying on their own emotional and intellectual resources naturally will seek plausible explanations for their individual behaviour,” they say.

**Reference**


**HIV-positive saliva not a 'deadly weapon’—NY court**

ALBANY, N.Y., June 7 | Fri Jun 8, 2012 1:54am IST

(Reuters)—An HIV-positive man who admitted to biting a police officer attempting to arrest him had his aggravated assault conviction overturned on Thursday by New York’s top court, which ruled the man’s saliva did not qualify as a deadly weapon.
The Court of Appeals, in throwing out the conviction of David Plunkett, ruled that body parts, saliva or anything that "comes with" a person cannot be considered deadly weapons under state law. In New York, aggravated assault requires the use of a "deadly weapon or dangerous instrument."

In 2006 the staff at a medical clinic in Ilion, about 70 miles east of Syracuse, called police to complain that Plunkett, a patient at the clinic, was causing a disturbance. Police said Plunkett, who had a history of mental illness, punched and bit one of the responding officers, according to court documents.

Herkimer County Court Judge Patrick Kirk in 2007 denied Plunkett's motion to dismiss the aggravated-assault charge, ruling that while Plunkett's teeth could not be considered a deadly weapon, his saliva could.

Plunkett pleaded guilty and was sentenced to 10 years in prison. In 2010, the Appellate Division, Fourth Department, found that by pleading guilty, Plunkett had forfeited his right to appeal.

The Court of Appeals on Thursday disagreed, finding that Plunkett could not have been guilty of aggravated assault because he did not possess a deadly weapon.

"A defendant can admit facts, but cannot by his or her admission mint an offense for which the law does not already provide," Chief Judge Jonathan Lippman wrote in a unanimous decision.

Plunkett argued on appeal that under state law, only substances that are "readily capable of causing death or other serious physical injury" can be considered deadly weapons.

The court on Thursday declined to weigh in on whether HIV can be spread through biting.

A number of studies have found saliva does not contain sufficient concentrations of HIV to transmit the virus to other people. According to the Centers for Disease Control and Prevention, "contact with saliva alone has never been shown to result in transmission of HIV."

Scott Schoettes, the HIV Project director for national gay-rights group Lambda Legal, said Thursday's ruling is the first in the country to state explicitly that no body part or fluid can be considered a deadly weapon.

"It's an important step forward" for HIV-positive people, said Schoettes, who wrote a brief on behalf of Plunkett. A contrary ruling, he added, would "criminalize HIV."

Herkimer County Acting District Attorney Jeffrey Carpenter said that Plunkett had also attempted to defecate, urinate and bleed on the officers and "taunted them with the fact that he had HIV."

"No one was seeking to punish (Plunkett) because he has HIV," Carpenter said, "but because he intentionally tried to infect another human being with that disease."

He said he was concerned that Thursday's decision could endanger police, emergency medical workers and medical professionals, and that he would push for legislation that would make it a crime to intentionally spread a communicable disease.

Plunkett's attorney, Audrey Baron Dunning, denied that her client had tried to infect the officers and said the ruling "is in line with the medical and scientific communities." (Reporting by Dan Wiessner; Editing by Eric Walsh)

Are HIV Non-Progressors Really Very Slow Progressors?
Published on Friday, 24 February 2012 00:00
Written by Liz Highleyman

HIV positive people traditionally classified as long-term non-progressors or viral controllers may in fact progress slowly over time, according to research reported in the February 20, 2012, edition of the open-access journal *PLoS ONE*. These findings suggest that so-called non-progressors may in fact benefit from antiretroviral therapy and could provide clues to aid in development of immune-based therapies.

Since the early years of the epidemic researchers have noted that a small proportion of people with HIV seem to be long-term non-progressors (LTNPs) who maintain stable CD4 T-cell counts and do not experience opportunistic illness despite the absence of antiretroviral therapy (ART). An even smaller subset dubbed HIV controllers or "elite controllers" maintain undetectable viral load without treatment.

To learn more about this unusual group, Sundhiya Mandalia and colleagues analyzed medical records from all patients with HIV-1 seen at Chelsea and Westminster Hospital in London between 1988 and 2010. LTNPs were defined as individuals who were HIV positive for more than 7 years, ART-naive, had no history of opportunistic illness (defined as any symptomatic manifestation of HIV disease), and had a stable normal CD4 cell count.

The researchers compared people who had a history of stable CD4 counts below normal (< 450 cells/mm³), or those whose levels fell below normal at least once, versus those whose levels always
remained within the normal range. Further, within these 2 groups, they identified individuals with HIV RNA consistently below the limit of detection.

**Results**

- Out of 14,227 patients in the hospital database, 5417 were diagnosed as HIV positive more than 7 years ago, and among these, 1204 had never been prescribed ART.
- Within this group, 239 people (20%) had CD4 counts that had consistently remained within the normal range.
- Patients with stable normal and stable below-normal CD4 counts were similar with regard to sex (both > 90% men) and age (median 40 years), but there were significantly fewer Caucasians in the consistently normal group.
- The estimated median time to progression (defined as T-cell decline or clinical progression) for the stable normal CD4 group was 6.2 years, significantly longer than the 4.0 years for patients with stable below-normal counts (P < 0.001).
- Among the 1204 long-term positive, ART-naive patients, 312 (26%) were consistently asymptomatic.
- Within this group, 110 (35%) maintained CD4 counts within the normal range; these patients had an estimated median time to progression of 9.1 years, compared with 7.3 years for those whose CD4 count fell below normal at least once.
- 258 (83%) of the 312 ART-naive asymptomatic patients had unstable or declining CD4 counts, of whom 95 (37%) had counts consistently within the normal range; the estimated median time to progression for this group was 5.8 years—similar to the 4.6 years for the 163 patients (63%) with a history of below-normal CD4 counts.
- 50 ART-naive patients were found to have long-term stable CD4 cell counts.
- Within this group, 13 were classified as LTNPs with CD4 counts consistently in the normal range, while the remaining 37 had at least 1 below-normal measurement.
- 1 of the 13 LTNPs (8%), and 3 of the 37 with at least 1 low CD4 count, met the viral load criteria to be classified as HIV controllers.

Based on these findings, the investigators determined that few HIV positive people in this and other studies are LTNPs or HIV controllers. Out of all current HIV patients seen at their hospital, 13 (0.2%) met the LTNP criteria, including 3 controllers (0.05%).

"This study suggests that by using varying selection criteria, disease progression is very likely in the majority of people living with HIV-1," they wrote. "The patients who had not progressed within the study period are likely to do so, as demonstrated in the analysis of individuals found to have long-term stable low CD4 T-cell counts compared to those with unstable CD4 T-cell counts."

They raised the possibility that "many more" people living with HIV may actually be LTNPs or HIV controllers, "but due to the absence of clinical manifestations of disease these individuals have not yet attended an HIV-1 testing facility and consequently have not been diagnosed as HIV-1 positive."

Researchers should develop universal definitions of these patient groups, they recommended, to facilitate comparison across populations.

"Studying patients at the extreme of this distribution may enable discovery of correlates of HIV-1 positive disease progression, leading to identification of targets to be manipulated by novel therapeutic approaches, with the ultimate goal of inducing delayed disease progression, retarding ART initiation and alleviating pill burden and toxicity," the authors elaborated in their discussion.

"Large cohorts of well-defined HIV-1 positive patients will be essential for future investigation of genetic associations with HIV-1 control and delayed disease progression," they continued, "as the unique immunological and virological responses demonstrated by LTNP and [HIV controllers] may provide clues towards both the change in disease status of these patients over time, and provide insights for HIV-1 preventative or therapeutic vaccine development."

2/24/12

**Reference**


**HIV Gene Therapy Shows Long-term Safety and Activity after 11 Years**

Published on Wednesday, 02 May 2012 00:00
Written by Press Release
T cells shown with magnetic beads during laboratory process (Image courtesy Penn Medicine)

Genetically modified T-cells engineered to attack HIV were still present and showed continued antiviral activity, with no serious adverse outcomes, 11 years after administration, according to log-term follow-up data from 3 studies described in the latest issue of *Science Translational Medicine*.

Gene therapy is among the many experimental approaches being explored as a functional cure for HIV. One strategy involves modifying patients' T-cells with a zinc finger nuclease to delete CCR5 coreceptors on the cell surface, which makes them resistant to HIV entry. A similar approach is being tested using hematopoietic stem cells, which give rise to all blood cells.

In 1998 Carl June at the University of Pennsylvania—one of the lead researchers on the zinc finger studies—and colleagues began testing a different type of gene therapy, using a retroviral vector to insert into T-cells an antigen receptor that recognizes HIV envelope proteins. These 3 trials have now accumulated more than 500 person-years of data. Although the patients have remained on antiretroviral therapy, their modified T-cells continue to show activity against HIV. The gene therapy also appears safe over the long term. All study participants are healthy overall and none have developed leukemia, a potential concern when using such vectors to alter cells.

Below is an edited excerpt from a press release issued by the University of Pennsylvania describing the new findings.

**Genetically Modified T Cell Therapy Shown to be Safe, Lasting in Decade-Long Study of HIV Patients**

*Results open up field of T cell gene therapy for use in other diseases*

Philadelphia May 2, 2012—HIV patients treated with genetically modified T cells remain healthy up to 11 years after initial therapy, researchers from the Perelman School of Medicine at the University of Pennsylvania report in the new issue of *Science Translational Medicine*. The results provide a framework for the use of this type of gene therapy as a powerful weapon in the treatment of HIV, cancer, and a wide variety of other diseases.

"We have 43 patients and they are all healthy," says senior author Carl June, MD, a professor of Pathology and Laboratory Medicine at Penn Medicine. "And out of those, 41 patients show long term persistence of the modified T cells in their bodies."

Early gene therapy studies raised concern that gene transfer to cells via retroviruses might lead to leukemia in a substantial proportion of patients, due to mutations that may arise in genes when new DNA is inserted. The new long-term data, however, allay that concern in T cells, further buoying the hope generated by work June's team published in 2011 showing the eradication of tumors in patients with chronic lymphocytic leukemia using a similar strategy.

"If you have a safe way to modify cells in patients with HIV, you can potentially develop curative approaches," June says. "Patients now have to take medicine for their whole lives to keep their virus under control, but there are a number of gene therapy approaches that might be curative." A lifetime of anti-HIV drug therapy, by contrast, is expensive and can be accompanied by significant side effects.

They also note that the approach the Penn Medicine team studied may allow patients with cancers and other diseases to avoid the complications and mortality risks associated with more conventional treatments, since patients treated with the modified T cells did not require drugs to weaken their own immune systems in order for the modified cells to proliferate in their bodies after infusion, as is customary for cancer patients who receive stem cell transplants.

To demonstrate the long-term safety of genetically modified T cells, June and colleagues have followed HIV positive patients who enrolled in three trials between 1998 and 2002. Each patient received one or more infusions of their own T cells that had been genetically modified in the laboratory using a retroviral vector. The vector encoded a chimeric antigen receptor that recognizes the HIV envelope protein and directs the modified T cell to kill any HIV-infected cells it encounters.

As is standard for any trial, the researchers carefully monitored patients for any serious adverse events immediately after infusion—none of which were seen. Additionally, because of the earlier concerns about long-term side effects, the U.S. Food and Drug Administration also asked the team to follow the patients for up to 15 years to ensure that the modified T cells were not causing blood cancers or other late
effects. Therefore, each patient underwent an exam and provided blood samples during each of the subsequent years.

Now, with more than 500 years of combined patient safety data, June and colleagues are confident that the retroviral vector system is safe for modifying T cells. By contrast, June notes, the earlier, worrying side effects were seen when viral vectors were used to modify blood stem cells. The new results show that the target cell for gene modification plays an important role in long-term safety for patients treated. "T cells appear to be a safe haven for gene modification," June says.

The multi-year blood samples also show that the gene-modified T cell population persists in the patients' blood for more than a decade. In fact, models suggest that more than half of the T cells or their progeny are still alive 16 years after infusion, which means one treatment might be able to kill off HIV-infected cells for decades. The prolonged safety data means that it might be possible to test T cell-based gene therapy for the treatment of non-life threatening diseases, like arthritis.

"Until now, we've focused on cancer and HIV-infection, but these data provide a rationale for starting to focus on other disease types," June says. "What we have demonstrated in this study and recent studies is that gene transfer to T cells can endow these cells with enhanced and novel functions. We view this as a personalized medicine platform to target disease using a patient's own cells."

The project was supported by a grant from the National Institutes of Health (1U19AI082628), the University of Pennsylvania Center for AIDS Research, and the Infectious Diseases Clinical Research Program, a Department of Defense program funded in part with federal funds from the National Institute of Allergy and Infectious Diseases under InterAgency Agreement Y1-AI-5072.

Reference

Pregnancy: Why Mother's Immune System Does Not Reject Developing Fetus as Foreign Tissue
ScienceDaily (June 7, 2012) — Researchers at NYU School of Medicine have made an important discovery that partially answers the long-standing question of why a mother's immune system does not reject a developing fetus as foreign tissue.

"Our manuscript addresses a fundamental question in the fields of transplantation immunology and reproductive biology, namely, how do the fetus and placenta, which express antigens that are disparate from the mother, avoid being rejected by the maternal immune system during pregnancy?" explained lead investigator Adrian Erlebacher, MD, PhD, associate professor of pathology and a member of the NYU Cancer Institute at NYU Langone Medical Center. "What we found was completely unexpected at every level."

The researchers discovered that embryo implantation sets off a process that ultimately turns off a key pathway required for the immune system to attack foreign bodies. As a result, immune cells are never recruited to the site of implantation and therefore cannot harm the developing fetus.

The study, funded by grants from the National Institutes of Health and the American Cancer Society, appears in the June 8 issue of Science.

A central feature of the body's natural immune defense against transplanted foreign tissues and pathogens is the production of chemokines as a result of the local inflammatory response. The chemokines recruit various kinds of immune cells, including activated T cells, which accumulate and attack the tissue or pathogen. The chemokine-mediated recruitment of activated T cells to sites of inflammation is an integral part of the immune response.

During pregnancy however, the foreign antigens of the developing fetus and the placenta come into direct contact with cells of the maternal immune system, but fail to evoke the typical tissue rejection response seen with organ transplants.

Several years ago, Erlebacher and his research team found that T cells, poised to attack the fetus as a foreign body, were somehow unable to perform their intended role. The finding prompted the researchers to wonder if perhaps there was some sort of barrier preventing the T cells from reaching the fetus. They turned their attention to studying the properties of the decidua, the specialized structure that encases the fetus and placenta, and there, in a mouse model, they found new answers.

The research team has discovered that the onset of pregnancy causes the genes that are responsible for recruiting immune cells to sites of inflammation to be turned off within the decidua. As a result of these changes, T cells are not able to accumulate inside the decidua and therefore do not attack the fetus and placenta.
Specifically, they revealed that the implantation of an embryo changes the packaging of certain chemokine genes in the nuclei of the developing decidua's stromal cells. The change in the DNA packaging permanently deactivates, or "silences," the chemokine genes. Consequently, the chemokines are not expressed and T cells are not recruited to the site of embryo implantation.

Also of note, the observed change in the DNA packaging was a so-called 'epigenetic' modification, meaning a modification that changes gene expression without the presence of a hereditable gene mutation.

"These findings give insight into mechanisms of fetal-maternal immune tolerance, as well as reveal the epigenetic modification of chemokine genes within tissue stromal cells as a modality for limiting the trafficking of activated T cells," Dr. Erlebacher said. "It turns out that the cells that typically secrete the chemotaxtractants to bring the T cells to sites of inflammation are inhibited from doing so in the context of the pregnant uterus. The decidua appears instead as a zone of relative immunological inactivity."

Inappropriate regulation of this process, Dr. Erlebacher explained, could cause inflammation and the accumulation of immune cells at the maternal-fetal interface, which could lead to complications of human pregnancy, including preterm labor, spontaneous abortion and preeclampsia.

Erlebacher and his team will next look to see if these epigenetic modifications are also present within the human decidua, and whether the failure to generate them appropriately is associated with complications of human pregnancy. He explained that the study's findings also raise the possibility that the same kind of mechanism could enhance a tumor's ability to survive inside its host. The findings could have implications for autoimmune diseases, organ transplantation and cancer, as well as pregnancy.

"This is a very exciting finding for us because it gives a satisfying explanation for why the fetus isn't rejected during pregnancy, which is a fundamental question for the medical community with clear implications for human pregnancy," Dr. Erlebacher said. "It also reveals a new modality for controlling T cell trafficking in peripheral tissues that could provide insight into a myriad of other conditions and diseases."

**Journal Reference:**

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**The So Called HIV Cured "Berlin" Patient Still Has Detectable HIV in His Body**

At the "International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies" held in Sitges, Spain, June 5-8, data have been presented showing that the Berlin patient still has low levels of HIV although he remains seronegative against HIV.

The last day of the "International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies" was dedicated to HIV cure.

Sharon Lewin from Melbourne, Australia, gave a plenary lecture about the different possible strategies than can be tested to reach an HIV cure. There are actually two kinds of cure, either functional (HIV remains but is undetectable without antiretroviral therapy), or sterilizing (HIV no longer detectable and the patient becomes seronegative against HIV).

The only current case of a cure is the "Berlin patient" who received 2 bone marrow transplants for acute leukemia in 2006. The bone marrow donor was chosen to be deleted on the CCR5 gene, making his cells resistant to HIV infection.

Eighteen months after the transplants, he was reported as seronegative without any trace of HIV detectable in his body (N Engl J Med. 2009 Feb 12;360(7):692-8.). These data were confirmed in December 2011 and the word of cure used for the first time (Blood. 2011 Mar 10;117(10):2791-9. Epub 2010 Dec 8.).

New data presented at the Sitges workshop by Dr S. Yukl group from San Francisco challenged these results as they showed persistence of low levels of HIV viremia in this patient, and HIV DNA in his rectal cells.

These HIV strains were found to be different from those initially present in this patient back in 2006, and different from each other.

Although HIV could have evolved and persist over the last 5 years, these data also raise the possibility that the patient has been reinfected.

More studies are in progress to know if this seronegative HIV individual can infect other subjects if he has unsafe sex.
African HIV Activists Want a New Model for Prevention

Christian Science Monitor, (06.08.2012) Fredrick Nzwili

The “ABC” message (Abstinence, Be faithful, and Condomize) that has been used worldwide to prevent the spread of HIV is being criticized in parts of Africa as ineffective.

African faith leaders have designed a new strategy called “SAVE” (Safer practices, Access to Treatment, Voluntary Counseling and testing, and Empowerment) to replace ABC. Fifteen African countries have adopted SAVE, and Malawi is expected to adopt it soon.

A 2011 UNAIDS report said the highest HIV infection rates remain in sub-Saharan Africa, even as infections have dropped by 20 percent. This decline has been linked to changes in behavior and increased knowledge of HIV, both attributable to ABC.

For many groups in Africa, including faith groups, ABC is seen as not effective enough because it fails to curb the stigma of AIDS, which pushes the epidemic underground and hinders universal access to HIV diagnosis and treatment.

In addition, AIDS activists say scientific advances as well as cultural changes in Africa make it necessary to redesign AIDS messages. Mother-to-child HIV transmission still exists, and levels of infection among people in relationships has increased.

ABC's problem is that it takes a moral and sexual approach only which does not work in African cultures, according to Canon Gideon Byagumisha, a Ugandan cleric. He believes a comprehensive strategy is needed that addresses HIV in its entirety.

ABC also does not teach people other strategies to help prevent the spread of HIV. “Abstinence, for example, [also] needs condom use, safe blood, safe circumcision, microbicide, vaccines and so forth,” said Byagumisha. “ABC is somehow inaccurate because it seems to portray that once you are faithful you don’t get HIV,” he said. “Yet we know there are very faithful people, there are people who are virgins at marriage, who end up being positive. This means that faithfulness is not safeness.”

Health Class May Be Waived

Los Angeles Times, (06.09.2012) Howard Blume

High schools in the Los Angeles Unified School District may not have to offer a one-semester health course that used to be required for graduation. At least for next year, “the district will continue to allow schools that are electing to choose an alternate option for meeting the health requirement to continue,” Supt. John Deasy said in a June 6 memo to LAUSD’s Board of Education. The document lists potential exceptions to such a requirement that eventually could apply to all high schools.

Some districts have dropped health classes, which are not needed for admission to California’s college system, to save money. However, LAUSD officials recently agreed to continue offering health courses, after an earlier proposal to do away with the requirement led parents, teachers, and students opposed to the move to descend on board meetings.

California law requires high schools to teach students about AIDS and STDs, but these units can be offered in health classes or incorporated into other courses.

Four LAUSD high schools managed by a nonprofit entity under Mayor Antonio Villaraigosa’s control do not require a health class to graduate. Seven other large high schools plan to drop the course next year, said Bennett Kayser, a member of the LAUSD board who said he is prepared to ask for the board’s involvement in the matter.

“I was shocked by this,” said Kayser. “We asked to make sure there was a comprehensive health class taught in high school and we get a memo saying how you can get waivers to avoid it.”

Another member, Steve Zimmer, said that while flexibility and local control are important, “youth health is a tipping-point issue that affects whether students are successful in school.”

Deasy and other district officials had no comment on the memo.

African Cholera Vaccine Trial

For the first time, an oral cholera vaccine is used to control an active epidemic of the bacterial disease.

By Cristina Luiggi | June 12, 2012

Although oral cholera vaccines have been available since the 1980s, it wasn’t until very recently that the World Health Organization (WHO) considered using them as a means to control large, active cholera outbreaks. Following a much-debated and delayed vaccination trial in Haiti—which began last April, some 6 months after the cholera outbreak started—the government of Guinea has partnered with the
global charity Médecins Sans Frontières (MSF), also known as Doctors Without Borders, to vaccinate more than 100,000 people—making it the first time an oral cholera vaccine is used in Africa to control an active epidemic.

“Until very recently, no one was using this as an extra tool to control cholera,” Iza Ciglenecki, the project manager for diarrheal diseases at MSF who led the effort in Guinea, told Nature. “We hope to add to the evidence base regarding this vaccine to help develop an intervention criteria for the control of cholera in outbreaks.”

WHO first recommended the use of the vaccine during active epidemics in March 2010—months before the cholera epidemic took hold in Haiti. However, the organization initially opposed implementing the control measure in Haiti, for several logistical reasons, including the very limited availability of vaccines, the difficulty of reaching affected and vulnerable people in time, and the worry that resources would be better spent on cleaning up contaminated water supplies and improving sanitation.

Over the next 6 months, officials at WHO will be monitoring the efficacy of the vaccination campaign in Guinea and will be collecting data that will inform how best to deliver the oral medicine during the chaos of an ongoing cholera epidemic.

DNA Methylation Declines with Age
Newborns carry more epigenetic markers than nonagenarians, providing clues to the mechanisms underlying aging.
By Sabrina Richards | June 11, 2012

Aging is associated with loss of an epigenetic marker that helps control gene expression, according to new research published today (June 11) in Proceedings of the National Academy of Sciences, with a centenarian carrying some 7 percent fewer methylated DNA bases than a newborn. Researchers posit that reductions in methylation may be one of the mechanisms underlying the aging process.

“It’s one of the first studies to look at aging from an epigenetic point of view,” said Willis Li, at the University of California, San Diego, who did not participate in the research. Other research, including Li’s own in Drosophila, has shown that the amount of heterochromatin—histone modifications that result in tight chromosome packing—also appears to decline with an organism’s age. The new study further supports the idea that epigenetic modifications, in addition to genetic factors, play a critical role in aging, said Li.

Searching for clues to why some people live long healthy lives and some succumb to early to aging, scientists have discovered that genetic factors only contribute about 10 percent to longevity, while environmental factors contribute about 90 percent, said senior author Manel Esteller of the University of Barcelona. Knowing that epigenetic modifications, such as cytosine methylation, are responsive to environmental stimuli, Esteller and his collaborators wondered if they could be a reliable indicator of physiological aging.

The scientists first compared the DNA methylation epigenome—the genome-wide level and location of methylated cytosines located next to guanines (CpG)—in circulating T cells from a newborn and a centenarian. The general level of methylation of the centenarian’s genome (73 percent), they found, was lower than the newborn’s (80 percent). Looking at a 26-year-old’s genome, they found an intermediate level of methylation.

Examining more closely the patterns of methylation in the newborn’s and centenarian’s genomes gave hints that Esteller thinks may help explain how loss of methylation affects cellular function and leads to aging. While most areas of the centenarian’s genome were less methylated—such as genes with tissue-specific expression patterns, suggesting the possibility that the centenarian’s T cells were expressing genes they shouldn’t, like neuron- or testes-restricted genes—a few regions showed greater methylation. Many promoters of tumor-suppressor genes, for example, showed higher levels of methylation, suggesting a possible connection with age-associated increases in cancer risk, Esteller said.

When Esteller and his colleagues extended the study to 19 more newborns and 19 people in their 90s, they found similar differences in their genomes’ methylation patterns. Furthermore, explained Esteller, they were able to use the epigenetic patterns to predict the age—newborn or nonagenarian—of their samples.

As tantalizing as these differences are, it’s still not clear how the epigenetic changes factor into the aging process, said Karl Kelsey, a molecular biologist who studies epigenetic biomarkers for cancer at Brown University, who was not involved in the study. “We don’t yet fully understand the phenotypic consequences of epigenetics,” he said, and “it’s unclear what’s underlying the loss [of methylation].”
It could be that DNA methyltransferases become less active as age progresses, for example, adding fewer methyl groups after each cell division. Alternatively, changes in metabolism and diet could change the intake of folate, the nutrient from which the methyl groups are derived. Understanding the mechanism of these epigenetic changes, as well as their consequences, will be an important next step for understanding how the new findings relate to aging, Kelsey said.

In the meantime, Esteller hopes to discover whether manipulating the epigenome of mice will extend their lifespans. If maintaining methylation really can stave off aging, it may offer therapies for preventing neurodegenerative disorders, he said, and possible aid children suffering from premature aging disorders, who show epigenetic changes similar to the nonagenarians’.

Much remains to be explained, said Li, but “more and more people are aware of the epigenetic impact factor on aging.”


The Fungus Among Us
Researchers find a slew of new fungal species inhabiting the human gut, and suggest a link to an inflammatory bowel disease.
By Bob Grant | June 11, 2012
The microbiome—that teeming mass of essential and coevolved bacteria and viruses that makes humans more microbe than man—just got a little more diverse. A team of researchers led by scientists at Cedars-Sinai Medical Center, Los Angeles, California, has revealed a veritable garden of fungal species, dozens of which have never been described before, growing inside the human body. And they link the fungi to the inflammatory bowel disease colitis in a paper published in Science last week.

Cedars-Sinai’s David Underhill, the immunologist who led the team, said that studying the function of the fungal species that inhabit the human gut is an emerging field. “There’s not a whole lot out there at this point,” he told Wired Science. “People have understood that fungi are there, but that’s been a relatively vague notion.”

Underhill and his colleagues performed experiments with a mouse model that carried immune deficiencies that specifically made the animals unable to clear fungal cells from their systems. The mice developed colitis-like symptoms but recovered when the researchers gave them an antifungal drug. They then made the link to humans by discovering that many of the patients with severe colitis at Cedars-Sinai had similar gene-mediated immune deficiencies along with a suite of internal fungal species.

Many questions about the role of the internal fungal community remain to be answered, according to Underhill. “People study [the microbiome’s effect on human health] in the context of the gut bacteria, in the context of viruses in our microflora,” he told Wired. “You can map all those questions to fungi.”

Naturally Resistant HIV Foils Therapy
New computational modeling suggests pre-existing HIV drug resistance mutations may contribute more to drug failure than previously thought.
By Sabrina Richards | June 8, 2012
HIV’s rapid mutation rates can lead to the evolution of drug resistance in HIV-positive patients receiving antiretroviral therapy, but naturally occurring resistance mutations can also accumulate to establish highly resistant HIV strains, according to new models published today (June 7) in PLoS Computational Biology. If true, the models suggest new interpretation for why HIV drug therapy can fail right off the bat.

“The paper is interesting, and may be important for getting scientists to think about evolution of drug resistance,” said Andrew Read, an evolutionary biologist at Pennsylvania State University who did not participate in the study. “The mechanism of drug resistance seems straightforward, but it’s not.” Even relatively simple questions, like whether drug resistance can be avoided by cycling between two different drugs, randomly assigning the drugs, or giving all patients both, have yet to be answered, added Read, who studies the evolution of malaria drug resistance.

Scientists have been debating the relative contributions of pre-existing mutations and mutations that arise after therapy begins to HIV drug resistance since the mid-1990s, explained Robert Shafer, who studies mechanisms of evolved HIV drug resistance at Stanford University but was not involved in the project. It’s generally understood that a multi-drug regimen works to prevent resistance from becoming established by forcing the HIV virus to acquire several mutations—raising the “genetic barrier” to resistance—and making it highly unlikely that viruses carry enough mutations before therapy, said Shafer.
This makes pre-existing mutations of relatively little concern in well-resourced countries, he noted, but of more concern in resource-limited nations, where drugs may be less efficacious.

But several, though not all, studies show that HIV drug resistance is more likely to be established early, within the first year of treatment, rather than several years in, suggesting to Pleuni Pennings of Harvard University that pre-existing mutations may be a contributing factor. It’s important to understand where HIV drug resistance originates, Pennings said, to help clinicians design therapy accordingly.

So Pennings created several models using data from published clinical trials of HIV therapy to estimate probabilities of drug resistance mutations being pre-existing or evolving later. She made a simple assumption—that one drug resistance mutation was enough for combined drug therapy to fail—and drew on studies of drug cocktails that included non-nucleoside reverse transcriptase inhibitors (NNRTI), which viruses can often resist with just one mutation, plus two other drugs of different classes. Pennings looked at three situations: when HIV-positive patients initiate therapy for the first time; when pregnant HIV-positive mothers are administered a single dose of the NNRTI nevirapine (which helps prevent mother-to-child HIV transmission but is associated with development of maternal drug resistance); and when patients intermittently interrupt their treatment regimens.

Pennings’s model showed that pre-existing mutations could explain drug resistance and treatment failure in all three cases. Moreover, the probability that patients initiating treatment for the first time would become resistant to drugs due to pre-existing mutations was equal to that faced by patients who had interrupted treatment long enough that their viral loads had rebounded to pre-treatment levels.

Not everyone agrees that one mutation can establish drug resistance. “I feel it is too simplistic and not entirely plausible” that one mutation would be enough for multi-drug therapy to fail, said Roger Kouyos, who studies HIV dynamics at the Swiss Federal Institute of Technology (ETH) Zürich in Switzerland. It’s unlikely that resistance mutations against all three drugs in a regimen would exist before treatment. If one did pre-exist therapy, Kouyos contended, drug cocktails keep viral replication so low that it’s difficult for the virus to acquire the other mutations it needs to escape control—unless the patient adheres imperfectly to their regimen, providing a “drug holiday” where the virus can acquire additional mutations. Pennings, in turn, points to studies showing that resistance to one drug of a three-drug cocktail can lead to therapy failure.

But this simplicity may be good, argued Sergei Kosakovsky Pond, who studies HIV evolution at the University of California, San Diego, but did not collaborate on the study. If models get too complicated, he explained, “you can make them do almost anything” by plugging in the right numbers. At the least, said Kosakovsky Pond, Pennings’s study makes an argument for looking closer at pre-existing mutations, whose contributions to drug resistance may not be fully appreciated by scientists in the field. What the model does not do, he notes, is show the pre-existing mutations contribute to drug failure when several mutations are necessary to establish resistance.

Pennings hopes her models will prompt clinicians to re-evaluate their approach to HIV therapy. Strategies to prevent drug resistance typically focus on improving patient adherence to drug regimens—which requires a life-long commitment. But it might be possible instead to nip early drug therapy failure in the bud by employing a quick hit of drugs, like boosted protease inhibitors, that don’t come in an easy-adherence single pill but are harder for the virus to acquire resistance mutations against, followed by a conventional single-pill cocktail. Patients might then be able to minimize their risk of pre-existing mutations from capsizing their therapy by adhering to a cumbersome, expensive pill regimen for only a short time.

In the future, Pennings would like to extend her models to data from “real world” therapy interruptions from the clinically controlled interruptions used in the current project. It may also be possible, she said, to apply her simple equations to drug resistance in other diseases, like cancer.

Kosakovsky Pond hopes these results will prompt scientists and clinicians to survey patients’ HIV pools for these variants and design therapies accordingly when identifying low-frequency drug resistance mutations becomes more financially feasible.

Whatever HIV researchers think of Pennings’s models and assumptions, Read hopes the paper’s counterintuitive assertions “prompt them to action” and stimulate more evolutionary research into the mechanisms of HIV drug resistance.


EllenHunt, Microbiologist. Gadfly. Royal pain. My new id that will, hopefully, survive for a while. Collapse. It is pretty obvious that sooner or later HIV will generally escape current medications given the level of transmission. With researchers finding that it takes 200 contacts to transmit HIV in the MSM
community, the level of activity is obviously high and many partners are common in the core group that forms the bulk of HIV cases. If it takes 1,000 contacts to transmit HIV between medicated parties (many of whom will be on drug holidays) that just slows things down, it certainly doesn’t stop the evolution of resistance. And of course, I.V. drug use is on the upswing. Plus the majority of those infected don’t know it.

We know that there is a cycle of transmission that includes sex-holidays in Haiti, various African nations, etc. New methods will be necessary.

**Study shows that use of darunavir/ritonavir and etravirine in HIV treatment as a prevention method is biologically plausible**

Michael Carter  
Published: 13 June 2012  
A pharmacokinetic study suggests that ritonavir-boosted darunavir (*Prezista*) and etravirine (*Intelence*) achieve high concentrations in semen and rectal tissue, and could therefore help avert HIV transmission and infection, especially in gay men. Concentrations of these antiretrovirals were monitored over an eight-day period in HIV-negative volunteers. The study is published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*.

The US investigators believe their findings “provide pharmacologic plausibility for the use of darunavir plus ritonavir and etravirine in secondary HIV prevention, in both infected and uninfected individuals”.

Antiretroviral therapy has a central role in combination HIV prevention efforts. *Treatment that suppresses viral load has been shown to reduce the risk of transmission in heterosexual couples by 96%.* Anti-HIV drugs can also reduce the risk of infection with HIV when used a pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Incidence of HIV remains high in gay men and they are therefore a priority for the use of HIV treatment as prevention.

It is currently unknown if specific combinations of antiretroviral drugs are more effective at preventing infection with HIV or onward transmission of the virus. “Defining the antiretroviral exposures in biological compartments that are vulnerable to acquisition and are sources of infection, such as rectal tissue and semen, could assist in selecting regimens for HIV prevention,” explain the authors.

They therefore designed a pharmacokinetic study lasting eight days involving twelve healthy HIV-negative men. Concentrations of darunavir/ritonavir and etravirine in blood, semen and rectal tissue were monitored intensively on day one and again on days seven/eight.

The participants had a median age of 27 years and were racially diverse. All tolerated the medications well.

After the first dose, all three drugs were detected in blood, semen and rectal tissue.

Levels of darunavir were between 82 and 92% lower in semen than blood one hour after the first dose. After multiple doses, exposure in semen was 80 to 85% lower than in blood. However, concentrations of the drug in semen accumulated 2 to 2.8-fold after multiple dosing.

Ritonavir was not detected in semen until two hours after the first dose. Peak exposure was reached eight hours post-dose. After the first dose, ritonavir exposures in semen were between 89 and 95% lower than in blood, and after multiple doses exposure was 93% lower. Exposure to the drug in semen accumulated over the study, increasing by 1.4 to 2.3-fold.

Two hours after the first dose, etravirine was detectable in semen. Exposure to the drug was between 83 and 87% in semen after this first dose compared to blood, and exposure was 85 to 88% lower after multiple dosing. Once again, the drug accumulated in semen after multiple dosing (3.6 to 5-2 fold).

The investigators found that unbound levels (the element of the drug that has pharmacologic effect) of all three drugs were higher in semen compared to blood. This is highly significant for the preventive use of the drugs. The authors explain: “As blood plasma protein binding decreases, there is a greater amount of protein-unbound drug available to cross cellular membranes and distribute to physiological compartments…we measured protein-unbound concentrations in seminal plasma and confirmed that lower protein binding exists for all three antiretrovirals in this compartment.”

All three drugs were therefore capable of suppressing viral load in semen. The investigators comment: “The unbound concentrations in semen are higher than in blood and could be effective at suppressing HIV replication in the male genital tract.”

There was also evidence that the study medications could prevent exposure to HIV during anal sex.
One hour after the first dose, concentrations of all three drugs were significantly higher in rectal tissue compared to blood (darunavir, 1.1 to 1.2-fold higher; ritonavir, 5.8 to 12-fold higher; etravirine, 15 to 16-fold higher).

Levels of the three antiretrovirals remained higher in rectal tissue compared to blood after multiple doses (darunavir, 2.3 to 2.7-fold higher; ritonavir, 13 to 27-fold higher; etravirine, 7.5 to 9.7-fold higher). Exposure to these drugs also accumulated with multiple dosing.

“The quick penetration and sustained concentrations of darunavir and etravirine in rectal mucosa are desirable characteristics for the prevention of HIV acquisition,” write the researchers. “Future investigations will determine if these concentrations in rectal tissue and semen can fully suppress viral shedding.”

Reference

Latest Effort to End Ban on Gays Donating Blood
The Advocate, (06.11.2012) Neal Broverman
In a letter sent June 11, Sen. John Kerry of Massachusetts and Rep. Mike Quigley of Illinois urged US Department of Health and Human Services Secretary Kathleen Sebelius to rescind the policy that prohibits men who have had sex with men (MSM) since 1977 from donating blood. They are supporting a proposed pilot study to assess the deferral policy, which has been under attack for many years. Senators from Colorado, New Jersey, Michigan, Washington, New Hampshire, New York, Hawaii, Vermont, and Alaska also signed the appeal to HHS.

The letter gives many reasons in support of a policy change, including advances in blood screening technology, policy changes in other nations, and opposition from the nation’s blood banks which, the letter states, have called the current ban “medically and scientifically unwarranted.”

In addition, heterosexuals with certain risk factors for infectious diseases are allowed to donate after a relatively short deferral period, which the writers find “inconsistent and indefensible.”

One recommendation was to find a way to distinguish between high-risk and low-risk MSM. For example, the questionnaire might ask about whether the prospective donor is in a monogamous relationship or takes effective preventive measures.

The letter cites a June 2010 meeting of the HHS Advisory Committee on Blood Safety and Availability, which reviewed the lifetime deferral policy. The committee concluded “that the current ban on gay and bisexual men is ‘suboptimal’ because it allows high-risk individuals to donate while prohibiting low-risk donors from contributing, and it should be changed as a result,” the members of Congress wrote.

Finally, the letter urges vigilance to avoid any real or perceived discrimination. It stated that “a blanket deferral of MSM for any length of time both perpetuates the unwarranted discrimination against the bisexual and gay community and prevents healthy men from donating blood without a definitive finding of added benefit to the safety of the blood supply.”

Census of microbes in healthy humans reported ****
Trillions of microbes inhabit the human body, occupying virtually every nook and cranny. And most of the time, this relationship is a friendly one, with microbes helping to digest food, strengthen the immune system and ward off dangerous pathogens.

But despite their prominent roles, researchers have understood little about which microbes reside in specific sites of the body. Now, a consortium of some 200 U.S. scientists at Washington University School of Medicine in St. Louis and elsewhere report findings from the most comprehensive census of the microbial make-up of healthy humans.

The research, published June 14 in *Nature* and in several Public Library of Science (PLoS) journals, offers new details and even some surprises.

For example, the researchers found that even healthy people typically carry low levels of harmful bacteria in and on their bodies. But when a person is healthy, these pathogens don’t cause disease; they simply coexist in an abundance of beneficial microbes. Now, scientists can investigate why some pathogens can suddenly turn deadly, an endeavor that will refine current thinking on how microorganisms cause disease.

“It’s not possible to understand human health and disease without exploring the massive community of microorganisms we carry around with us,” says George Weinstock, PhD, associate director of The Genome Institute at Washington University and one of the project’s principal investigators. “Knowing which microbes live in various ecological niches in healthy people allows us to better investigate what goes awry in diseases that are thought to have a microbial link, like Crohn’s and obesity, and why dangerous pathogens sometimes, but not always, cause life-threatening illnesses.”

Washington University and its Genome Institute played a major role in the new research, known as the Human Microbiome Project. The five-year initiative was funded with $153 million from the National Institutes of Health (NIH), with some $32 million coming to the university. Genome Institute scientists decoded about half of the 5,000 specimens from nearly 250 healthy volunteers.

Washington University also was one of two geographically distinct sites that enrolled study participants. The other center was Baylor College of Medicine in Houston.

“Data generated from this study has the added potential to provide scientists with new insights into how local environments shape the composition of microbes that are found in healthy individuals,” says co-investigator Mark Watson, MD, PhD, associate professor of pathology and immunology.

Many scientists regard humans as supra-organisms, a synergistic community of both human and microbial cells that is more than the sum of its parts. Microbial cells in the human body are key players; they outnumber human cells by at least 10 to one.

To get a handle on the healthy human microbiome, the researchers sampled 15 body sites in men and 18 in women, including areas of the mouth (nine sites, including the teeth), skin (two behind the ear and each inner elbow), nose, vagina (three sites) and lower intestine (stool). In St. Louis, most samples were collected at the School of Medicine. Teeth and gum samples were collected at Saint Louis University’s dental school.

In all, the scientists identified more than 10,000 species of microbes that occupy the human ecosystem, documenting the impressive diversity of microbial life in the human body with more accuracy than earlier estimates.

“Our bodies are part of a microbial world,” says Weinstock, who also is a professor of genetics and microbiology. “You can think of our ecosystems like you do rain forests and oceans, very different environments with communities of organisms that possess incredible, rich diversity.”

Using new genomic techniques, Genome Institute scientists including Erica Sodergren, PhD, research associate professor of genetics, and Makedonka Mitreva, PhD, research assistant professor of genetics, took an inventory of the microbes in the samples by sequencing a gene found in all microbes. This gene, 16S rDNA, serves as a barcode of life to indicate which species are there.

The Genome Institute team also sequenced the DNA of entire microbial communities in a subset of samples, to catalog the genes present, as well as to identify viruses, fungi and other non-bacterial organisms.

The researchers noted unique communities of microbes in every site in the body. Interestingly, the microbial communities that live on the teeth are different from those in saliva. And the most diverse collection of microbes was found to live on the skin, which might be expected because it is the body’s barrier to the outside world.
The scientists also reported that the body’s collection of microbes contributes more gene activity than humans themselves. While the human genome includes some 22,000 genes, it’s a mere fraction of the 8 million genes that are part of the human microbiome.

These microbial genes are critical to good health. Those in the gastrointestinal tract, for example, allow humans to digest foods and absorb nutrients that our bodies otherwise could not handle. Microbial genes also produce vitamins and compounds that naturally suppress inflammation in the intestine.

Also, confirming earlier, smaller studies, the new research shows that components of the human microbiome clearly change during an illness. When a patient is sick or takes antibiotics, the species of the microbiome may shift substantially as one bacterial species or another is affected. Eventually, however, the microbiome settles into a state of equilibrium, even if the previous composition is not completely restored.

As part of the Human Microbiome Project, the NIH funded a number of studies to look for links between particular communities of microbes in the body and illness. Results of some of this research, reported in PLoS, underscore the clinical applications of microbiome research to improve human health.

At Washington University, researchers led by Gregory A. Storch, MD, the Ruth L. Siteman Professor of Pediatrics, examined the microbes in the noses and blood of children who developed sudden, high fevers that couldn’t be traced to a specific cause. Unexplained fever is a common problem in children under age 3, and they are often treated with antibiotics as a precaution, which contributes to antibiotic resistance.

Storch and his colleagues, including Kristine Wylie, PhD, a postdoctoral research associate at The Genome Institute, found that specimens from the sick kids contained more species of viruses, some of them novel, than children without fever, who also were included in the study as a comparison. Fever may be part of the body’s defense against disease-causing viruses, but the researchers also showed that children without fever carried viruses, though in lower numbers. Understanding the difference between viral infections with and without fever will be important in applying microbiome techniques in the clinic, the scientists say.

In another project, Weinstock and his Genome Institute colleagues, along with Katherine Pollard, PhD, and her team at the University of California, San Francisco, identified previously unknown microbial taxa in stool samples from 11 healthy individuals. While these new, not-yet-named microbes were found in relatively low levels, the research indicates they may be quite common because they were found in multiple volunteers.

And in research at St. Louis Children’s Hospital, Phillip Tarr, MD, the Melvin E. Carnahan Professor in Pediatrics, and neonatologist Barbara Warner, MD, professor of pediatrics, and others are investigating whether a life-threatening gastrointestinal illness in premature babies is linked to microbes in the intestinal tract. Necrotizing enterocolitis affects about 10 percent of premature babies, usually in the first month of life, and is fatal in 15 percent to 30 percent of cases.

The researchers are collecting stool samples from premature babies to identify and quantify differences between the microbial communities of the infants who develop the illness and those who don’t. This information may provide a foundation for developing ways to prevent or cure the illness.

“The future of microbiome research is very exciting,” Weinstock says. “This large-scale effort will open doors in many areas of medicine to improve our understanding of good health and the treatment and prevention of disease.”


Scripps research scientists show lack of single protein results in persistent viral infection

LA JOLLA, CA – June 13, 2012—Scientists from The Scripps Research Institute have shown a single protein can make the difference between an infection clearing out of the body or persisting for life. The results also show where the defects occur in the immune system without the protein and offer the possibility that targeting this signaling pathway could be beneficial for treatment of persistent viral infections in humans. Currently hundreds of millions of people around the world are afflicted with persistent viral infections such as HIV, HCV, and HBV.

The new study is published in the June 14, 2012 issue of the journal Cell Host & Microbe. In the new study, a team led by Scripps Research Professor Michael Oldstone showed what happened when a mouse engineered without the protein TLR7 was infected with lymphocytic choriomeningitis virus (LCMV), a virus employed to study the response of the immune system to microbes. While normal mice
infected with a LCMV variant called Cl 13 could clear a persistent infection in 60 to 90 days, TLR7-deficient mice were unable to purge the infection throughout their lives.

"It is well known that RNA from many viruses, including influenza, HIV, and hepatitis C, induce signaling through TLR7," said Kevin Walsh, a research associate in Oldstone's lab and the first author of the study. "We demonstrated that TLR7 plays a significant role in the generation of immune responses required to clear persistent LCMV infection."

'Biological Warfare'
In terms of the constant biological warfare between host and microbes, the body is not so much a temple as it is a medieval city. An infectious agent can invade through the skin or mucosa, essentially scaling the walls. Once it's inside it has to deal with the body's first responders, called Toll-like receptors (TLR). These receptors are a pattern-recognition system to alert the immune system. TLRs form the first line of defense specifically by recognizing molecules of the invading pathogen.

Ten TLRs have been identified in humans. One of these, TLR7, is located inside the cell within endosomes and the RNA of viruses are detected after they have entered the cell. "TLR7 is a very important receptor in terms of viruses," noted Oldstone.

In the current study, the researchers chose to use LCMV to understand the role of TLR7. LCMV is, according to Oldstone, "has been, and continues to be a Rosetta Stone to explain basic concepts in immunology and virology."

Once it was clear that the absence of TLR7 compromised the immune system's ability to clear LCMV infection, Oldstone, Walsh, and their colleagues explored what was happening downstream of the receptor.

Interestingly, the research demonstrated that even when immune memory cells, which "learn" to fight an infection and impart long-term immunity, were transferred from TLR7-sufficient mice to TLR7-deficient mice, those deficient mice still couldn't clear the infection.

"The environment within TLR7-deficient mice suppressed the ability of these memory cells to clear the infection," said Walsh.

Surprisingly Tired Cells
The team noticed several unexpected things. First, in the TLR7-deficient mice, there was a profusion of tired T cells. "You see more T cells in TLR7-deficient mice early after infection, but they don't actually clear the infection," said Walsh. "Even though there were more of them, they were less functional."

Second, immune system B cells were severely hampered; specifically, the differentiation and maturation of B cells to plasma cells, cells responsible for generating antiviral antibody, was aborted. Thus, both essential arms of the immune system, cellular and humoral, required to clear viral infection were compromised.

Exhausted T cells produce fewer molecules to attack and destroy infected cells. Exhaustion occurs in TLR7-sufficient environments, too—but in those cases there is a resurrection of the T cells 60 to 90 days following infection with LCMV Cl 13, which allows the body to purge the virus. In the TLR7-deficient environment, this resurrection never happens. The exhausted T cells linger, as does the infection. T cell exhaustion is also found in HIV and hepatitis B and C infection.

"A number of phenomena that LCMV uses to cause a persistent infection is the same that HIV, hepatitis C and B use," said Oldstone. "That's what makes our observation important. It means that if you understood what is in the environment with loss of TLR7 signaling and how to correct that, you'd have a better chance of treating those persistent human infections. We know how to treat it in the mouse, and people are working very hard to do the treatments in humans."

Novel Mechanism Involved in Key Immune Response
ScienceDaily (June 13, 2012) — A team of researchers at Lawson Health Research Institute and Western University have identified a novel way that a common virus, called adenovirus, causes disease. In doing so, they have discovered important information on one of the body's key immune responses. Their findings, published June 13 in Cell Host & Microbe, may have implications for infectious diseases and cancer.

Adenovirus infections most often cause mild illnesses of the respiratory system, resulting in runny noses, coughs and sore throats. However, researchers have been interested in adenoviruses since the 1960s, when it was discovered that they can cause tumors in rodents. These tumors arise because adenovirus infected cells divide uncontrollably and escape the immune response, which are hallmarks of cancer.
One key component of antiviral immunity is interferon. "Interferons are proteins made and released by cells in response to the presence of viruses, bacteria, parasites or cancers," says Dr. Joseph Mymryk, a scientist at Lawson and a tumor virologist at London Health Sciences Centre. "Adenovirus is completely resistant to interferon."

Past studies have identified some of the ways in which adenovirus overcomes the interferon response, but Dr. Mymryk and Greg Fonseca, PhD Candidate and lead author on the study, have identified a new mechanism that relies on changes in epigenetic regulation. Epigenetics is an emerging field of study which involves non-genetic factors that cause an organism's genes to express differently.

The production of interferons is responsible for the majority of symptoms commonly associated with viral infection including fever, chills, muscle aches, and malaise. When a cell is exposed to interferon it increases the production of about 300 cellular genes that defend the cell from infection. The researchers have discovered that interferon-regulated genes require a specific epigenetic modification called monoubiquitination of histone 2B (H2B) to work. "There is still much to learn about this modification, but our studies are the first to show that it is absolutely required for the interferon response," says Fonseca. "This finding was totally unanticipated."

"Each cell has thousands of different genes and they can all be regulated in weird and wonderful ways," says Dr. Mymryk. "The monoubiquitination of H2B specifically results in large increases in the transcription of genes. We found that the interferon response uses this modification for the rapid increases in gene transcription (which leads to gene expression) that are needed to change the cell environment to respond to and stop the viral infection. What the virus does is essentially block the formation of the complex that performs the monoubiquitination of H2B, thereby blocking its function."

Although the medical consequences of adenovirus are typically modest, the study's findings have implications in a broad range of diseases because of how influential the interferon response is to how we respond to infectious diseases and cancer.

"Many cancers are non-responsive to interferon," says Fonseca. "If we can more fully understand the mechanism of interferon response, we may be able to better treat these cancers. Overall, many of the tricks adenovirus uses may be similar to those used by other viruses and cancer cells."

Journal Reference:

Early Gut Bacteria Regulate Happiness
ScienceDaily (June 12, 2012) — UCC scientists have shown that brain levels of serotonin, the 'happy hormone' are regulated by the amount of bacteria in the gut during early life. Their research is being published June 12 in the international psychiatry journal, Molecular Psychiatry.

This research shows that normal adult brain function depends on the presence of gut microbes during development. Serotonin, the major chemical involved in the regulation of mood and emotion, is altered in times of stress, anxiety and depression and most clinically effective antidepressant drugs work by targeting this neurochemical.

Scientists at the Alimentary Pharmabiotic Centre in UCC used a germ-free mouse model to show that the absence of bacteria during early life significantly affected serotonin concentrations in the brain in adulthood. The research also highlighted that the influence is sex dependent, with more marked effects in male compared with female animals. Finally, when the scientists colonized the animals with bacteria prior to adulthood, they found that many of the central nervous system changes, especially those related to serotonin, could not be reversed indicating a permanent imprinting of the effects of absence of gut flora on brain function.

This builds on earlier work, from the Cork group and others, showing that a microbiome-gut-brain axis exists that is essential for maintaining normal health which can affect brain and behavior. The research was carried out by Dr Gerard Clarke, Professor Fergus Shanahan, Professor Ted Dinan and Professor John F Cryan and colleagues at the Alimentary Pharmabiotic Centre in UCC.

"As a neuroscientist these findings are fascinating as they highlight the important role that gut bacteria play in the bidirectional communication between the gut and the brain, and opens up the intriguing opportunity of developing unique microbial-based strategies for treatment for brain disorders," said Professor John F Cryan, senior author on the publication and Head of the Department of Anatomy & Neuroscience at UCC.
This research has multiple health implications as it shows that manipulations of the microbiota (e.g. by antibiotics, diet, or infection) can have profound knock-on effects on brain function. "We're really excited by these findings" said lead author Dr Gerard Clarke. "Although we always believed that the microbiota was essential for our general health, our results also highlight how important our tiny friends are for our mental wellbeing."

**Journal Reference:**
G Clarke, S Grenham, P Scully, P Fitzgerald, R D Moloney, F Shanahan, T G Dinan and J F Cryan. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry, June 12, 2012 DOI: 10.1038/mp.2012.77*

**Protein Residues Kiss, Don't Tell: Genomes Reveal Contacts, Scientists Refine Methods for Protein-Folding Prediction**

ScienceDaily (June 12, 2012) — José Onuchic has become an expert at connecting the dots, but finding connections merely implied by the dots ... well, that's quite a trick.

The Rice University biophysicist and his team have created a tool to do just that for proteins and, in the process, have advanced the art of predicting their form and function.

In this case, the dots are amino acid molecules known as residues that link together in chains to form proteins. Proteins are the workhorses that carry out the biological tasks essential to every living thing, but before they can go to work, they fold.

Each protein has its own characteristic, folded shape, and various diseases, including cancer, have been linked to proteins that misfold or otherwise misbehave.

As computers grew more powerful over the past three decades, scientists have created many methods to predict how a particular chain of residues is likely to fold and the purpose the resulting protein serves.

Onuchic and colleagues at the Center for Theoretical Biological Physics have developed a tool, known as direct coupling analysis-fold (DCA-fold), that enhances existing methods. Details of their research appear June 12 in the online version of the *Proceedings of the National Academy of Sciences* (PNAS). The center is currently based at the University of California at San Diego (UCSD) but is relocating to Rice’s BioScience Research Collaborative.

While most protein-folding researchers look at the sequence of amino acids in a protein, either through X-ray crystallography of folded proteins or through computer simulations, Onuchic and his colleagues stepped back to look at the DNA sequences that serve as the blueprints for the proteins. By exploiting the increasingly large database of genomic sequence information, they’re able to increase the accuracy of predicting the structures of folded proteins.

They start by finding points in the protein-encoding genome sequences that appear to change at the same time, even though they may be separated by great distances along the chain. The implication, Onuchic said, is that at some point in the protein’s evolutionary history, the amino acids made contact, liked what they saw and kept in touch. In more technical terms, a benefit to the protein’s purpose was realized and conserved.

"A lot of the decisions made through the biological process don’t depend on a strong partner," said Onuchic, Rice’s Harry C. and Olga K. Wiess Chair of Physics and a professor of physics and astronomy, chemistry, biochemistry and cell biology. "It’s like the protein comes, kisses you once, and goes away; it’s what we call very weak interaction, which we’re never going to be able to see with current methods."
"But those weak interactions can cause a conformational change, transfer a phosphorus or start an entire cascade of signals," he said.

Onuchic, lead authors Joanna Sulkowska and Faruck Morcos, postdoctoral researchers at UCSD, and their colleagues looked deeply into the genomes of bacteria to gather 15 protein models; the scientists took from them about 1,000 distinct protein-coding sequences, enough for DCA-fold to be statistically accurate.

"When you look at the evolution of a particular protein in these bacteria and see just one residue change from one sequence to the next, that's probably random," Onuchic said. "But if two change at the same time, the probability is that they're changing together. It's a good sign that these things probably interact with each other."

Spotting those interactions is difficult in the proteins themselves, at least with current methods, he said. Crystallization, for instance, freezes a protein in time but provides no evidence of interactions that happened on the way to the finished product. And while computer simulations that align protein sequences are improving, their accuracy is not as good as it needs to be, he said.

But direct coupling analysis of protein-coding genes spots positions in sequences conserved across genomes that change together—a change that could only happen through mechanical contact.

DCA-fold finds those subtle interactions that other methods miss. Energy landscape theories developed by Onuchic and his team predict how those interactions nudge the protein through its process. The combined result eliminates possibilities from the range of forms a protein might take.

Onuchic sees that as a way to pull a signal from all the noise.

"The entire game here is to show that by adding the genomic data to folding simulations, we can aid in structure prediction," Onuchic said. "Here, we get at least 1,000 bacterial sequences that are part of the same protein family but are not necessarily structurally similar. Then we compare the sequences and figure out which pairs of amino acids change at the same time. Although previous correlation methods could give approximate answers, our model is much more accurate.

"Once we know there's a high probability that these two amino acids came together at some point, we're constrained. If the sequence data tells me we can have structure a, b or c, we can then look to see which is consistent with the pair of contacts we now know about from the genomic data and eliminate the wrong predictions."

The new paper was one of three published by Onuchic and his colleagues this month. A second, also in PNAS, examines proteins that not only knot but sometimes form slipknots. (Read about that here.) The third, which appeared in PLoS One and on which Onuchic was a co-author, analyzes how the Interleukin-1 beta protein resolves the conflicting energetic demands of its residues as it folds.

All of this work brings Onuchic and his colleagues from UCSD who are joining Rice closer to the purpose of their move: To bring all the data they've accumulated on biological systems to bear on the treatment of cancer.

Eukaryotic cells like those in humans (and unlike those in simple bacteria) produce many thousands of proteins; with rapid advances in the capability to sequence genomes, the researchers hope to apply their technique to look for what causes diseases and how to cure them.

"I think DCA has enormous potential," Onuchic said. "The amount of genome data that's being created is growing exponentially. In the future, if we're patient, instead of comparing sequences of different bacteria as we do here, perhaps we can do time evolution of sequences. Then we can figure out if a particular disease mechanism comes from a pair of residues that switch at the same time—and instead of looking at different animals, we can see changes in one patient over time."

Journal Reference:
Joanna I. Sułkowska, Faruck Morcos, Martin Weigt, Terence Hwa, and Jose N. Onuchic. Genomics-aided structure prediction. PNAS, 2012 DOI: 10.1073/pnas.1207864109

U.S. Africa Command Establishes Regional Task Forces To Combat Malaria In Africa
"Two new task forces being [established] by U.S. Africa Command [Africom] have set their sights on one of the biggest killers on the continent: the mosquito," the American Forces Press Service reports. "Ninety percent of the world's malaria-related deaths are reported in Africa, and the disease kills some 600,000 African children each year," the news service notes, adding, "Africom incorporates malaria prevention into much of its theater engagement, distributing mosquito nets and teaching new diagnostic techniques during training events throughout Africa."

"But at the African soldier's suggestion, Africom went to work to establish regional task forces to help partner nations create a unified front against the problem," the article continues. "Ultimately, this
supports the concept of 'stability through health,' [Army Col. John Andrus, Africom's deputy surgeon and medical logistics division chief,] said," the news service writes, adding, "Helping partner nations protect their military forces against disease supports the bigger goal of establishing professional militaries that are trusted by their populations and able to respond to crises, he explained" (Miles, 6/13).

**Childhood virus infection linked to prolonged seizures with fever**

**One-third of febrile seizures associated with roseola virus**

New research shows that human herpesviruses (HHV)-6B and HHV-7, commonly known as roseola virus), account for one third of febrile status epilepticus (FSE) cases. Results of the FEBSTAT prospective study now available in *Epilepsia*, a journal published by Wiley-Blackwell on behalf of the International League Against Epilepsy (ILAE), suggest that HHV-6B may be involved in the development of epilepsy and further research is urgently needed.

FEBSTAT is a multi-center study of the consequences of FSE, designed to identify the factors that increase the risk of injury to the hippocampus, an area of the brain responsible for long-term memory and implicated in the development of temporal lobe epilepsy. The FEBSTAT study is funded by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH).

According to previous research, up to 5% of children under the age of five have febrile seizures, making it the most common type of seizure, with peak incidence at age 2. While brief or simple febrile seizures are most common, 5%–8% of cases are prolonged and meet the criteria for status epilepticus (SE)—a critical condition where a persistent seizure lasts more than 30 minutes. Experts suggest that FSE accounts for 5% of FS; however, FSE accounts for 25% of all childhood SE and for more than 70% of SE cases that occur in the second year of life. FSE is associated with increased epilepsy risk, particularly temporal lobe epilepsy (TLE).

"One aim of the FEBSTAT study is to determine the frequency of HHV-6A, HHV-6B, and HHV-7 as a cause of FSE and whether infection with any of these herpesviruses increases the risk of brain injury and epilepsy," said lead author Dr. Leon Epstein a, pediatric neurologist at the Northwestern University Feinberg School of Medicine and Ann & Robert H. Lurie Children's Hospital of Chicago.

The team enrolled 199 children between the ages of 1 month and 5 years, who presented with FSE and received an assessment for herpesvirus infection within 72 hours of the episode. Viremia was detected using polymerase chain reaction (PCR) that identified the presence of HHV-6A, HHV-6B or HHV-7A DNA and RNA. In conjunction with PCR results, researchers used antibody titers to determine if the infection was a primary or reactivated herpesvirus.

Findings indicate that approximately one third of children with FSE had HHV-6 or HHV-7 viremia. HHV-6B viremia was detected in 32% of pediatric participants, with 38 and 16 children having primary and reactivated infection, respectively. Researchers found that 7% of children had HHV-7 viremia at baseline and 2 children had HHV-6/7 primary co-infection. There were no apparent differences in age, illness type, fever, seizure structures, or acute imagining abnormalities in children with or without one of the herpesviruses.

FEBSTAT researchers will continue to follow the 199 children involved in the study, expecting up to 40% of this pediatric population to develop TLE. The FEBSTAT study will determine whether there is an association between prolonged febrile seizures caused by HHV-6B viremia and the development of TLE. The current study adds to evidence from previous research by Donati et al. and by Fotheringham et al who detected HHV-6 in brain samples of patients with TLE.

"TLE could take 8 to 11 years to develop following an episode of FSE, so more time is needed before the role of HHV-6B is fully understood," concludes Dr. Epstein. "If the FEBSTAT study finds that FSE caused by HHV-6B leads to TLE, this insight would provide a basis for clinical trials of antiviral and anti-inflammatory therapies to prevent TLE."


**The Battle Against HIV**

In the battle against HIV/AIDS conditions on the frontlines are constantly in flux as treatment, research and policy evolve. The landmark HIV Prevention Trials Network (HPTN) 052 study, which established that antiretroviral treatment in people who are HIV positive decreases the likelihood of transmitting HIV to their sexual partners, was no exception. One year after publication the study serves as a case study of
ethical challenges faced at every stage of the research trial process in the new paper “Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey,” published in the June 2012 issue of Clinical Trials.

HPTN 052 was designed to investigate two questions related to the use of antiretroviral treatment (ART). First, can ART be used to prevent sexual transmission of the HIV virus, and second, is earlier use of ART better for the health of someone who is already HIV positive? In 2007, the full trial began at 13 sites in 9 countries, with 1763 couples enrolled. In each couple, one partner was HIV-positive and one HIV-negative.

“HPTN 052 provides useful real-world examples of the types of ethical difficulties faced when conducting research that has profound implications for public health and how these difficulties can be managed in order to both protect the participants and do good science,” says Jeremy Sugarman, MD, MPH, MA, co-author of the paper and deputy director for medicine of the Johns Hopkins Berman Institute of Bioethics. To address the research questions, study participants were randomly assigned to two groups – one that would receive ART earlier, and the other at a later stage of HIV progression. This became a source of ethical tensions as the trial progressed and enthusiasm for earlier ART treatment grew, whereas previously it had been considered potentially unsafe. For example, in November 2009 the World Health Organization (WHO) issued new guidelines recommending that ART treatment begin earlier.

The deliberation and evolving guidance on ART treatment “brought into sharp focus the ethical tensions inherent to a moral obligation to intervene and the sometimes-conflicting need for gathering data to develop evidence-based practices,” write Sugarman and his co-authors Myron S. Cohen, MD, and MaryBeth McCauley, M.P.H.

The authors point to the “constant threat” from observational and ecological study data, and the official guidelines they inspire, as posing a critically important ethical lesson of HPTN 052: whether and how a randomized trial should respond in light of them. “As these necessary changes were made, they threatened the very research that might support or refute the recommendations themselves,” they write. The authors credit the Data and Safety Monitoring Board (DSMB), which met 11 times during the trial, for helping make critical calls as new developments arose during the trial, and maintaining essential communication with the investigators and Institutional Review Boards.

Yet even as HPTN 052 was being designed, ethical questions were raised as to the potential “coercion” of participants who would otherwise not have access to ART. The authors agree that “the unavailability of ART at the research sites reflected long-standing issues of global justice,” but point out that initiatives coinciding with (but separate from) the trial by the WHO, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, as well as the President’s Emergency Plan for AIDS Relief (PEPFAR) made ART much more widely available without having to enroll in HPTN 052.

The authors also address the question of the study’s potential to encourage unsafe sex for the sake of research results into the transmissibility of HIV, a common ethical issue raised in HIV research. The authors assert that “including a ‘prevention package’ is ethically obligatory,” and should include methods known to be effective and accessible to participants.

“Throughout the course of the trial, the search for ‘scientific truth’ had to be weighed along with the rights and welfare of the subjects,” said Sugarman.

Though some of the results of HPTN 052 were published in May 2011, the trial is still ongoing and will continue as planned until 2015, to assess long-term outcomes of early versus late ART treatment.

Atomic-resolution view of a receptor reveals how stomach bacterium avoids acid

EUGENE, Ore. — (June 14, 2012) — University of Oregon scientists have discovered how the bacterium *Helicobacter pylori* navigates through the acidic stomach, opening up new possibilities to inactivate its disease-causing ability without using current strategies that often fail or are discontinued because of side effects.

Their report—online ahead of regular publication July 3 in the journal *Structure*—unveils the crystal structure of *H. pylori*’s acid receptor TlpB. The receptor has an external protrusion, identified as a PAS domain, bound by a small molecule called urea and is poised to sense the external environment. TlpB is the first bacterial chemoreceptor of known function shown by crystallography to contain an extracellular PAS domain, the researchers reported.

"It is a beautiful structure, and this domain has never been seen before in this class of proteins," said co-author S. James Remington, professor of physics and member of the UO Institute of Molecular Biology. Captured at the atomic resolution of 1.38 angstroms, it is the first new, significant structural view in 20 years of the class of receptors used by bacteria to navigate their chemical environment.

*H. pylori*, a Gram-negative bacterium, was first identified in 1982 and shown to be associated with stomach ulcers and stomach cancer. While its mode of transmission is not precisely understood, the bacterium is found in the stomach of half of the people in the world, said co-author Karen Guillemin, professor of biology and also a member of the Institute of Molecular Biology. To fight *H. pylori* infections, patients generally are treated with broad-spectrum antibiotics, but the bacterium is becoming resistant and treatment fails in about 30 percent of cases.

As part of the new UO study—led by postdoctoral researcher Emily G. Sweeney and doctoral student J. Nathan Henderson, now a postdoctoral researcher at Arizona State University—researchers manipulated the atomic structure of the protein to disrupt its ability to bind urea, and demonstrated that the urea is the key to how the bacterium senses and avoids acid.

When the receptor is unable to bind urea, Guillemin said, the bacteria became confused and were unable to navigate away from high acid. "We found that this urea binding is absolutely crucial for this protein to act as an acid sensor," she said.

"We now have significant new insights into how acid sensing works at the atomic level which is important for *H. pylori*’s life in the stomach" Guillemin said. "The health implications are this: If we disrupt the binding of urea, we can confuse the bacteria and potentially block their ability to reach the stomach lining where they cause damage."

The new research so far only presents "snapshots along the way" of the *H. pylori*’s signaling process, Remington said. More study is needed to understand the mechanisms involved, but the new structure now lets researchers see the some 3,000 individual atoms—and where they are located—in the newly discovered urea-binding protein domain.
“This interdisciplinary research team worked together to approach a problem and provide fundamental new knowledge about this bacterium’s basic structure,” said Kimberly Andrews Espy, vice president for research and innovation at the UO. “As a result, we are able to understand the discovery in the context of disease and how human health might benefit.”

**Oregon man contracts plague saving mouse from cat**
By David Ferguson
Thursday, June 14, 2012 14:12 EDT
An unidentified Oregon man is hospitalized in critical condition with what doctors believe is Oregon’s fifth case of plague in the last 15 years, according to a report in *The Oregonian*. The rural Crook County man was bitten on the hand on Saturday, June 2 as he tried to take a struggling mouse away from a neighborhood cat. He fell ill several days later and was admitted to St. Charles Medical Center-Bend in Bend, OR. It’s not clear which of the animals bit the man or gave him the disease.

Plague is caused by the bacterium *Yersinia pestis* and manifests in the bodies of its victims in three ways. The Oregon man was admitted to the hospital with fever and classic signs of bubonic plague, so named for the painful, pus-filled black boils or “buboes” that swell and sometimes burst at the neck, groin and armpits. These lesions form when the patient’s lymph nodes expand out of control, filling with dead bacteria and spent white blood cells, the debris from a fierce battle being waged in the bloodstream.

As of Tuesday, however, the victim’s illness was trending more toward septicemic plague, a manifestation of the disease wherein *Yersinia* attacks the circulatory system, causing severe abdominal pain, bleeding from the nose, mouth and rectum, high fever and tissue necrosis. The deadliest but least common form of plague is pneumonic plague, which invades the lungs and drowns the patient in the fluids that result from their body’s attempt to fight off the illness.

Plague is treatable with modern antibiotics, but is so virulent and damaging to the body’s systems that it’s important to diagnose and treat the disease early. The so-called “Black Death” killed more than a third of the population of Europe in the Middle Ages. It’s rare today, although it has never been entirely eliminated.

Oregon has seen four plague deaths since 1934, all in rural areas. The disease spreads through the bites of fleas that have fed on the blood of infected rodents. Once entrenched in a victim’s system, however, plague can be passed from human to human by way of contact with bodily fluids.

Crook County Health Department spokesperson Karen Yeargain told the *Oregonian* that tests to determine whether the man has contracted plague are still pending, but his symptoms are strongly indicative of the disease. A plague vaccine exists, but it went off the market in the U.S. when cases dropped in the mid twentieth century.

**Judge Dismisses Lawsuit on ’40s US STD Experiments**
US District Judge Reggie Walton has dismissed a lawsuit against US officials on behalf of Guatemalans who were subjected to experiments in the 1940s that exposed them to syphilis, gonorrhea, and chancroid.

The lawsuit on behalf of victims and their heirs came after revelations that Guatemalan prisoners, mental patients, soldiers, and orphans had been deliberately infected with the STDs without their consent. The researchers, who were funded by the predecessor of the National Institutes of Health, were studying the effects of penicillin.
Walton acknowledged that the study was a “deeply troubling chapter in our nation's history.” However, he ruled that federal law bars claims against the United States based on injuries suffered in a foreign country, and he granted the US government’s motion to dismiss the suit.

Walton also dismissed constitutional claims made against several current US officials, including Department of Health and Human Services Secretary Kathleen Sebelius, ruling that such claims must be made against those who were personally involved in the illegal conduct.

Guatemalan officials said last year that they have determined that 2,082 people were victims of the experiments, while US authorities found 1,308.

President Barack Obama, Secretary of State Hillary Rodham Clinton, and Sebelius all have apologized for the research, which came to light only after a Wellesley College medical historian uncovered the records in 2009.

Walton said the plaintiffs’ pleas “are more appropriately directed to the political branches of our government, who, if they choose, have the ability to grant some modicum of relief to those affected by the Guatemala study.”

[PNU editor’s note: On Friday, CNN.com reported that victims of the experiment and their heirs will appeal Walton’s dismissal. “Naturally, we are disappointed by the decision and strongly disagree that these doctrines of immunity apply under the extreme circumstances of this case,” Terrence Collingsworth, the plaintiffs’ attorney, said in a statement.]

**High School Sex Numbers Rising: Schools Get 'F,' Says Planned Parenthood**

*Commercial Appeal (Memphis)*, (06.14.2012) Linda A. Moore

New data from CDC’s Youth Risk Behavior Survey indicate the number of Memphis City Schools (MCS) high-school students who reported risky sex behaviors in 2011 remained level or increased from 2009.

The biannual survey found that 62.2 percent of participating Memphis students said they had had sexual intercourse, up from 61.6 percent in 2009. Some 15.6 percent reported first sex prior to age 13, compared with 12.1 percent in 2009. And in 2011, 25.3 percent said they had sex with four or more partners; in 2009, that figure was 23 percent.

Last year, 22.8 percent of Memphis respondents said they had never been taught about HIV/AIDS in school, compared with 20.6 percent in 2009.

“Those students weren’t getting the kind of sex education they need to prevent [STDs] and pregnancies,” said Joan Carr, community affairs director at Planned Parenthood Greater Memphis Region. The problem is exacerbated by new legislation mandating an exclusive focus on abstinence in the state’s family life curriculum, which does not address students who are or have been sexually active, she noted.

Tennessee does not require sex education after the ninth grade, though MCS offers high-school students an intensive, year-long course focused on healthy relationships and the prevention of STDs and pregnancy, a district spokesperson said.

Further, “[MCS] follows the Michigan Model for its Family Life Curriculum. This age-appropriate curriculum begins in the elementary level in grade four and extends to the high-school level,” the spokesperson said.

**Microbiome analysis helps understand cause of chronic sinus condition, suggests cure**

A study of the microbiome of the human nose provides clues to the cause of a chronic sinus condition and potential strategy for a cure. Researchers from the University of California, San Francisco report their findings today at the 2012 General Meeting of the American Society for Microbiology.

Chronic rhinosinusitis (CRS) is characterized by inflammation of the nasal and paranasal sinuses lasting over 12 weeks. Patients suffering from this disease experience a variety of symptoms including congestion, fatigue, and even depression and it can lead to other conditions such as asthma, meningitis and aneurysms. Annually, it is estimated to be responsible for as many as 22 million office visits and more than 500,000 emergency department visits in the U.S. with healthcare costs reaching as high as $3.5 billion. The causes of chronic rhinosinusitis are not completely understood. This has hampered development of long-lasting, definitive treatments.

“With the fast-growing body of literature that demonstrates associations between the human microbiome composition and several diseases such as asthma and obesity, we hypothesized that a nasal
microbiome exists and plays a role in CRS development," says Nabeetha Nagalingam, a researcher on the study.

In the study Nagalingam and colleagues compared the nasal microbial communities of 10 CRS patients and 10 healthy individuals. They found that patients with CRS had a depleted nasal microbiome, characterized by a significant reduction in bacterial diversity and an overgrowth of one type of bacteria, Corynebacterium spp.

"We investigated our hypothesis that C. tuberculostearicum in the setting of a depleted microbiome can induce pathophysiology consistent with sinusitis using a mouse model," says Nagalingam.

To recreate a depleted microbiome, mice were administered antibiotics for 7 days before they were infected with C. tuberculostearicum. Mice who were given the antibiotic before exposure displayed symptoms of sinusitis. Mice that were not first treated with antibiotics but exposed to the bacteria did not.

"From our human microbiome comparative profiling, we noted that lactic acid bacteria, including Lactobacillus sakei, were significantly depleted in patients with CRS and postulated that this bacterium may have a protective role against CRS development," says Nagalingam. Once again using the mouse model they showed that L. sakei inhibited the growth of C. tuberculostearicum and could prevent infection, even with a depleted nasal microbiome.

"These findings suggest that manipulation of microbial communities to restore colonization by beneficial species identified in this study may represent a novel and efficacious approach for prevention or management of CRS," says Nagalingam.

**Brothers in arms:**

**Commensal bacteria help fight viruses**

PHILADELPHIA – Healthy humans harbor an enormous and diverse group of bacteria and other bugs that live within their intestines. These microbial partners provide beneficial aid in multiple ways – from helping digest food to the development of a healthy immune system. In a new study published online in the journal *Immunity*, David Artis, PhD, associate professor of Microbiology, and Michael Abt, PhD, a postdoctoral researcher in the Artis lab, Perelman School of Medicine, University of Pennsylvania, show that commensal bacteria are also essential to fight off viral infections.

"From our studies in mice, we found that signals derived from these beneficial microbes are essential for optimal immune responses to experimental viral infections," says Artis. "In one way we could consider these microbes as our 'brothers in arms' in the fight against infectious diseases." Artis is also an associate professor of Pathobiology in the Penn School of Veterinary Medicine.

Signals from commensal bacteria influence immune-cell development and susceptibility to infectious or inflammatory diseases. Commensal microbial communities colonize barrier surfaces of the skin, vaginal, upper respiratory, and gastrointestinal tracts of mammals and consist of bacteria, fungi, protozoa, and viruses. The largest and most diverse microbial communities live in the intestine.

Previous studies in patients have associated alterations in bacterial communities with susceptibility to diabetes, obesity, cancer, inflammatory bowel disease, allergy, and other disorders. Despite knowing all of this, exactly how commensal bacteria regulate immunity after being exposed to pathogens is not well understood.
To get a better picture of how these live-in bacteria are beneficial, the Artis lab used several lines of investigation. First, they demonstrated that mice—treated with antibiotics to reduce numbers of commensal bacteria—exhibit an impaired antiviral immune response and a substantially delayed clearance of a systemic virus or influenza virus that infects the airways. What’s more, the treated mice had severely damaged airways and increased rate of death after the experimental influenza virus infection, demonstrating that alterations in commensal bacterial communities can have a negative impact on immunity against viruses.

Next, they profiled the genes that were expressed in immune cells called macrophages isolated from the antibiotic-treated mice. These data revealed a decreased expression of genes associated with antiviral immunity. In addition, macrophages from antibiotic-treated mice showed defective responses to interferons, proteins made and released in response to viruses, bacteria, parasites, or tumor cells. Under normal circumstances, interferons facilitate communication between cells to trigger the immune cells that attack pathogens or tumors. The antibiotic-treated mice also had an impaired capacity to limit viral replication. However, when mice were treated with a compound that restored interferon responsiveness, protective antiviral immunity was re-established.

"It is remarkable that signals derived from one type of microbe, in this case bacteria, can have such a profound effect on immune responses to viruses that are a very different type of microbe," says first author Abt. "Just like we would set a thermostat to regulate when a heater should come on, our studies indicate that signals derived from commensal bacteria are required to set the activation threshold of the immune system."

Taken together, these lines of evidence indicate that signals from commensal bacteria beneficially stimulate immune cells in a way that is optimal for antiviral immunity. "Although more work needs to be done, these findings could illuminate new ways to promote better immunity to potentially life-threatening viral infections," adds Artis.

### Immune System May Protect Against Alzheimer’s Changes in Humans

ScienceDaily (May 25, 2012) — Recent work in mice suggested that the immune system is involved in removing beta-amyloid, the main Alzheimer’s-causing substance in the brain. Researchers have now shown for the first time that this may apply in humans.

Researchers at the Peninsula College of Medicine and Dentistry, University of Exeter with colleagues in the National Institute on Aging in the USA and in Italy screened the expression levels of thousands of genes in blood samples from nearly 700 people. The telltale marker of immune system activity against beta-amyloid, a gene called CCR2, emerged as the top marker associated with memory in people.

The team used a common clinical measure called the Mini Mental State Examination to measure memory and other cognitive functions.

The previous work in mice showed that augmenting the CCR2-activated part of the immune system in the blood stream resulted in improved memory and functioning in mice susceptible to Alzheimer’s disease.

Professor David Melzer, who led the work, commented: "This is a very exciting result. It may be that CCR2-associated immunity could be strengthened in humans to slow Alzheimer’s disease, but much more work will be needed to ensure that this approach is safe and effective."

Dr Lorna Harries, co-author, commented: "Identification of a key player in the interface between immune function and cognitive ability may help us to gain a better understanding of the disease processes involved in Alzheimer’s disease and related disorders."

Alzheimer’s disease is the most common form of dementia and affects around 496,000 people in the UK.

**Journal Reference:**

### Normal Bacterial Makeup Has Huge Implications for Health

ScienceDaily (June 13, 2012) — For the first time, a consortium of researchers organized by the National Institutes of Health, including a University of Colorado Boulder professor, has mapped the normal microbial makeup of healthy humans.
The team made up of 200 researchers from the Human Microbiome Project Consortium, or HMP, and based at 80 research institutions, reports that while nearly everyone carries pathogens—which are microorganisms that cause illness—pathogens cause no disease in healthy individuals. Instead, they coexist with their host and the rest of the human microbiome, which is the collection of all microorganisms living in the human body.

Although the human body contains trillions of microorganisms—outnumbering human cells by 10 to one—they make up only 1 to 3 percent of human body mass but play a vital role in human health, said CU-Boulder Associate Professor Rob Knight of the BioFrontiers Institute. "Many people were sampled so we could get a better idea of variability, and how microbes work together in complex communities," he said.

The trick now is to understand why some pathogens turn deadly under what conditions, said Knight, also a faculty member in the chemistry and biochemistry and computer science departments.

The new findings on the microbial mapping project were published in a series of reports published June 14 in the journal Nature and several journals in the Public Library of Science, or PLoS. Launched in 2007, the HMP received $156 million from the NIH Common Fund, an initiative that finances high-impact, large-scale research. Knight is a co-author on the two Nature studies.

In 2009, a group of researchers from CU-Boulder and the Washington University School of Medicine in St. Louis led by Knight developed the first atlas of bacterial diversity across the human body. The study, published in Science magazine, used swab samples from nine volunteers targeting 27 specific sites on the body, showing humans carry "personalized" bacterial communities that vary widely from our foreheads and feet to our navels and noses.

"By better understanding this microbial variation we can begin searching for genetic biomarkers for disease," said Knight. "Because the human microbiome is much more variable than the human genome, and because it also is much easier to modify, it provides a much more logical starting point for personalized medicine."

In the new 2012 studies, HMP researchers sampled 242 healthy U.S. volunteers—129 males and 113 females—collecting tissues from 15 body sites in men and 18 body sites in women. The researchers collected samples at up to three "time-points" from each volunteer at places including the mouth, nose, skin, ears, elbows and lower intestine. According to Knight, each body site can be inhabited by organisms that are as different from each other as are microbial communities from oceans and deserts.

Instead of isolating and culturing individual pathogens—an inefficient method—the team purified all human and microbial DNA in each of more than 5,000 samples and analyzed them with DNA sequencing machines. It then used computers to sort through the data and identify specific genetic signals found only in bacteria—the variable genes of bacterial ribosomal RNA that help form the cellular structures that manufacture protein and can identify the presence of different microbial species.

Focusing on the microbial signature allowed the HMP researchers to ignore the human genome sequences and analyze only bacterial DNA, said Knight. In addition, "metagenomic" sequencing—sequencing all of the DNA in a microbial community—allowed the researchers to study the metabolic capabilities encoded in the genes of the microbial communities.

"Like 15th century explorers describing the outline of a new continent, HMP researchers employed a new technological strategy to define for the first time the microbial makeup of the human body," said NIH Director Francis Collins. "This lays the foundation for accelerating infectious disease research previously impossible without this community resource."

Other CU-Boulder participants in the HMP include faculty members Norman Pace, Andrew Martin and Manuel Lladser, postdoctoral researchers Jose Clemente and Catherine Lozupone, graduate students Antonio Gonzalez and Daniel McDonald and recent CU-Boulder graduate Dan Knights.

The HMP researchers calculated that more than 10,000 microbial species occupy the human "ecosystem," said Knight. The researchers believe they have now identified between 81 and 99 percent of all genera of microorganisms in healthy adults in the United States. In one of the new Nature studies led by Dr. Jeffrey Gordon of Washington University and involving Knight, the team demonstrated that at least in the gut, children and adults from other countries like Malawi and Venezuela differ dramatically from adults in the United States in terms of their microbial communities.

"We are only beginning to scratch the surface of understanding how the human microbiome develops from infancy to adulthood across cultures and across habitats within the human body," said Knight. "Of particular interest are non-Western populations that do not develop the suite of diseases associated with the Western lifestyle, including obesity, inflammatory bowel disease, asthma and allergies."

Knight said HMP researchers have found the plethora of microbes on the human body contributes more genes responsible for human metabolism than people do. While the human genome carries roughly
22,000 protein-coding genes, the human microbiome contributes about 8 million unique protein-coding genes. If it weren't for bacteria in the gastrointestinal tract, humans could not fully digest foods and absorb nutrients.

Microbes not only break down proteins, lipids and carbohydrates in the gut, they produce beneficial compounds like vitamins and anti-inflammatories. One surprising discovery by the researchers was that the distribution of microbial metabolic activities matters more than the species providing them, said Knight.

In the healthy gut, for example, there always will be a population of bacteria needed to help digest fats. But it may not always be the same bacterial species carrying out the job—the bacteria appear to be "pinch-hitting" for each other, said the researchers.

The HMP is currently funding additional clinical studies looking for associations between the microbiome and diseases. The studies include looking at changes in the vaginal microbiome of pregnant women; analyzing viral DNA in the nostrils of children with unexplained fevers; investigating the role of the gut microbiome in Crohn's disease, ulcerative colitis and esophageal cancer; charting the relationship of skin bacteria to psoriasis, dermatitis and immunodeficiency; and understanding the role of the microbiome in childhood disorders like pediatric abdominal pain and intestinal inflammation.

NYTimes, June 18, 2012

**Tending the Body's Microbial Garden**

**By CARL ZIMMER**

For a century, doctors have waged war against bacteria, using antibiotics as their weapons. But that relationship is changing as scientists become more familiar with the 100 trillion microbes that call us home — collectively known as the microbiome.

“I would like to lose the language of warfare,” said Julie Segre, a senior investigator at the National Human Genome Research Institute. “It does a disservice to all the bacteria that have co-evolved with us and are maintaining the health of our bodies.”

This new approach to health is known as medical ecology. Rather than conducting indiscriminate slaughter, Dr. Segre and like-minded scientists want to be microbial wildlife managers.

No one wants to abandon antibiotics outright. But by nurturing the invisible ecosystem in and on our bodies, doctors may be able to find other ways to fight infectious diseases, and with less harmful side effects. Tending the microbiome may also help in the treatment of disorders that may not seem to have anything to do with bacteria, including obesity and diabetes.

“I cannot wait for this to become a big area of science,” said Michael A. Fischbach, a microbiologist at the University of California, San Francisco, and an author of a medical ecology manifesto published this month in the journal Science Translational Medicine.

Judging from a flood of recent findings about our inner ecosystem, that appears to be happening. Last week, Dr. Segre and about 200 other scientists published the most ambitious survey of the human microbiome yet. Known as the Human Microbiome Project, it is based on examinations of 242 healthy people tracked over two years. The scientists sequenced the genetic material of bacteria recovered from 15 or more sites on their subjects' bodies, recovering more than five million genes.

The project and other studies like it are revealing some of the ways in which our invisible residents shape our lives, from birth to death.

A number of recent reports shed light on how mothers promote the health of their children by shaping their microbiomes. In a study published last week in the journal PLoS One, Dr. Kjersti Aagaard-Tillery, an obstetrician at Baylor College of Medicine, and her colleagues described the vaginal microbiome in pregnant women. Before she started the study, Dr. Aagaard-Tillery expected this microbiome to be no different from that of women who weren't pregnant.

“In fact, what we found is the exact opposite,” she said.

Early in the first trimester of pregnancy, she found, the diversity of vaginal bacteria changes significantly. Abundant species become rare, and vice versa.

One of the dominant species in the vagina of a pregnant woman, it turns out, is Lactobacillus johnsonii. It is usually found in the gut, where it produces enzymes that digest milk. It's an odd species to find proliferating in the vagina, to say the least. Dr. Aagaard-Tillery speculates that changing conditions in the vagina encourage the bacteria to grow. During delivery, a baby will be coated by Lactobacillus johnsonii and ingest some of it. Dr. Aagaard-Tillery suggests that this inoculation prepares the infant to digest breast milk.
The baby’s microbiome continues to grow during breast-feeding. In a study of 16 lactating women published last year, Katherine M. Hunt of the University of Idaho and her colleagues reported that the women’s milk had up to 600 species of bacteria, as well as sugars called oligosaccharides that babies cannot digest. The sugars serve to nourish certain beneficial gut bacteria in the infants, the scientists said.

The more the good bacteria thrive, the harder it is for harmful species to gain a foothold.

As the child grows and the microbiome becomes more ecologically complex, it also tutors the immune system. Ecological disruptions can halt this education. In March, Dr. Richard S. Blumberg of Harvard and his colleagues reported an experiment that demonstrates how important this education is.

The scientists reared mice that lacked any microbiome. In their guts and lungs, the germ-free mice developed abnormally high levels of immune cells called invariant natural killer T cells. Normally, these cells trigger a swift response from the immune system against viruses and other pathogens. In Dr. Blumberg’s mouse-free mice, however, they caused harmful inflammation. As adults, the mice were more likely to suffer from asthma and inflammatory bowel disease.

This experiment parallels studies of children in recent years. Children who take high levels of antibiotics may be at greater risk of developing allergies and asthma later on, many researchers have suggested.

Dr. Blumberg and his colleagues found that they could prevent the mice from becoming ill by giving them bacteria while they were still young. Acquiring a microbiome as an adult did not help the rodents.

The Good With the Bad

The diversity of species that make up the microbiome is hard to fathom. But it is even more difficult to understand how the immune system copes with this onslaught. In any one person’s mouth, for example, the scientists of the Human Microbiome Project found about 75 to 100 species. Some that predominate in one person’s mouth may be rare in another person’s. Still, the rate at which they are being discovered indicates that there may be as many as 5,000 species of bacteria that live in the human mouth.

“The closer you look, the more you find,” said Susan M. Huse of the Marine Biological Laboratory in Woods Hole, Mass., a contributor to the microbiome project.

Although the project has focused largely on bacteria, the microbiome’s diversity is wider. For example, our bodies also host viruses.

Many species in the human “virome” specialize in infecting our resident bacteria. But in the DNA samples stored in the Human Microbiome Project’s database, Kristine Wylie of Washington University and her colleagues are finding a wealth of viruses that target human cells. It is normal, it seems, for people to have a variety of viruses busily infecting their human hosts. “It’s really pretty striking that even in these healthy people, there really is a virome,” Dr. Wylie said.

The microbiome also includes fungi. In the June 8 issue of the journal Science, David Underhill, a research scientist at Cedars-Sinai hospital in Los Angeles, and his colleagues reported on a wealth of fungal species in the guts of humans and other mammals. In mice, for example, they cataloged 100 species of fungi that are new to science, along with 100 already known. This diversity is all the more remarkable when you consider that it is tolerated by an immune system that has evolved to fight off microbes. Scientists have only a dim understanding of how the system decides which to kill and which to tolerate.

Immune cells fight fungal infections, for example, with a protein called dectin-1, which attaches only to fungi. But Dr. Underhill and his colleagues found that dectin-1 is also essential for tolerating harmless fungi. When they engineered mice that couldn’t produce dectin-1, the mice responded to harmless fungi by producing so much inflammation that their own tissues were damaged.

It’s a good thing that the immune system can rein itself in, because the microbiome carries out many services for us. In the gut, microbes synthesize vitamins and break down tough plant compounds into digestible bits.

Skin bacteria are also essential, Dr. Segre said. “One of the most important functions of the skin is to serve as a barrier,” she said. Bacteria feed on the waxy secretions of skin cells, and then produce a moisturizing film that keeps our skin supple and prevents cracks — thus keeping out invading pathogens.

Restoring Order to the System

Antibiotics kill off harmful bacteria, but broad-spectrum forms can kill off many desirable species, too. Dr. Fischbach likens antibiotics to herbicides sprayed on a garden. The herbicide kills the unwanted plants, but also kills off the tomatoes and the roses. The gardener assumes that the tomatoes and roses will grow back on their own.

In fact, there’s no guarantee the microbial ecosystem will automatically return to normal. “It’s one of those assumptions we make today that will seem silly in retrospect,” Dr. Fischbach said. Indeed, some
bacteria are adapted for invading and establishing themselves in disrupted ecosystems. A species called Clostridium difficile will sometimes invade a person’s gut after a course of antibiotics. From 2000 to 2009, the number of hospitalized patients in the United States found to have C. difficile more than doubled, to 336,600 from 139,000. Once established, the antibiotic-resistant C. difficile can be hard to eradicate.

Now that scientists are gaining a picture of healthy microbiomes, they are optimistic about restoring devastated ones. “I don’t know that we’re quite on the cusp of being able to do that well at this point. But I think at least the data is starting to argue that these might be possibilities,” said Barbara Methé of the J. Craig Venter Institute, a principal investigator on the microbiome project.

One way to restore microbiomes may be to selectively foster beneficial bacteria. To ward off dangerous skin pathogens like Staphylococcus aureus, for instance, Dr. Segre envisions applying a cream infused with nutrients for harmless skin bacteria to feed on. “It’s promoting the growth of the healthy bacteria that can then overtake the staph,” she said.

**Bacterial Transplants**

Adding the bacteria directly may also help. Unfortunately, the science of so-called probiotics lags far behind their growth in sales. In 2011, people bought $28 billion of probiotic foods and supplements, according to the research firm EuroMonitor International. But few of them have been tested as rigorously as conventional drugs.

“I think the science has been shoddy and flimsy,” said Dr. Fischbach (who is on the scientific advisory board of Schiff Nutrition International).

Nonetheless, he sees a few promising probiotic treatments. A growing number of doctors are treating C. difficile with fecal transplants: Stool from a healthy donor is delivered like a suppository to an infected patient. The idea is that the good bacteria in the stool establish themselves in the gut and begin to compete with C. difficile. This year, researchers at the University of Alberta reviewed 124 fecal transplants and concluded that the procedure is safe and effective, with 83 percent of patients experiencing immediate improvement as their internal ecosystems were restored.

Dr. Alexander Khoruts of the University of Minnesota and his colleagues want to make fecal transplants standard practice. They can now extract bacteria from stool, “removing the ‘ick’ factor,” as he puts it.

Dr. Khoruts and his colleagues have federal approval to start formal clinical trials on fecal transplants. Eventually, he would like to develop probiotic pills that contain just a few key species required to build the intestinal ecosystem.

“People are starting to take this seriously,” Dr. Fischbach said. “This is a therapy that’s going to help a lot of people.”

Other conditions potentially could be treated by manipulating the microbiome. Scientists have linked obesity, for example, to changes to the gut’s ecosystem. When scientists transfer bacteria from obese mice to lean ones, the lean mice put on weight.

How this happens is still unclear, but some studies suggest that an “obese” microbiome sends signals to the body, changing how cells use sugar for energy and leading the body to store extra fat.

Researchers at the Academic Medical Center in Amsterdam are running a clinical trial to see if fecal transplants can help treat obesity. They have recruited 45 obese men; some are getting transplants from their own stool, while others get transplants from lean donors. The scientists are finding that the transplants from lean donors are changing how the obese subjects metabolize sugar.

While these initial results are promising, there is no evidence yet that the obese subjects are losing weight. Dr. Fischbach cautions that it may take a while to figure out how to manipulate the microbiome to make people healthy.

And it may take even longer to persuade doctors to think like ecologists.

“The physicians I know really like things that are clear and crisp,” Dr. Fischbach said. “But like any ecosystem, the microbiome is not the kind of place to find simple answers.”

June 18, 2012

**Teacher With HIV Sues Calif. School for Wrongful Termination**

Matthew Edmondson, a gay middle school science teacher, has filed a lawsuit against The Pegasus School in Huntington Beach, California, for workplace discrimination and wrongful termination because he has HIV, according to a statement from Bisnar Chase Personal Injury Attorneys, LLP, which represents him. In October 2011, Edmondson changed his HIV medication, which caused adverse side effects and forced
him to take time off—but no more than his allotted 10 days during the 2011 to 2012 school year. The head of school and the director, who both knew of Edmonson’s side effects, allegedly waged a discrimination campaign. They forced him to sign a confidential agreement and release, which led to his leaving the school two days later. The lawsuit seeks compensatory and general damages for emotional distress and pain and suffering.

**HIV Superinfections Appear Common**
*Voice of America News*, (06.12.2012) Joe DeCapua

A new study in Uganda suggests that people infected with HIV can pick up a second strain more commonly than might be expected. However, other people with HIV who continue risky behavior apparently resist such superinfections, a difference scientists are hoping could prove useful to vaccine research.

“A superinfection occurs when an individual is initially infected with a strain or strains of HIV. And then at some point later on, after that person has developed an initial immune response to their first infecting strain, at that later time point they come into contact through risky behavior with a second viral strain and then are superinfected with that second strain,” said Dr. Andrew Redd, lead author of the study.

“What we found in our study was that when we looked at a general population of heterosexuals in Uganda, we found that it actually isn’t as rare as what we thought,” Redd said. “From what we can tell, individuals who get superinfected respond to treatment just fine, and it lowers their viral load and they get healthier.” Superinfection with a strain already antiretroviral-resistant “would be a major problem” but “doesn’t seem to be a huge risk so far,” he said.

Of people who are somehow protected against superinfection despite taking risks, “One question would be what natural immune response to their initial infection is protecting them from the superinfection,” said Redd. “And if we can figure that out, that may give us a very interesting avenue to pursue for HIV vaccine research.” Current vaccine strategies that attempt to “recreate the natural immune response may be insufficient to protect an individual from infection,” he said.


**Trainer’s Secret Is Too Big a Weight to Bear**
*News and Observer (Raleigh NC)*, (06.18.2012) Katelyn Ferral

Chapel Hill-based personal trainer Rob Hill is one of eight HIV-positive patients participating in an ongoing study at the University of North Carolina testing the use of a lymphoma drug to lure the virus out of hiding. The study’s first phase was a success; the second phase starts in August.

Hill is known by clients for his athleticism and discipline. Until recently, what most did not know was his personal struggle with heroin addiction and his HIV diagnosis. The path that Hill took to get off drugs and out of an unhealthy lifestyle also isolated him. He worried about what others would think if they knew.

Hill is sharing his story now as a way to help others in a similar situation, and to dispel the fears some may have about people with HIV. He hopes that by opening up, he can live like a “regular human being.”

Laurel Gropper, a Chapel Hill optometrist, and her husband, Carl Stice, are clients of Hill’s. They were among the first he told about his HIV infection. "I thought, ‘Oh my gosh, how strong a person to be able to live with this, to live with this kind of secret and endure the fear of what could be going on for him and his body [and decide] he was going to make a change,’” said Gropper. “I don’t know too many people that would have that much courage on all levels.”

June 19, 2012

**'Breast Best' Policy Challenged in South Africa**
by Darren Taylor

ZIDINDI, SOUTH AFRICA—In September last year, South Africa’s health minister Aaron Motsoaledi implemented a drastic and highly contentious measure.

He announced that the government would no longer provide a free six-month supply of formula milk to HIV-infected mothers. Instead, its health facilities would encourage the women to exclusively breastfeed for at least the first six months of their babies’ lives. That is, to give their infants nothing to eat or drink other than breast milk – not even water.
In a country with the most people infected with HIV in the world, Motsoaledi’s decision was controversial, because it’s the breast milk of HIV-positive mothers that contains the virus. Critics slammed the minister as irresponsible, saying his policy would place many babies at risk of getting HIV.

But doctors at a hospital in an isolated part of South Africa’s Eastern Cape province praised the minister’s action as brave and visionary and said it would ultimately result in many lives being saved.

In fact, Zithulele Hospital in Oliver Tambo District has advocated exclusive breastfeeding since 2006, in an area where one out of every four mothers is infected with HIV.

“These women worry that they’re going to give their babies HIV through their breast milk. And that is a risk; one has to acknowledge that,” said Dr. Ben Gaunt, Zithulele’s head doctor. But, he maintained, this risk is far lower than the chances of their infants eventually falling ill, or dying, of malnutrition, pneumonia or diarrhea.

Every year, thousands of South African children die of these preventable illnesses, which are exacerbated by poverty and inadequate public health services.

Breast milk contains a mother’s antibodies that ward off these sicknesses. But feeding babies younger than six months mixes of breast milk, formula feed, solid food and water makes them much more vulnerable to potentially fatal illnesses, including HIV, Gaunt insisted. Medical studies prove that babies who are mixed fed by HIV-infected mothers are up to five times more likely to contract the virus.

Doctors say the additional substances damage the sensitive lining of the infants’ intestines, which protects them against infection.

According to the Handbook of HIV Medicine, written by international HIV experts to guide doctors who are treating the condition, an infant fed formula is six times more likely to die of an infectious disease in the first two months of life than a baby who’s breastfed.

“Are some children going to get HIV because their HIV-positive mothers are breastfeeding them? Unfortunately, yes,” said Gaunt, while adding, “But the policy is going to save so many other young lives that it makes total sense to implement it.”

Three casualties
Gaunt’s wife, Taryn, is also a doctor at Zithulele Hospital and co-heads its pediatric HIV section. She said the clinic has seen only three babies who were born HIV-negative become HIV-positive while being breastfed in the past five years.

Her husband responded, “That’s distressing; it’s distressing for everyone. (But) that is public health policy; there are going to be people who don’t have an optimal outcome because of the choices that we’ve made. But we have to accept that for the vast majority of people, if they were to follow that (exclusive breastfeeding) policy the outcome will be better.”

However, none of the three youngsters who contracted HIV through breastfeeding at Zithulele were given Nevirapine. Medical researchers have found that if infected mothers breastfeed their babies exclusively for six months and give the infants a daily dose of this antiretroviral drug, the risk of them getting the virus reduces from about 20 percent to less than two percent.

It’s been government policy since April 2010 to provide HIV-infected mothers who are breastfeeding with Nevirapine. Another of the hospital’s doctors, Liz Gatley, said, “As far as I know we haven’t yet had a baby that’s become positive while breastfeeding (and taking) the Nevirapine syrup.”

Breastfeeding triumphs
When Gatley began working at Zithulele three years ago, she said she couldn’t find a single mother who was exclusively breastfeeding. But now she said the practice is common among women attending the hospital’s HIV clinic.

“I know it’s a bold thing to say but I would say 80 percent or more of those women, almost all of them are breastfeeding – exclusively breastfeeding.”

Dr. Taryn Gaunt maintained that this figure is closer to nine out of every 10 mothers who are now only giving breast milk to their infants for half a year, in conjunction with Nevirapine, mainly because they’re terrified of passing HIV on to their children.

Gatley agreed that fear of their kids getting infectious diseases is a “huge motivating factor” encouraging the women to solely breastfeed. “I asked one woman, ‘Why are you different? Why are you only giving your child milk from your breast?’ And she said she’d seen so many babies that weren’t breastfed die of something as simple as diarrhea,” she said.

Ben Gaunt and his colleagues meticulously explain the consequences of feeding children substances other than breast milk to mothers. Most other public hospitals in South Africa don’t offer this level of intensive, time consuming counseling. The result, said Gatley, is that many mothers in the country and
even in Oliver Tambo District continue to mix feed, opening their babies up to possibly life-threatening diseases.

**Mixed feeding common**

A study by South Africa’s Medical Research Council shows that mothers in the country rarely breastfeed exclusively. According to the report, only one out of 10 infants in South Africa is solely breastfed by three months of age; this decreases to only two percent of six-month-old babies.

This ensures that breastfeeding remains a dangerous practice for HIV-infected mothers, when they don’t do it exclusively. Then the possibility of their babies contracting HIV from them magnifies significantly.

The experience of the health workers of Zithulele in Oliver Tambo District supports this research.

“Almost all the women in this area can’t afford to formula feed. So they dilute the formula, they mix it with (porridge) which is not appropriate for a tiny baby. They sometimes give the babies flour and water. And those babies come in (to hospital) sick,” said Gatley.

Many babies she sees have severe malnutrition, and she said this is directly as a result of their not being breastfed. “They get really swollen and their skin starts peeling and those patients are usually quite sick. And they’ve reached the end of their ability to compensate,” explained Gatley.

Ben Gaunt lamented that mixed feeding starts extremely early in South Africa, with mothers feeding solid mixes to babies as young as three weeks.

“A three week old doesn’t have a gut that can handle solids. We hear about all kinds of horrible feeding practices—everything from women using teaspoons of flour to make the water look white because they can’t afford formula,” said Gaunt.

To make matters worse, babies are more often than not given water—water that in underdeveloped parts of South Africa is usually polluted.

“Every single water source here is contaminated, which isn’t a surprise because 80 percent of the people use the forest as a toilet. So once the rains come, it washes (feces) out into the rivers,” said Gaunt.

**A disaster**

Ncedisa Paul, a healthcare advisor working for the Philani NGO in Oliver Tambo District, praised Zithulele Hospital’s achievements in getting women who visit the facility to exclusively breastfeed.

But, she added, she sees a far different reality on the ground in the region.

“Almost all the mothers that I visit mix feed because of a lack of support and the stigma attached to HIV infection,” said Paul. She pointed out that word had in recent years spread around the area that exclusively breastfeeding is a “sure indication” that someone is HIV-positive.

“Those mothers are discriminated against in all sorts of horrible ways so they end up mix feeding their babies, to try to convince people that they’re not HIV-positive, or to keep their status secret. When this happens, they usually pass the HIV on to their babies. It’s a disaster here in this place,” Paul said.

**Status and advertising**

Another problem in the district and across South Africa, she added, is that feeding babies expensive formula milk is a powerful status symbol.

“The mothers think they are very grand if they feed their babies formula, and mothers who breastfeed are seen as low members of society. So you find many poor mothers going into heavy debt just to keep their babies supplied with formula,” said Paul.

She’s also convinced that intensive advertising campaigns by international companies manufacturing formula milk are seriously damaging South Africa’s efforts to get mothers to breastfeed.

“Mothers see the adverts for milk formula and on the company posters there are these photos of smiling, fat babies. The mothers see that fat child and immediately they think formula is best and they stop breastfeeding,” said Paul.

Yet despite the factors counting against the success of the exclusive breastfeeding policy in South Africa, Dr. Ben Gaunt remains optimistic.

“It’ll work,” he insisted. “It’ll work when we get all public hospitals on board to advocate it properly. It’ll eventually save many, many lives and we’ll reach a point where we’ll wonder why it wasn’t instituted two decades ago.”
Low-cost Australian HIV test to reach poor
17:03 AEST Wed Jun 20 2012
Michelle Henderson, AAP National Medical Writer

A crucial new low-cost blood test for HIV sufferers in developing countries that could help 33 million people worldwide may be available later this year.

The simple test developed by researchers at Melbourne's Burnet Institute shows how much damage the HIV virus has done to the immune system and whether lifesaving antiretroviral drugs are required.

The finger-prick blood test would ideally target developing African and Asian countries where laboratories and expensive equipment normally needed to carry out the tests are scarce, said Co-head of Burnet's Centre for Virology Professor Suzanne Crowe.

The CD4 test, which gives on-the-spot results in 40 minutes, measures an individual's CD4 levels, which indicate whether HIV is progressing to AIDS.

"It will tell the health worker if the person's immune system has declined to the level where they require treatment for HIV," said Prof Crowe, who developed the test with Burnet Institute deputy director Associate Professor David Anderson.

Prof Anderson said the device could provide cost-effective testing for up to 33 million patients worldwide.

Another CD4 test is currently available for developing countries but it is more expensive, requires medical equipment and trained health workers to extract blood from veins.

The new test will cost less than $2, which would probably be subsidised by governments or philanthropic organisations, and works a bit like a pregnancy test in terms of its immediacy, Prof Crowe said.

Currently, people in remote areas in developing countries may have to walk for days to reach a clinic for HIV tests, with results often taking weeks.

The individual would then need to return to the clinic for follow-up tests to determine if antiretroviral drugs are needed.

While antiretroviral drugs are available, in order to qualify people need a CD4 test to prove they have a weakened immune system.

"It's a catch-22 at the moment because often the drugs are available but the test to give them access to the treatment is too expensive or not available," Prof Crowe told AAP.

"This will be a test which circumvents all of that."

Prof Crowe said with same day test results, HIV sufferers could potentially start drug treatment on the same day.

The approach would prevent losing contact with people who failed to return for follow-up consultations—a major hurdle to people missing out on treatment at the right time, Prof Crowe said.

The new test, which was licensed for commercial development this week to Omega Diagnostics Group, can be carried out by a health worker without a laboratory.

It doesn't require medical equipment, electricity, batteries or refrigeration.

Prof Crowe said the test would hopefully be available by the end of 2012.

Aid agencies in Papua New Guinea, India and South Africa are likely to be the first to access the test.

HIV Frontlines: The Doctor Who Cured HIV
An Interview With Gero Hütter, M.D.
By Myles Helfand
From TheBodyPRO.com
June 19, 2012

This isn't another story about the "Berlin patient"—a.k.a. Timothy Brown, the first, and to date the only, man who's ever been considered "cured" of his HIV infection. His story has been told many times, in many ways, and in many publications—including ours, so there's no need to retell it.

By comparison, we've seen relatively little about the man who cured him: Gero Hütter, M.D., an oncologist in Berlin who was previously unknown in the HIV field. And with good reason: Until the Berlin patient, Hütter had never treated an HIV-infected cancer patient before, nor had he conducted any HIV-related research studies.

While in New York City for a speaking engagement, Dr. Hütter was kind enough to visit with us. Relaxed and mild-mannered, he discussed the Berlin patient's case—how he approached it, how he weighed the risks and the benefits, and what we've learned from the process. He also shared his thoughts
on how the case transformed his career, and on what needs to happen for the HIV/AIDS medical community to repeat the Berlin patient's success and yield a second "cured" patient (and a third, and a fourth, and ...).

**Table of Contents**

- The Makings of a Miracle
- The Evolution of a Cancer Doctor
- Looking Toward the Future

**The Makings of a Miracle**

Explain to me how a clinician who is trained as a hematologist and a cancer researcher ends up being the guy who changes the way we think about the approach to an eventual cure for HIV.

[Laughs] This is what I always want for my patients: I want the best treatment. This was a challenge, from when I saw Timothy and I realized that we have to do this transplantation. For me, it was the first patient with HIV which received **allogeneic transplantation**.

We know from patients with leukemia that eradication is achievable. And we cannot accept, in patients with leukemia, that any of these leukemia cells will survive, because they are the basis of any relapse of leukemia. So you have to cure these patients and get rid of the leukemia. And if this works with leukemia, why shouldn't it work with HIV?

**You make it sound like it's such a natural, logical conclusion. But we've known about this mutation—that people whose CD4 cells don't have the CCR5 receptor are largely immune to most forms of HIV—we've known this since the mid-to-late '90s. Yet nobody had thought to try this before.**

That's not quite correct. There are several others who had this idea before me. And they had made approaches to realize that. For example: the StemCyte [Cord Blood Bank] built up cord blood units, with tested cord blood units for the CCR5 mutation in 2001.

The gene therapy approaches targeting CCR5, they are older than the Timothy Brown case. But this case has supported their work. The techniques were available, and the idea was available, but it needed something that enhances the whole development.

After the Timothy Brown case was published, the funding and the support for such new approaches were opened, and now the development has come much more quickly and rapidly.

**When you first thought to do this, this was a shot in the dark, right? Timothy's prognosis was pretty grim. No one had actually attempted this type of treatment before. Did you think, "Might as well give it a shot"?**

Yeah. I would have felt better if I had tested it before. [Laughs] I knew it was probably possible. It's not easy to test the same condition in animals, but you could see some effects in animals.

In this case, it was clearly a shot in the dark. I studied the literature. I looked in PubMed, up and down, to see if there was anything published on this point: What happens if a patient who is HIV infected changes the CCR5 phenotype? And I found absolutely nothing. It's never been tested before, not even in vitro.

This was very surprising. It could be that no one really thought about this possibility. And the other explanation could be that they have tested it, it's gone wrong and no one got published. I was a little bit nervous about this point.

We were a little bit scared that we didn't really know what could happen: You have high selective pressure against the virus, when we changed this immune system to CCR5 depleted cells, and no one really could say how the virus would behave.

[But then we realized that] the worst thing would be that he changes his tropism to the CXCR4 receptor, and then as long as he takes his antiretroviral medication, there's no harm for the patient. So we got optimistic that we could dare this experiment and that the risks are not too, too big.

**I think it's easy for a lot of us to grasp on to this and say, "Here is the cure. Here is the future. Here is where it's going to happen." I'm guessing you've heard this kind of question a lot: "Is this the path forward?"**

Yeah. If you look at the HIV research, we have no better answers for cure questions than what we have now with the CCR5 receptor, gene therapy. We have approaches in targeting, unmasking and killing, specifically, reservoir cells. But they are all connected with the cure question.
And the cure question, 10 or 5 years ago, was no real question. If someone said to you, "I want to cure HIV," all you'd have to say is, "You're mad. This is not possible. This is a retrovirus which degrades, and you can't get rid of the genomic material." This was the dogma of this case.

The way of thinking about cure has changed a little bit. This makes the process open for alternatives to the current antiretroviral therapy—it does not have to be only the stem cell approach. There are other approaches derived from this case, which are also promising.

**We've known for a while that the CCR5 receptor is the primary way through which HIV enters a CD4 cell. But there's still so much that we don't really know about the CCR5 receptor. How much have we learned over the past few years?**

Very little. We know that the CCR5 deletion is much older than HIV, and the mutation appeared thousands of years ago. The distribution, what we see now—in Europeans, this deletion is high; in Africans and Asians it is absent—this is a distribution which happened in the last 10,000 years. There must be some kind of advantage for these carriers, and we don't know all the reasons why.

We don't know exactly the function of CCR5. We know that it probably plays a role in another infection, the West Nile virus infection. But all of the details are very unclear. There are some studies focusing on carriers of the CCR5 deletion, and whether they have high risk of any other disease. But these associations are very weak; there's no clear association of any disease with the deletion.

**Why hasn't there been a Patient No. 2 yet?**

We have had requests from other institutions—taken together, I think we have now 15 other patients with HIV in need of urgent transplantation, because of leukemia, lymphoma, and so on. And some of them had just one [potential donor match]. Who gets that donor that was tested and was CCR5 negative?

Some had many potential donors—60, 120, such as Timothy had—but sometimes mathematics fail. And the probabilities [of success] are 1 percent.

So this is a problem. I think it's a question of time. If you wait long enough, you will find a patient who will have the same conditions like Timothy.

The other point is that we don't have access to every patient who has the possibility to do this. There are many more patients with HIV who get transplants by allogeneic transplantation than we get information about. Because some institutions didn't really know about [the Timothy Brown] case. Some knew about this case and said, "Oh, this is so uncommon, this mutation; it doesn't make sense to test for it." They didn't start with it. If you don't start with the investigation, you will never find a second patient.

This is the biggest problem, I think: We have information about less than 5 percent of all these patients who get transplantation. If we have access to all of these and test them, the probability is much more higher to find a second patient.

**Is this a uniquely European thing that you did? Could what you did with Timothy Brown not have been done anywhere else?**

No: They tried it, too, in the U.S. But the circumstances are not like in Europe, or especially not Germany. We have in Germany a unique situation: We have 80 million Germans, and 3.5 million of them are registered in donor registries. It's very high. It's the highest proportion in the whole world.

**Do you know how that compares to the U.S.?**

You have 7 to 8 million in the U.S. But the difference, the second difference, is: These 8 million in the U.S. are derived from hundreds of stem cell registries. Every county, every state, every hospital, every institution has its own registry. And in Germany we have a central registry for all of these. So it's much easier to assess these registered donors.

That's also the reason why it works so well. You can do this in any country, but it works so well [in Germany] because we have this central registry, with a large number of registered donors. This was part of the success.

**The Evolution of a Cancer Doctor**

**How many HIV-positive cancer patients had you treated before you met Timothy?**

None.

**Was he the first HIV-positive patient that you had interacted with?**

No. I've seen many HIV patients, through my students and sometimes my medical training. But most HIV/cancer patients, they are old patients or they are in other departments with specialized HIV treatment. It's uncommon that an HIV patient would come to our department. It's only the case if they have diseases like leukemia or aggressive lymphoma, which cannot be treated by other institutions.

**The bulk of your practice and the bulk of your research: Where had that been focused on, up until 2006?**

My research focus was on leukemias, on resistance against chemotherapy and stem cell treatment.
Had that always been your passion? Or is that something that developed out of your education?
It has a little bit development, but I started with my scientific area with my doctoral thesis. It was based on resistant phenomena against chemotherapy.

How much of your clinical and research focus has continued to be on chemotherapy resistance since news of Timothy Brown broke?
Now I'm not working clinically anymore. I changed my position to an institution which specially is for collecting and producing stem cell products or other blood-derived products. This is not clinical work. A great part of my work is now research.

Is it research on how stem cells can be used to treat all diseases, or does it focus specifically on HIV?
It's for other diseases. But part of this research project is how to use it in the case of HIV, yes.

What kind of research have you been able to do?
We have focused on the molecular things which are associated with the CCR5 deletion. Because not everything is quite clear about this deletion—why some effects are also measurable in the transplantation setting. We know that people who have this deletion, the CCR5 deletion, they have better survival if they receive kidney grafts, after kidney transplantation. Normally, transplantation of the kidney has a survival rate of 5 to 10 years. People who have this mutation, their kidney will not be rejected.

So CCR5 deletion is part of this effect in nature. We have other immune system phenomena which have not really described what's behind this phenomenon.

Where is your research focused right now?
Our stem cell unit is focused on treating this population of hematopoietic stem cells for hematological patients. But we have also done research on mesenchymal stem cells, which can be used for regenerative medicine. This whole stem cell area is covered from our institution.

Is regenerative medicine the idea that, if you lose a finger, it can grow back the finger? Or is that a little far-fetched?
I think this is not going to be in the next few decades. It probably is not possible. But you can replace part of tissues if you have injuries, or loss of some special tissues. Or you can rebuild a heart muscle, with mesenchymal stem cells. These cover small areas of possibility; it's very hard to rebuild whole organs, or limbs. This is science fiction, I think.

But if you’re an HIV/HCV-coinfected person, and you're cirrhotic, is there a potential that down the road this kind of research can lead to some liver regeneration?
Probably. I don’t know—I wouldn't exclude this possibility.

Looking Toward the Future
Before you came here this morning, you gave a talk at St. Luke's-Roosevelt Hospital Center. What was it about?
I covered the Berlin patient story: what things we already know from the results; what is unclear and what is not detected; what are the consequences of the case; and how we can go on with this approach.

How many of these talks have you given over the past few years?
[Laughs] Oh, many. I like the idea of promoting the CCR5 story. Many people have heard of it, or read. But I think there are some details which are still [not known] for many people who didn’t read it very carefully and have [ideas] of this case which are not quite true. So it's probably good to remember, then, what are the facts, and what we can learn from this case.

In addition to not knowing the details of the Berlin patient case, you mentioned earlier that some medical institutions don’t think to test allogenic transplant donors to see if they have the CCR5 deletion. Is that one of the reasons that you’ve been speaking—to try to increase that level of education and communication?
Yeah. I want to promote the fact that we can do this testing for free [at our institution]. Someone will say, “Oh, no. Don’t do this testing; it will cost us too much.”

I say, “No. It doesn’t cost anything. I will cover all the costs.” But they are always unsatisfied. Some say, ”Yeah, we have such a patient. But we want to do this testing alone. We don’t need your help.”

They have made, here in the U.S., a trial for patients where they specifically look for CCR5-deleted cells, and for a few patients with leukemia and so on. It’s an NIH [U.S. National Institutes of Health] trial. And all of [the people involved in] this study hadn't made contact with me. I found out about it from their presentation at CROI that they started it.
So you just hope that you make the connections and that ultimately it will start to come together.
I'm hoping for everything. I support every work which is in this direction. So, go on, if you have patients. This transcript was edited for clarity. Special thanks to Terri Wilder, the director of HIV/AIDS education and training at the Center for Comprehensive Care at St. Luke's-Roosevelt Hospital Center, for arranging and facilitating this interview.

Nobel fight over African HIV centre
Laureates question choice of interim scientific director.
19 June 2012
A fledgling AIDS research centre in Cameroon, already struggling to find a scientific leader, is now facing insurrection from an unlikely quarter: a group of 35 Nobel prizewinners.

The laureates are calling for the centre's interim scientific director, fellow prizewinner Luc Montagnier, to be removed from the part-time post. Observers say that unless the leadership crisis is resolved quickly and decisively, it could harm the prospects of the Chantal Biya International Reference Centre (CIRCB) in Yaoundé.

The centre has a comprehensive AIDS research and health-care programme, in particular testing and treating newborn babies to reduce maternal transmission of HIV. It is the only research institution in central Africa with the technology and expertise to monitor people with HIV thoroughly, and one of the few African sources of hard data about the spread of the disease. It has an annual budget of about US$1 million, an array of international collaborations and around 20 local staff members, most of whom trained abroad.

Nature has learned that the Nobel laureates wrote on 9 June to Paul Biya, president of Cameroon, asking him to reconsider Montagnier's appointment. Montagnier, head of the World Foundation for AIDS Research and Prevention in Paris, shared the 2008 Nobel Prize in Physiology or Medicine for discovering HIV.

The laureates argue that his embrace of theories that are far from the scientific mainstream, as well as what they claim are anti-vaccination views, risk hurting the CIRCB's research, health-care programme and reputation. Montagnier has suggested, for example, that water can retain a 'memory' of pathogens that are no longer present; that the DNA sequences of pathogens emit electromagnetic waves that could be used to diagnose disease; and that stimulating the immune system with antioxidants and nutritional supplements may help people to fight off AIDS.

High-profile opposition
The letter was coordinated by Richard Roberts, a Nobel-prizewinning molecular biologist and chief scientific officer of New England Biolabs in Ipswich, Massachusetts, who also wrote personally to Biya on 4 June, to resign from the CIRCB's scientific board. Roberts says he is concerned that Montagnier plans to pursue his unorthodox research at the centre. Several other board members have also resigned.

Robert Gallo, head of the Institute of Human Virology at the University of Maryland, Baltimore, who had battled with Montagnier over which of them had discovered HIV, has also entered the fray. On 4 June, Gallo wrote to Biya expressing concerns similar to those of the Nobel laureates and informing Biya that his institute, a founding sponsor of the CIRCB, was immediately severing its links with the centre.

Montagnier deplores what he describes as "ad hominem attacks" and "plain lies", and says that there is an "ignominious campaign" against him and his group. He says that history is full of pioneers whose ideas were at first given a chilly reception by a conservative research community. "I believe this is happening again to me, and it is very sad that it involves Nobel Prize laureates attacking a fellow laureate," he says.

The last straw for Montagnier’s critics seems to have been his appearance in May alongside vaccine sceptics at a conference in Chicago, Illinois, organized by US patient-advocacy groups AutismOne and Generation Rescue. Montagnier’s talk, on his hypothesis that bacterial infections may be one of many causes of autism spectrum disorder, states: “There is in the blood of most autistic children — but not in healthy children — DNA sequences that emit, in certain conditions, electromagnetic waves.”

Montagnier defends his research, pointing out that some clinicians have observed improvements in symptoms of autism after long-term treatment with antibiotics. He says that he has never argued that vaccination could cause autism. “Many parents have observed a temporal association, which does not mean causation, between a vaccination and the appearance of autism symptoms,” he says. “Presumably
vaccination, especially against multiple antigens, could be a trigger of a pre-existing pathological situation in some children.”

**Leadership crisis**

The CIRCB, founded in 2006, is named after President Biya’s wife, who has championed efforts to fight AIDS in Africa. Montagnier’s AIDS foundation was a founding partner; Montagnier is also president of the now-defunct scientific advisory board, and vice-president of the management board.

The current crisis compounds problems caused by the centre’s lack of stable full-time leadership. In March, its management committee appointed Montagnier to replace former interim scientific director Vittorio Colizzi, an AIDS researcher on secondment from the Tor Vergata University in Rome, who had held the post since 2009. Colizzi was standing in until a full-time scientific director could be hired, but a recruitment process last year failed to settle on an agreed candidate. Some candidates had also expressed misgivings about the job, because at the time the scientific director and administrative director had to share power, a situation that caused tensions, says Colizzi. To address this issue, a presidential decree issued on 31 May merged the positions to create the post of permanent director, with full control of the centre. The move should make it much easier to attract a leading scientist to the post, says Jacques Theze, an immunologist at the Pasteur Institute in Paris, a former member of the CIRCB’s scientific board.

The decree also required that many of the centre’s posts and committees be disbanded or renewed, creating an uncertain transitional period. On the day that Roberts resigned, for example, the scientific board was officially dissolved, and no clear timetable has been set to reestablish it. Colizzi is concerned that this deprives the centre of its main mechanism for enforcing rigorous peer-review and ethical oversight of research proposals. Montagnier says that he intends to continue all research previously approved by the board, and that he will ask the next board to review the programme. He also plans to embark on new research, including a “key project” using his electromagnetic-wave theory to detect reservoirs of HIV in the body that persist after antiretroviral treatment. Any new projects, including his own, will need to be approved by the centre’s science board and ethics committee, he says.

Jean Stéphane Biatcha, head of the centre’s management board and a presidential adviser, recognizes the “very serious disagreement” but says that the president and the Ministry of Health will quickly enact the 31 May decree, and so will renew the scientific advisory board and begin the search for a permanent director.

Theze says that he would have preferred Montagnier’s detractors to have taken a more diplomatic approach, and warns that the high-level criticism, and the resulting controversy, risks tarnishing the credibility and reputation of the centre, which he says is unfair, because the CIRCB has enormous potential. He worries that the episode might also discourage scientists from applying for the position of director.

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486, 301–302
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doi:10.1038/486301a

**References**

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Sixty-one Zimbabwean lawmakers have volunteered to undergo public HIV testing and counseling on June 22 to raise public awareness of the disease and fight stigma. Twenty-eight male legislators also will undergo circumcision, which research has shown reduces men’s risk of contracting HIV through sex.

“We want to inspire the people that we represent,” said lawmaker Blessing Chebundo, chair of the Zimbabwe Parliamentarians Against HIV/AIDS, which formed in March.

Chebundo explained that the lawmakers will not be obliged to publicize their HIV test results. While members of the public and AIDS advocates applaud the move by the lawmakers, some say not revealing their HIV results weakens the outreach.

Sipho Mahlangu, of the Zimbabwe National Network of People Living with HIV/AIDS, said: “It’s a welcome development, but we expect one or two, or all of them to come out in the open and share their results. This will be the basis of their advocacy to create greater awareness.”

“The point is never to publicize one’s results,” Chebundo responded. “The point is for people to be able to know their status and act responsibly. And when the nation as a whole knows the level of infection, we are then able to make proper arrangements in terms of prevention.”

Zimbabwe has seen a steady decline in HIV prevalence over the past ten years due to heightened public awareness and fear of infection, according to a survey published in February 2011 by the US journal PLoS Medicine. In addition, experts say increased condom use and steady supplies of HIV drugs from donor agencies have played a vital role.

**Haley Vetoes Bill Providing Access to HPV Vaccine**

*Associated Press*, (06.19.2012)

A bill that would have allowed South Carolina’s public health agency to provide information on and free access to a vaccine that protects against human papillomavirus has been vetoed by Gov. Nikki Haley. The measure called for the parents of sixth-graders to be provided with a brochure on HPV, the STD that causes most cases of cervical cancer. Parents of seventh-graders would have had the option of having their children vaccinated. Both the brochure and the shots were dependent upon funding being provided. Haley said the funding provision meant the bill did nothing, and that the legislation represented a suspended unfunded mandate. She also said she does not want the government distributing information on a vaccine that parents should discuss with their family physician. Rep. Bakari Sellers, who sponsored the bill, said the governor is putting politics ahead of women’s health.

**Drug combo much better than AZT alone at preventing mother-to-infant HIV transmission**

Non-breastfed babies born to HIV-positive mothers who didn’t receive antiretroviral therapy during pregnancy are routinely given zidovudine, commonly known as AZT, shortly after birth to prevent mother-to-child transmission of the virus that causes AIDS.

While effective, this strategy doesn't always protect the infant from acquiring the virus during the mother's labor and delivery. But a new UCLA-led study published June 21 in the *New England Journal of Medicine* finds that a two- or three-drug combination given to infants within 48 hours of birth can reduce the risk of such intrapartum HIV acquisition by about half, compared to AZT alone.

“Our research demonstrates that even in very high-risk situations where mothers are only identified as being HIV-positive when they give birth or shortly after birth, there is still an effective strategy that can be undertaken to prevent transmission of HIV to the baby,” said Dr. Karin Nielsen-Saines, a professor of pediatric infectious diseases at the David Geffen School of Medicine at UCLA and the study’s lead investigator. "While giving AZT alone to the infant can reduce intrapartum transmission to some degree, our data demonstrates that with the use of two- or three-drug regimens to the baby, you can cut transmission to half of what can be achieved with AZT alone."

The study is the first randomized controlled study of post-exposure HIV prophylaxis for babies born in countries where the standard of care is to give the child AZT to prevent infection, said Nielsen-Saines, who is also a member of the UCLA AIDS Institute. Babies born to HIV-infected mothers who have not received antiretroviral therapy (ART) stand a 25 percent chance of becoming infected during the mother's pregnancy or at birth. Their chances increase to about 40 percent when they are breastfed, which is why HIV-positive women are advised not to breastfeed in many countries.

The study involved 1,684 formula-fed infants born to HIV-positive mothers in the United States, Brazil, Argentina and South Africa. Within 48 hours of birth, researchers assigned the newborns to one of
three groups: 566 were placed in the AZT-alone group; 562 in AZT plus nevirapine group; and 556 in a group receiving AZT, nelfinavir and lamivudine.

Of the 1,684 infants, 140 were found to be infected with HIV — 97 were born with the infection (transmission occurred during pregnancy) and 43 were infected during the birth process.

Among the babies who became infected during the birth process, 24 in the AZT-alone group were found to be infected at 3 months of age, compared with 11 in the AZT/nevirapine group and 12 in the AZT/nelfinavir/lamivudine group. Using Kaplan–Meier statistics, this translated into a transmission of 4.8 percent in the AZT-alone group, 2.2 percent in the two-drug group and 2.4 percent in the three-drug group. (Kaplan–Meier estimates incorporate survival probabilities, time in follow-up and other factors.)

Therefore, giving two or three drugs to babies born to mothers who had received no HIV treatment significantly reduced HIV transmission, compared with AZT alone.

The researchers also found that the two-drug therapy was less toxic to the infants than the three-drug alternative.

Nielsen-Saines noted that the findings are applicable only to high-risk infants — those whose mothers didn't receive antiretroviral therapy during pregnancy. Babies born to HIV-positive women who are being effectively treated with antiretrovirals throughout pregnancy already have a less than 1 percent chance of acquiring HIV from their mothers.

"Our results support combination ART regimens instead of zidovudine alone for prophylaxis in the infants of mothers who have not received antenatal ART," the researchers write. "Ease of use, reduced toxicity, availability, and low cost suggest that zidovudine plus nevirapine is an attractive option for prophylaxis in infants at high risk for perinatal HIV-1 infection."

Children Exposed to HIV in the Womb at Increased Risk for Hearing Loss
ScienceDaily (June 20, 2012) — Children exposed to HIV in the womb may be more likely to experience hearing loss by age 16 than are their unexposed peers, according to scientists in a National Institutes of Health research network.

The researchers estimated that hearing loss affects 9 to 15 percent of HIV-infected children and 5 to 8 percent of children who did not have HIV at birth but whose mothers had HIV infection during pregnancy. Study participants ranged from 7 to 16 years old.

The researchers defined hearing loss as the level at which sounds could be detected, when averaged over four frequencies important for speech understanding (500, 1000, 2000, and 4000 Hertz), that was 20 decibels or higher than the normal hearing level for adolescents or young adults in either ear.

"Children exposed to HIV before birth are at higher risk for hearing difficulty, and it's important for them—and the health providers who care for them—to be aware of this," said George K. Siberry, M.D., of the Pediatric, Adolescent, and Maternal AIDS Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the NIH institute that leads the research network.

The study was published online in The Pediatric Infectious Disease Journal.

Compared to national averages for other children their age, children with HIV infection were about 200 to 300 percent more likely to have a hearing loss. Children whose mothers had HIV during pregnancy but who themselves were born without HIV were 20 percent more likely than to have hearing loss.

"If parents and teachers know the child has a hearing problem, then they may take measures to compensate in various communication settings, such as placement in the front of the classroom or avoiding noisy settings," explained Howard Hoffman, M.A., director of the Epidemiology and Statistics Program at the National Institute on Deafness and Other Communication Disorders (NIDCD), which provides funding to the network for studies related to hearing and language.

Even a mild hearing loss in children can delay the acquisition of language skills. More severe hearing loss may require the use of assistive devices, such as a hearing aid. Information on hearing and deafness is available from NIDCD.

To determine the types of hearing loss the children experienced, the researchers conducted these evaluations:

- Physical examination of the ear canal
- Evaluation of the middle ear function, how sound vibrations are transmitted through the middle ear bones
- Responses to tones presented over earphones

Hearing loss may occur from damage to the bones and structures in the ear canal and inner ear, or from damage to the nerves leading to the brain.
First author Peter Torre III, Ph.D., of San Diego State University, led the study with Hoffman, Siberry and six other coauthors. Collaborators were from the Harvard School of Public Health, Boston; the University of Kansas, Lawrence; and Tulane University School of Medicine, New Orleans. The research was conducted as part of the Pediatric HIV/AIDS Cohort Study network, led by NICHD in cooperation with and with cofunding from NIDCD and several other NIH institutes, including: the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Heart Lung and Blood Institute, and the National Institute on Alcohol Abuse and Alcoholism.

More than 200 children and teenagers participated. All had been exposed to HIV before birth, and about 60 percent were HIV-positive at the time of the study. Researchers conducted hearing tests on the children if their parents or caregivers had reported hearing problems, they had low scores on a standard test of language or their health care providers detected hearing problems during standard hearing screenings.

The researchers classified participants who could not hear tones below a certain volume as having hearing loss with difficulties in quiet and noisy settings. The researchers documented a greater proportion of hearing loss cases among HIV-positive children and found that those who had developed AIDS at any point were even more likely to have hearing loss—even if the disease was under control at the time of the study.

Earlier studies have found that children with HIV are susceptible to middle ear infections. Repeated middle ear infections can cause hearing loss. However, in 60 percent of cases in the study, hearing loss was the result of problems with the transmission of sound from the nerves of the ear to the brain, rather than to damage in the middle ear resulting from ear infections.

"Although ear infections are more common among children with HIV, these do not appear to be the reason their hearing is more likely to be compromised," said Torre. Previously found that vitamin D supplements might help protect the bones of people taking the anti-HIV drug tenofovir.

**Journal Reference:**
Peter Torre, Bret Zeldow, Howard J. Hoffman, Ashley Buchanan, George K. Siberry, Mabel Rice, Patricia A. Sirois, Paige L. Williams. Hearing Loss in Perinatally Human Immunodeficiency Virus-Infected and Human Immunodeficiency Virus-Exposed but Uninfected Children and Adolescents. The Pediatric Infectious Disease Journal, 2012; DOI: 10.1097/INF.0b013e31825b9524

**Chicago Woman Cured of Sickle Cell Disease****

ScienceDaily (June 18, 2012) — Chicagoan Ieshea Thomas is the first Midwest patient to receive a successful stem cell transplant to cure her sickle cell disease without chemotherapy in preparation for the transplant.

University of Illinois Hospital & Health Sciences System physicians performed the procedure using medication to suppress her immune system and one small dose of total body radiation right before the transplant.

The transplant technique is relatively uncommon and is a much more tolerable treatment for patients with aggressive sickle cell disease who often have underlying organ disease and other complications, says Dr. Damiano Rondelli, professor of medicine at UIC, who performed Thomas's transplant.

The procedure initially allows a patient’s own bone marrow to coexist with that of the donor. Since the patient’s bone marrow is not completely destroyed by chemotherapy or radiation prior to transplant, part of the immune defense survives, lessening the risk of infection. The goal is for the transplanted stem cells to gradually take over the bone marrow’s role to produce red blood cells—normal, healthy ones.

Thomas, 33, had her first sickle cell crisis when she was just 8 months old. Her disease became progressively worse as an adult, particularly after the birth of her daughter. She has spent most of her adult life in and out of hospitals with severe pain and has relied on repeated red blood cell transfusions. Her sickle cell disease also caused bone damage requiring two hip replacements.

"I just want to be at home with my daughter every day and every night," said Thomas, who depends on family to help care for her daughter during her frequent hospitalizations.

This type of stem cell transplant is only possible for patients who have a healthy sibling who is a compatible donor.

Thomas’ sister was a match and agreed to donate blood stem cells through a process called leukapheresis. Several days prior to leukapheresis, Thomas’ sister was given drugs to increase the number
of stem cells released into the bloodstream. Her blood was then processed through a machine that collects white cells, including stem cells. The stem cells were frozen until the transplant.

Last Nov. 23, four bags of frozen stem cells were delivered to the hospital’s blood and marrow transplant unit. One by one, the bags were thawed and hung on an IV pole for infusion into Thomas. The procedure took approximately one hour. Her 13-year-old daughter, Miayatha, was at her bedside.

Six months after the transplant, Thomas is cured of sickle cell disease and no longer requires blood transfusions.

"The donor cells have taken over completely, and blood tests show no sickle cell disease," said Rondelli, director of the blood and marrow transplant program at UI Hospital. Thomas continues to take medication to prevent rejection of the donor stem cells.

About 25 adults have received a similar chemotherapy-free stem cell transplant for sickle cell disease in recent years at the National Institutes of Health in Bethesda, Md. Approximately 85 percent have been cured.

"Sickle cell disease is devastating—both emotionally and physically," said Dr. Dennis Levinson, a private rheumatologist in Chicago and clinical associate professor of medicine at UIC, who has taken care of Thomas for the past 16 years. "I’ve been terribly frustrated with Ieshea’s disease over the years, and I’ve cared for many other sickle cell patients who have died."

Levinson says the stem cell transplant provides new hope for patients who often live day-to-day on painkillers and who are often misunderstood by clinicians. As the former chief of medicine at the now closed Michael Reese Hospital, he said he has cared for many patients with sickle cell anemia and was determined to seek out the best treatment option for Thomas.

Sickle cell disease primarily affects people of African descent. It is an inherited defect of the red blood cells that causes them to be shaped like a crescent, or sickle. These abnormal cells deliver less oxygen to the body’s tissues and can result in severe pain, stroke and organ damage.

Approximately one in every 500 African Americans born in the U.S. has sickle cell disease. The disease affects 80,000 Americans of different ethnic backgrounds.

**Crucial Immune Fighter Role of STING Protein Revealed**

ScienceDaily (June 18, 2012) — Researchers at Weill Cornell Medical College have unlocked the structure of a key protein that, when sensing certain viruses and bacteria, triggers the body’s immediate immune response.

In the journal *Molecular Cell*, scientists describe the double wing-like crystal structure of this key protein, known as STING, which is a soldier on the front-line of the body’s defense against pathogens. Researchers also show STING in action, displaying evidence of a bacterial infection—an action that launches the body’s innate immune response.

"Activation of STING is crucial to the ability of the human body to pick out bits of molecules secreted by pathogens, including many different viruses and bacteria, and alert the human body that they are there. By solving the structure of this protein, we now know how they do this crucial task," says the study’s lead author, Dr. Qian Yin, a postdoctoral associate in the laboratory of Dr. Hao Wu, professor of Biochemistry at Weill Cornell Medical College.

"The STING structure provides a remarkable example of the pathogen-host interactions in which a unique microbial molecule directly engages the innate immune system," says Dr. Wu, the study’s senior investigator and director of the Lab of Cell Signaling at Weill Cornell.

While the findings have no immediate clinical significance, they might be useful in helping to make vaccines against pathogens more effective. "Based on the structure we have of STING interacting with molecules secreted from bacteria, we may be able to design new molecules that induce a stronger, more persistent immune response," says Dr. Yin.

**STING’s wings and tail respond to invaders**

All plant and animal life use an innate immune response to recognize and respond to an assault by pathogens. This primitive response is immediate, but not long-lasting or protective; the secondary, adaptive immune response sets up the long-term defense.

Previously, scientists thought the innate response was generic, but recently, investigators uncovered proteins expressed by cells of the innate immune system that identify specific molecular patterns linked to microbial pathogens. STING was recently identified as a member of a family of proteins that is involved in this pattern recognition task. It is specifically tasked at finding viruses that have double-stranded DNA genomes, and with locating bacteria.
While STING does not confront viruses or viral molecules directly, with bacteria, STING is on the lookout for small molecules that bacteria use to communicate within their cellular bodies. These molecules are cyclic-di-GMP, produced by most bacteria, and cyclic-di-AMP, used by bacteria that grow inside the cells of a host.

However STING is activated, the end result is the same, Dr. Yin says. STING induces a response from interferon, which activates other immune cells that kill the invading parasites.

The crystal structure of STING developed by the research team explains the overall structure of the protein. The second structure of STING, bound to cyclic-di-GMP, explains how the protein can recognize and pick up both cyclic-di-GMP and cyclic-di-AMP. This and other published data suggests how STING activates an immune response.

Dr. Yin describes STING's structure as two wings, which form the bottom and sides that hold cyclic-di-GMP. "It is like two people holding out their left or right hands, wrists joining and palms facing each other, and holding something in their palms."

"The amazing thing is STING only binds to cyclic-di-GMP and, to a lesser degree, cyclic-di-AMP, leaving all other nucleotides in the human body quite safe—meaning it is not picking up natural human molecules," she says. "To use the hands analogy again, only cyclic-di-GMP and cyclic-di-AMP can fit into the space between the two hands. Other nucleotides are too small and they will slip."

The researchers also propose that once STING's wings picks up cyclic-di-GMP, the molecule frees up the tail of STING's protein? which then engages with other proteins.

"We believe this movement of the tail section of the protein is the switch that turns on the interferon response," says Dr. Yin.

"This work has uncovered a number of unexpected insights into how STING works," says Dr. Wu. "By binding tightly only to tiny molecules produced by bacteria, which then turns on the interferon switch, it prevents the immune system from attacking the body's own cells."

**Journal Reference:**
Qian Yin, Yuan Tian, Venkataraman Kabaleeswaran, Xiaomo Jiang, Daqi Tu, Michael J. Eck, Zhijian J. Chen, Hao Wu. Cyclic di-GMP Sensing via the Innate Immune Signaling Protein STING. *Molecular Cell*, 2012; DOI: 10.1016/j.molcel.2012.05.029

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**Factors Associated with Uptake of Infant Male Circumcision for HIV Prevention in Western Kenya**

*Pediatrics* [doi:10.1542/peds.2011-2290](https://doi.org/10.1542/peds.2011-2290), (06.18.2012) Marisa R. Young, BA; and others

Three randomized trials have shown male circumcision decreases female-to-male HIV incidence by 60 percent. The study authors note that this research in sub-Saharan Africa has centered on adolescents and adults. Modeling suggests the cost-effectiveness of infant male circumcision in high to moderate seroprevalent regions. The authors examined parental decision-making and differences in characteristics of parents in western Kenya accepting or declining IMC services.

In 2010, the case-control study was conducted at five government hospitals in Nyanza province. Mothers and fathers accepting IMC comprised the cases, while controls were parents who declined such services. A 41-question survey was administered.

The study enrolled 627 mothers and 493 fathers. Multivariable logistic regression modeling showed factors associated with mothers accepting IMC were: father circumcised (odds ratio=2.30, *P*<.001) and agreement with father about IMC decision (OR=4.38, *P*<.001). Among fathers, factors associated with accepting IMC were: being circumcised (OR=1.77; *P*=.016) and agreement with mother about IMC (OR=11.0, *P*<.001). In most instances (66 percent), fathers were the primary decision-makers. Just 3 percent of parents said they would prefer a future son to remain uncircumcised.

“Fathers are important in the IMC decision-making process,” the authors concluded. “Fathers, as well as mothers, should be targeted for optimal scale-up of IMC services. Circumcision programs should offer services for males of all ages, as male circumcision at some age is highly acceptable to both men and women.”

**Boulder Firm Giving Condoms to Haitians**

*Denver Post*, (06.19.2012) John Mossman

Boulder-based Sir Richard’s Condom Co. has vowed to match each condom sale with a condom donation in order to combat HIV, STDS, and unintended pregnancies in developing nations. The first giveaway of 500,000 condoms is underway in Haiti.
Sir Richard’s is working with Boston-based Partners in Health, which has been active in Haiti since 1987. PIH is building a new hospital in Mirebalais, 30 miles north of Port-au-Prince, to help replace medical facilities damaged by the 2010 earthquake.

“PIH is deeply grateful for Sir Richard’s partnership in this mission,” said Christopher Hamon, who works for the nonprofit. “Reinforcing the importance of condom use and ensuring that condoms are available and accessible is key to our battle against the spread of HIV/AIDS.”

Sir Richard’s CEO Jim Moscou said the condoms will feature Haitian Creole-style packaging and will be delivered soon from the company’s manufacturing plant in Malaysia. “There is a huge global shortage of condoms,” Moscou explained. “We’re using the power of business for social good. Will we lose a few dollars? Yes. But that’s our commitment as a company.” Moscou hopes to do the giveaways twice a year. Beyond Haiti, Moscou sees potential partnerships and giveaways in Thailand and Uganda.

The World Health Organization estimates that less than 17 percent of contraceptive needs are met in developing countries today. Unwanted pregnancies have spiked in Haiti since the 2010 earthquake. An estimated 5 billion condoms are sold in the world each year, with the United States accounting for about 10 percent of sales.

**U.S. Senate Foreign Relations Committee Passes Senator Paul Simon Water For The World Act**

"In an exciting move for the water, sanitation and hygiene (WASH) community, the U.S. Senate Foreign Relations Committee passed the Senator Paul Simon Water for the World Act of 2011 (S 641), bringing the bill one step closer to becoming a law,” PSI's "Healthy Lives" blog reports (Petoskey, 6/20). "The bill, introduced by Senators Dick Durbin (D-Ill.) and Bob Corker (R-Tenn.), has broad bipartisan support in the Senate,” the ONE Blog notes, adding, "If enacted, the bill would provide better access to clean water and sanitation to the world’s poorest communities through an efficient and cost effective strategy" (Brennan, 6/20). "The House [HR 3658] and Senate versions of the legislation have some differences, but ultimately, both seek to provide safe drinking water, sanitation and hygiene for millions of people, largely by improving upon the 2005 Senator Paul Simon Water for the Poor Act and making the way that the United States provides foreign aid on water and WASH projects more efficient,” advocate Elizabeth Shope writes in the Natural Resource Defense Council’s "Switchboard" blog. She asks representatives to "call on the House Foreign Affairs Committee to move the bill" (6/20).

**Avian Flu Viruses Which Are Transmissible Between Humans Could Evolve in Nature**

ScienceDaily (June 21, 2012) — It might be possible for human-to-human airborne transmissible avian H5N1 influenza viruses to evolve in nature, new research has found.

The findings, from research led by Professor Derek Smith and Dr Colin Russell at the University of Cambridge, were published June 22 in the journal Science.

Currently, avian H5N1 influenza, also known as bird flu, can be transmitted from birds to humans, but not (or only very rarely) from human to human. However, two recent papers by Herfst, Fouchier and colleagues in Science and Imai, Kawaoka and colleagues in Nature reveal that potentially with as few as five mutations (amino acid substitutions), or four mutations plus reassortment, avian H5N1 can become airborne transmissible between mammals, and thus potentially among humans. However, until now, it was not known whether these mutations might evolve in nature.
The Cambridge researchers first analysed all of the surveillance data available on avian H5N1 influenza viruses from the last 15 years, focusing on birds and humans. They discovered that two of the five mutations seen in the experimental viruses (from the Fouchier and Kawaoka labs) had occurred in numerous existing avian flu strains. Additionally, they found that a number of the viruses had both of the mutations.

Colin Russell, Royal Society University Research Fellow at the University of Cambridge, said: "Viruses that have two of these mutations are already common in birds, meaning that there are viruses that might have to acquire only three additional mutations in a human to become airborne transmissible. The next key question is 'is three a lot, or a little?""

The scientists explored this key question using a mathematical model of how viruses replicate and evolve within a mammalian host and assessed the influence of various factors on whether the remaining three mutations could evolve in a single host or in a short chain of transmission between hosts.

The factors that increased the likelihood of mutations evolving are:

1. Random mutation. The replication mechanisms of influenza viruses don't make perfect copies. On average, every time an influenza virus replicates itself it makes approximately one mutation somewhere in the genome of each new virus. In each infected human there will be billions of viruses, and thus with many viruses replicating, multiple mutations can accumulate within a single host.
2. Positive selection. If some of the remaining mutations help the avian virus to adapt to mammals, then those mutations will make the viruses more fit and thus will be positively selected and preferentially accumulate.
3. Long infection. The longer someone is infected and producing new viruses, the more time there is for mutations to accumulate.
4. Functionally equivalent substitutions. The sets of substitutions identified by Fouchier and Kawaoka are unlikely to be the only combinations of substitutions capable of producing an aerosol transmissible virus. The probability of emergence increases with the number of combinations.
5. Diversity in the within-bird virus population. Given all of the mutations there are likely to be within a host due to random mutation, it is possible that the viruses from a bird that infect a human might have a mutation that would not be detected by routine surveillance. For example, if 100 virus particles from a bird infect a human and one of those particles had a key mutation, it would increase the probability of the mutation reaching high levels within a host even though routine sequencing would not detect it.
6. Transmission between mammals. If mammals are capable of transmitting viruses that have some but not all of the necessary substitutions it could increase the probability of an airborne transmissible virus evolving.

The factors that decreased the likelihood of mutations evolving are:

1. An effective immune response. An effective immune response would shorten the length of an infection and thus decrease the time available to accumulate mutations.
2. Deleterious substitutions. If any of the substitutions necessary for airborne transmission were harmful to the virus it would, on average, slow the accumulation of mutations.
3. Order of acquiring mutations. It is not currently known if the mutations for airborne transmissibility need to be acquired in a specific order. If they do, it would, on average, slow the accumulation of mutations.

"With the information we have, it is impossible to say what the exact risk is of the virus becoming airborne transmissible among humans. However, the results suggest that the remaining three mutations could evolve in a single human host, making a virus evolving in nature a potentially serious threat," said Derek Smith, Professor of Infectious Disease Informatics at the University of Cambridge. "We now know that it is in the realm of possibility that these viruses can evolve in nature, and what needs to be done to assess the risk more accurately of these mutations evolving in nature."

The scientists recommend the following activities be considered high priority for estimating and ameliorating the risk of emergence of aerosol transmissible H5N1 viruses.

First, additional surveillance in regions where viruses with airborne transmission enabling substitutions have been observed and in regions connected to those regions by bird migration and trade. Also, increased surveillance for mutations that might have the same function as those found by the Fouchier and Kawaoka labs.
Second, related to surveillance, some targeted sequencing of H5N1 viruses should be done by "deep sequencing" where the lab sequences many viruses from an individual host to look for viruses that might have accumulated the critical mutations, even if those viruses are just a small proportion of the viruses within an animal.

Third, further investigations are needed to determine which substitutions and combinations of substitutions that are not the same as, but have the same function as, the substitutions identified by the Fouchier and Kawaoka labs are capable of making viruses airborne transmissible between mammals.

Fourth, further studies are needed to elucidate the changes in within-host fitness and between-host transmissibility associated with each airborne transmission enabling substitution and combination of substitutions.

Professor Smith added: "The situation is similar to assessing the risk of an earthquake or tsunami. We don't know exactly when and where, but by increasing monitoring and research—some of which is already underway—scientists and public health officials will be able to increase the accuracy with which the risk can be assessed and to minimise those risks."

**Journal Reference:**

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**Immune System Molecule Weaves Cobweb-Like Nanonets to Snag Salmonella, Other Intestinal Microbes**

ScienceDaily (June 21, 2012) — A team of researchers led by UC Davis Health System has found that human alpha-defensin 6 (HD6)—a key component of the body's innate defense system—binds to microbial surfaces and forms "nanonets" that surround, entangle and disable microbes, preventing bacteria from attaching to or invading intestinal cells.

The research describes an entirely new mechanism of action for defensins, an important group of molecules known to bolster the defenses of circulating white blood cells, protect cellular borders from invasive pathogens and regulate which "friendly" microbes can colonize body surfaces. The discovery provides important clues to inflammatory bowel diseases, especially Crohn's disease, which may be caused, in part, by deficiencies in HD6 levels or function.

A paper describing the work appears in the June 22 issue of the journal Science.

"During the past 25 years, researchers have learned a lot about the biological function of defensins, but the role of HD6, a particular molecule that is highly expressed in the intestines, was a mystery," said Charles L. Bevins, professor of microbiology and immunology at UC Davis. "We now know that HD6 has a very unique role in the body's innate immune system. Its ability to latch onto microbial surfaces and self-assemble to cast a fibrous net around bacteria, including pathogens like Salmonella and Yersinia, as well as fungi and protozoan parasites, gives the intestine, a critical part of the body, a powerful and broad spectrum of defense against potential threats."

Bevins is co-senior author of the paper along with his UC Davis colleague Professor Andreas Bäumler, an expert in bacterial pathogenesis; UCLA Emeritus Professor Robert I. Lehrer, whose laboratory was the first to discover defensins in the early 1980s; and Professor Wuyuan Lu, a synthetic protein chemist from the University of Maryland School of Medicine whose work provided clues to HD6's subtle and unique properties. First author Hiutung Chu, a graduate student in the Bevins lab who is now a fellow at the California Institute of Technology, was a driving force on the nine-year quest to solve the HD6 puzzle.

**About the protein HD6**
Defensins are a family of structurally related, small peptides with antibiotic activity found throughout nature in plants and animals. Humans make six different alpha-defensins. Two of these, HD5 and HD6,
are secreted by Paneth cells, specialized secretory cells located within the folds of the small intestinal lining. HD5 has well-known antibacterial properties while the function of HD6 had been unknown. The defensin-rich secretions of Paneth cells work in conjunction with nearby intestinal stem cells to maintain micro flora balance and renew intestinal cellular surfaces.

Chu's graduate work focused on characterizing the biological activity of HD6 in studies using cultured intestinal epithelial cells and transgenic mouse models. Although Chu and Bevins anticipated HD6 activity would be very similar to other alpha-defensins, which kill pathogens by poking holes in the microbial membrane, their early research studies repeatedly showed that HD6 did not kill bacteria. Puzzled, they then looked for other possible functions, collaborating with UC Davis professors Angela Gelli and Scott Dawson to see if HD6 might kill only certain bacteria, fungi or parasites. It did not.

After two years into the project and feeling frustrated about the negative results, Bevins and Chu carefully reviewed the experimental data. That's when they recognized two crucial pieces of information. The first was that whenever HD6 was added to suspensions of either bacteria or fungi, a white haze, or precipitate, formed in the solution (see image below). The second was that early studies conducted in collaboration with Bäumler had shown that while HD6 did not kill the bacterial pathogen Salmonella, it protected transgenic mice from an otherwise lethal infection.

"When we put these two results together, we were able to systematically show that HD6 was inhibiting microbial invasion and uncover HD6's unique structure and function at multiple levels," said Bevins.

On the road to discovery
The UC Davis team then collaborated with Lehrer, whose research focuses on the study of defensins and other antimicrobial peptides that serve as natural antibiotics. In his laboratory, he had a surface plasmon resonance instrument that measured molecular binding in real time. This technique captured the progressive assembly of HD6 molecules, from binding to bacterial proteins at the microbial cell surface to the self-assembly to form fibrils and the sequential addition of fibrils (see images below).

Through the expertise of Lu, a synthetic protein chemist and expert in defensin structure and function relationships, the team obtained sufficient quantities of the highest-grade HD6 peptide and subtle molecular variants of HD6 to test their hypotheses experimentally. Lu was able to identify critical structural components of HD6 that enabled it to self-assemble into fibrils. One feature unique to HD6 is the manner in which four HD6 molecules combine to form a building block whose further assembly creates both fibers and nets. The researchers also found that changing just one of the 32 amino-acid residues of the HD6 molecule—histidine-27—impaired HD6's ability to form a tetramer in the x-ray crystal structure. As a result, HD6 lost the special binding that Lehrer found in his real-time experiments, blocked the ability of HD6 to form nanonets and abrogated its ability to inhibit bacterial invasion.

The Bäumler laboratory created vital bacterial mutants affecting the molecules that HD6 initially binds to on the surface of the microbe. When those molecules were knocked out in the transgenic mouse model, HD6 did not form the fibrils on the bacterial surface.

"This series of experiments provided the vital 'glue' to bind the many facets of the story together, and to convince ourselves and our peers that we had finally solved the mechanism of HD6 action," commented Bevins.

Clues to innate immunity and inflammatory bowel diseases
The UC Davis research describes how HD6 contributes to the body's innate immunity, which protects from microbes that the immune system might not have any experience in managing.

"The innate immune system has to be able to deal with diverse microbes that might have all kinds of tricks that cause infection," said Bevins. "After we've been exposed to a microbe or an infection the first time and survive it, the adaptive immune system can recognize and remember specific pathogens to generate immunity and to mount stronger defenses each time the pathogen is encountered. HD6 is a major player in helping the body prevent potentially dangerous pathogens from coming into close physical contact with intestinal epithelial cells, as well as the stem cells that continuously renew the epithelial cell surface."

Previously published studies from the Bevins lab have linked alpha-defensins and Crohn's disease, a chronic inflammatory bowel disease that investigators associated with HD5 and HD6 deficiencies. The secretions of these defensins typically occur at the base of the out pouches (so-called crypts) of the small intestinal surface, where they are ready to fend off bacteria that become dangerously close to the intestinal lining. Individuals with Crohn's disease, however, tend to accumulate invasive bacteria in this same area, developing a chronic inflammation that is self-perpetuating.

"With less of these important defense molecules, microbes that would normally exist in the gut, can irritate the intestinal surface and cause the chronic inflammation that characterizes Crohn's disease," said
Bevins. "We know a lot about HD5’s antimicrobial activities, so it makes sense why reduced HD5 levels might contribute or allow this condition to progress. Now we have a clue how HD6 levels play a role."

Future studies on Crohn’s disease by this team aim to better understand exactly why alpha-defensin-expression is reduced in individuals with Crohn’s disease, and perhaps devise strategies to boost the body’s production of these vital molecules.

"The multidisciplinary approach that we used to 'crack' the obscure and complex action of HD6 exemplifies the power of team science," Bevins said. "Not to be underestimated, however, is the courage and tenaciousness of graduate student Hiutung Chu in leading the experimental investigations. Many blind alleys were visited as we investigated this molecule, and those frustrating diversions can erode confidence and morale. Hiutung deserves tremendous credit for persevering through those setbacks."

**Journal Reference:**

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**Our Microbes, Ourselves: Billions of Bacteria Within, Essential for Immune Function, Are Ours Alone**

ScienceDaily (June 21, 2012) — Gut bacteria’s key role in immunity is tuned to the host species, researchers have found, suggesting that the superabundant microbes lining our digestive tract evolved with us—a tantalizing clue in the mysterious recent spike in human autoimmune disorders.

A new study reports that the superabundance of microbial life lining our GI tracts has coevolved with us. These internal bacteria, which are essential for a healthy immune system, are ultimately our evolutionary partners. In other words, humans may have co-evolved with gut bacteria unique to humans, which are not immunologically functional in other mammals.

This study, the first to demonstrate that microbes are specific to their host species, also sheds light on what’s called ‘the hygiene hypothesis.’ According to this idea, living in increasingly hyper-hygienic environments might contribute to recent spikes in childhood allergies, as these beneficial host-specific microbes are hindered by the plethora of antibacterial home products and cleaning chemicals.

"For every cell in your body that is you, that contains your specific genetic information, there are approximately nine foreign bacterial cells, primarily in your digestive tract and even on your skin," said Dennis Kasper, HMS professor of microbiology and immunobiology and senior author on the paper. "From the viewpoint of cell count, every human being is ninety percent microbial. Now we've found that these bacteria, which we need for optimal health, are species specific."

This paper will appear in the June 22 issue of *Cell*.

That 500 to 1,000 microbial species inhabit mammals has long been documented. Researchers have suggested that when it comes to digestion and other metabolic activities, the particular species of bacteria may not be significant provided the bacteria contain specific, helpful genes. In other words, a bacterium that breaks down food in the mouse gut can probably do the same in the human.

But the microbes that fortify our immune system have not been studied in this regard. Are they functionally unique, or would any species suffice?

To address this question, Hachung Chung, a postdoctoral researcher in Kasper’s lab, studied two groups of mice, both of which had been bred to lack microbial flora. For one group, she introduced microbial species that are natural to mice, and to the second, she introduced human microbes.

For both groups of mice, an equal quantity of microbes, and an equal diversity of species, soon flourished in their digestive tracts.

But despite this apparent similarity, when Chung examined the intestinal tissue, including intestinal lymph nodes, of mice from each of the two groups, she discovered that the mice with humanized microbes had surprisingly low levels of immune cells, levels equivalent to mice who lacked intestinal bacteria all together.

"Despite the abundant and complex community of bacteria that were in the human flora mice, it seemed like the mouse host did not recognize the bacteria, as if the mice were germ-free," said Chung.

Chung repeated the experiment, only this time populating a third group of mice with microbes common to rats. This new group showed the same immune system deficiency as the humanized mice. "I was very surprised to see that," Chung said. "Naturally, I would have expected more of a half-way response."
In a third experiment, Chung infected all the mice with salmonella. Almost from day one, the mice with human flora showed significantly higher levels of salmonella in their system than the mice with normal flora. The immune systems of the mice with human flora were effectively incapable of fending off the pathogenic bacteria.

"This raises serious questions regarding our current overuse of antibiotics, as well as ultra-hygienic environments that many of us live in," said Kasper. "If the bacteria within us are specific to us and necessary for normal immune system function, then it's important to know if we are in fact losing these vital bacteria. Are we losing the bacteria we have coevolved with? If that is the case, then this is yet further evidence supporting the idea that the loss of good bacteria is partly to blame for the increased rates of autoimmunity that we are now seeing."

**Journal Reference:**

**Prions and cancer: A story unfolding**
Prions, the causal agents of Mad Cow and other diseases, are very unique infectious particles. They are proteins in which the complex molecular three-dimensional folding process just went astray. For reasons not yet understood, the misfolding nature of prions is associated to their ability to sequester their normal counterparts and induce them to also adopt a misfolding conformation. The ever-growing crowd of misfolded proteins form the aggregates seen in diseases such as Parkinson's and Alzheimer's. Once misfolded, a protein can no longer exert its normal functions in the cell.

Now, a group led by Dr Jerson Lima Silva at the Federal University of Rio de Janeiro, Brazil, presents some new evidence that p53, a protein with the daunting task of suppressing tumor formation in the body, may show a typical prion-like behavior when mutated.

It has been known for some time that the buildup of p53 in the cell impairs the protein in preventing tumor growth. This has been observed in neuroblastoma, retinoblastoma, breast, and colon cancers. In a paper entitled "Mutant p53 aggregates into prion-like amyloid oligomers and fibrils: Implications for cancer" and published in the *Journal of Biological Chemistry*, the group shows that in breast cancer cell lines carrying the most common p53 mutation, the formation of amyloid-like aggregates of p53 proteins may explain the protein's lack of function.

Whether this prionoid behavior in fact represents a relevant cancer-related mechanism remains to be shown. Development of novel and ingenious strategies to prevent p53 misfolding and aggregation may be just one way to find out.

"We are planning pre-clinical tests with synthesized nucleic acids in an attempt to prevent the changing in conformation of normal p53, and avoid aggregates of misfolded protein," says Dr. Silva.

If successful, the strategy may help unveil unforeseen molecular mechanisms leading to tumor development. Considering that more than half of the cancers lose p53 function, this prionoid behavior may serve as a potential novel target for cancer therapy, dramatically transforming our way of thinking of cancer and treating cancer patients.

**Gut Microbes Battle a Common Set of Viruses Shared by Global Populations**
ScienceDaily (June 25, 2012) — The human gut is home to a teeming ecosystem of microbes that is intimately involved in both human health and disease. But while the gut microbiota is interacting with our body, they are also under constant attack from viruses. In a study published online in *Genome Research*, researchers have analyzed a bacterial immune system, revealing a common set of viruses associated with gut microbiota in global populations.

Viruses that prey on bacteria, called phages, pose a constant threat to the health of bacterial communities. In many ecological systems, viruses outnumber bacterial cells ten to one. Given the richness of bacteria in the human gut, it was not surprising that scientists have found that phages are also highly prevalent. But how can viruses targeting gut microbiota be identified? How do viral communities differ between people and global populations, and what could this tell us about human health and disease?

In this report, a team of scientists from Israel has taken advantage of information coded in a bacterial immune system to shed new light on these questions. Bacteria can "steal" small pieces of DNA from phages that attack them, and use these stolen pieces to recognize and respond to the attacker, in a manner similar to usage of antibodies by the human immune system. The stolen DNA pieces are stored in specific
places in the bacterial genome called CRISPR loci (clustered regularly interspaced short palindromic repeats).

"In our study we searched for such stolen phage DNA pieces carried by bacteria living in the human gut," said Rotem Sorek of the Weizmann Institute of Science and senior author of the study. "We then used these pieces to identify DNA of phages that co-exist with the bacteria in the gut."

Sorek's team used this strategy to identify and analyze phages present in the gut microbiota of a cohort of European individuals. They found that nearly 80% of the phages are shared between two or more individuals. The team compared their data to samples previously derived from American and Japanese individuals, finding phages from their European data set also present in these geographically distant populations, a surprising result given the diversity of phages seen in other ecological niches.

Sorek explained that their findings mean that there are hundreds of types of viruses that repeatedly infect our gut microbiota. "These viruses can kill some of our gut bacteria," said Sorek. "It is therefore likely that these viruses can influence human health."

The authors note that as evidence for the beneficial roles played by bacteria in the healthy human gut continues to mount, it is critical that we understand the pressures placed upon the "good" bacteria that are vital to human health. "Our discovery of a large set of phages attacking these good bacteria in our gut opens a window for understanding how they affect human health," Sorek added. Researchers can now begin to ask how phage dynamics in the gut changes over time, and what it might tell us about diseases, such as inflammatory bowel disease, and how to more effectively treat them.

Journal Reference:

Bacterial vaginosis is associated with higher risk of female-to-male transmission of HIV

An investigation led by UCSF has found that the risk of female-to-male HIV transmission is increased 3 fold for women with bacterial vaginosis, a common disorder in which the normal balance of bacteria in the vagina is disrupted

An investigation led by UCSF has found that the risk of female-to-male HIV transmission is increased three fold for women with bacterial vaginosis, a common disorder in which the normal balance of bacteria in the vagina is disrupted.

"Previous research has shown that bacterial vaginosis can increase a women's risk of becoming infected with HIV as much as sixty percent. Our study is the first to show that the risk of transmitting HIV is also elevated. Our findings point to the need for additional research to improve the diagnosis and treatment of bacterial vaginosis, which is extremely common in sub-Saharan Africa, the region of the globe with the highest burden of HIV," said the study's lead author, Craig R. Cohen, MD, MPH, professor of obstetrics, gynecology and reproductive sciences at UCSF.

The study is being published in the June 26th issue of PLoS Medicine.

The new research assessed the association between bacterial vaginosis and female-to-male HIV transmission risk in a prospective study of 2,236 HIV positive women and their uninfected male partners from seven African countries. After controlling for socio-demographic factors, sexual behavior, male circumcision, sexually transmitted infections, pregnancy and levels of HIV in the blood of the women with HIV, bacterial vaginosis was associated with a significantly increased risk for female-to-male transmission of HIV.

Bacterial vaginosis is a condition where the normal balance of microorganisms naturally found in the vagina is altered. This disruption of vaginal flora takes place when bacteria that are helpful are reduced and more harmful bacteria are increased. Besides increasing the risk of becoming infected with HIV, bacterial vaginosis can increase the risk of acquiring other sexually transmitted infections and increase the risk of preterm delivery. In addition, HIV-infected women with this disorder may have higher levels and greater shedding of the virus from the cervix and vagina.

"We looked at the increased shedding of HIV in the genital tract, but that was not sufficient to explain the increased risk of female-to-male HIV transmission. It is also possible that bacterial vaginosis causes inflammation and that could be a factor. We don't really understand the relationship between vaginal flora and inflammation," said Cohen.

In addition, he said, "we think it's likely that the sharing of genital tract microbiota between women and men may be implicated as a cause of the transmission risk. The interrelationship of the sharing of flora remains poorly understood and is an important avenue for future research."
Notwithstanding the need for better understanding of the role of vaginal flora, the development of more therapeutics for bacterial vaginosis, including better drugs and probiotics, would be a significant boost to women's health in general, as well as help decrease HIV acquisition and transmission risks, added Cohen.

**Take the Test and Risk Arrest?**

By Sean Strub on June 26, 2012 10:26 PM | No Comments

Today (June 27) is National HIV Testing Day and there will be a truckload of press releases encouraging people to get tested for HIV. Getting tested for HIV is a good thing; knowing one’s HIV status is important, both to protect one's own health as well as the health of one's partners.

But no one should get tested without also understanding the legal implications. HIV criminalization is real, it is happening all over the country and it is on the increase.

The slogan for National HIV Testing Day is "Take the Test and Take Control". That slogan rings hollow when it isn’t accompanied by information about the legal risks one undertakes when getting tested. The slogan one hears in some quarters is "Take the Test and Risk Arrest"; the fear of prosecution is discouraging HIV testing.

I believe it is unethical to encourage people to get tested without making sure they also understand the legal ramifications of a positive test result. In many parts of the country, once someone tests positive, they are told they must sign an "acknowledgement form" noting that they received their positive test result, were appropriately counseled and citing that state’s HIV criminalization statute.

Sometimes that form is given to the person moments after they get the test result, when the person is frequently in a state of semi-shock and in no position to be signing a legal document. Those forms have come back to haunt people in court at a later date, when they are used as proof that the person knew they had HIV and were obligated to disclose.

Even someone who is diligent about disclosing can be caught up in HIV criminalization prosecutions. A survey by POZ a few years ago showed that 28% of respondents had a circumstance where they believed they had disclosed but later found out that a sexual partner did not understand them and thought they had not disclosed. There have been many prosecutions that were revenge cases, a relationship that went bad and someone wanted to get even.

Every person with HIV is one disgruntled ex-partner away from ending up in a courtroom. The chorus of calls to get tested would be more credible and more honest if they also included tips on how and where to get tested anonymously and how to protect against the risk of HIV criminalization.

It discouraging to see all the AIDS organizations and other institutions cranking out press releases celebrating National HIV Testing Day while remaining silent about how HIV criminalization is ruining lives and locking up people with HIV.

If they really wanted people to get tested, they would work a lot harder at making it safe to do so.

**'War on Drugs' Is Fueling HIV Epidemic: Report**

*Agence France Presse*, (06.25.2012)

A report issued Tuesday by the Global Commission on Drug Policy says repressive law enforcement policies toward drugs are driving the HIV/AIDS epidemic by forcing users away from treatment and into high-risk environments. GCDP is calling on the UN to “acknowledge and address the causal links between the war on drugs and the spread of HIV/AIDS and drug market violence.”

“The public health implications of HIV treatment disruptions resulting from drug law enforcement tactics have not been appropriately recognized as a major impediment to efforts to control the global HIV/AIDS pandemic,” noted GCDP, whose members include six former presidents, four from Latin America; former EU foreign policy chief Javier Solana; and George Shultz, former US secretary of state under President Ronald Reagan.

The United States, Russia, and Thailand are experiencing the “devastating consequences” of ignoring scientific evidence about the relationship between HIV rates and law enforcement policies, the report says. “The war on drugs has failed, and millions of new HIV infections and AIDS deaths can be averted if action is taken now,” the authors concluded.
Calgary Doctors and Parents Want Catholic School Board to Revisit HPV Vaccine

*Canadian Press*, (06.25.2012)

Since 2008, the Calgary Catholic School Board has banned school-based vaccination against human papillomavirus. Local parents and doctors are asking the board and the Roman Catholic bishop who advises it to reconsider this policy.

“We are coming forward to ask trustees to put children first and to stress that publicly funded schools are owned by the public,” said Juliet Guichon, a legal scholar and assistant professor of community health sciences at the University of Calgary. Guichon, who is Catholic, said she made sure her children received the HPV vaccine even through it was not available through their school.

The HPV vaccine protects against strains of the STD linked to genital warts and about 70 percent of cervical cancers. Vaccination programs have been available for Canadian girls in grades five and nine since 2007.

“It’s important to stress bad things can happen and parents ought to protect their children against foreseeable, possible bad things,” Guichon said.

Bishop Fred Henry takes a different view. “If we don’t attempt to change sexual behavior that is responsible for transmission of [HPV], but attempt to solve the problem by getting a series of shots, then we don’t have to exercise self-control, nor develop virtue, but can use medicine to palliate our vices,” he said.

“All activities proposed for a Catholic school need to be assessed in the light of our faith and doctrine,” said Henry. “This is self-evidently necessary in the case of a vaccine against a disease that is transmitted by sexual activity, which impacts not only the physical but also the spiritual, psychological, and moral well-being of an individual.”

**Immune response to heart attack worsens atherosclerosis, increases future risk**

**Study finds mechanism behind recognized risk, suggests new treatment strategy**

A heart attack doesn’t just damage heart muscle tissue by cutting off its blood supply, it also sets off an inflammatory cascade that worsens underlying atherosclerosis, actively increasing the risk for a future heart attack. These findings from a study receiving advance online publication in *Nature* suggest an important new therapeutic strategy for preventing heart attacks and strokes, both of which are caused when atherosclerotic plaques rupture and block important blood vessels.

"We have known for a long time that heart attack patients are at increased risk for a second heart attack or a stroke, and now we know why," says Matthias Nahrendorf, MD, PhD, of the MGH Center for Systems Biology, senior author of the report from a team of researchers from the USA, Canada, Germany and the Netherlands. "The immune response to the infarct – tissue damaged by lack of oxygen – can accelerate the underlying disease by actually increasing the size and inflammation of the atherosclerotic plaque."

The study was designed to test the hypothesis that systemic inflammation caused by heart muscle damage would worsen pre-existing atherosclerosis. Using a mouse model genetically programmed to develop atherosclerosis, the researchers conducted a series of experiments showing that experimentally induced heart attacks led to the following:

- increased activity, in atherosclerotic plaques at a distance from the induced heart attack, of enzymes that break down the fibrous plaque cap, possibly leading to future rupture,
- accumulation of monocytes and other inflammatory immune cells in those atherosclerotic plaques,
- increased generation in the spleen of monocyte progenitors, along with changes in the function of those immune cells,
- increased release from the bone marrow of blood stem cells, which traveled to the spleen, triggered by increased activation of the sympathetic nervous system.

"The ancient fight-or-flight responses to injury stimulate immune cell activities that are involved in wound healing. But when the 'wound' is in the heart and caused by atherosclerosis, that increased activity actually accelerates the underlying disease,” Nahrendorf explains. "While most of this work was done in mice, we have hints that something similar may happen in human patients – for example, we found increased numbers of blood stem cells in the spleens of patients who had died shortly after a heart attack."

Ralph Weissleder, MD, PhD, a corresponding author of this study and director of the MGH Center for Systems Biology where the work was performed, adds that these findings set the stage for a totally novel approach to cardiovascular disease. Therapies directed to the sites of white blood cell production,
including the bone marrow or the spleen, may be able to prevent immune-system exacerbation of atherosclerosis. "This gives us potential new therapeutic targets that we had not thought about before. Clinically, we focus on reducing risk factors such as elevated cholesterol and blood pressure, but not inflammation. We hope our work can help change that," he says.

**New mechanism of bacterial pathogenesis discovered**

Scientists have identified a new mechanism of bacterial pathogenesis. The results of the research project, partly funded by the Academy of Finland, have been published in the journal *Proceedings of the National Academy of Sciences* of the United States of America (PNAS).

Bacteria that cause chronic infections have an amazing but yet poorly known ability to subvert immune response, live and produce offspring, enter and wake up from a dormant phase to cause, in some instances, deadly complications.

*Bartonella* bacteria cause chronic infections in mammals (incl. humans), and are typically transmitted to new hosts mainly by arthropod vectors such as fleas, lice and ticks, but also via direct tissue trauma (e.g. cat scratches).

One very notable feature of these bacteria is their ability to cause vasoproliferative tumours that resemble Kaposi's sarcoma in patients suffering from immunodeficiency (e.g. AIDS, aggressive cancer treatments, organ transplantation). If left untreated, these foci of inflammation maintain a chronic infection and contribute to transmitting bacteria to new hosts.

In his research, biologist Arto Pulliainen (University of Turku) has demonstrated that Bartonella henselae injects a protein called BepA into vascular endothelial cells and that this protein manipulates cAMP-mediated cell signalling using a previously unknown mechanism.

BepA directly binds the host cell adenylyl cyclase, which is an enzyme responsible for the production of cAMP. However, the binding of BepA to the adenylyl cyclase does not activate cAMP production per se, but the adenylyl cyclase rather becomes more sensitive to its natural activator, stimulatory G-protein (Gαs). The cellular concentration of cAMP increases and prevents the death of the host cell. BepA significantly prolongs the lifespan of the host cell and partly contributes to the formation of vasoproliferative tumours.

Several bacterial species are known to manipulate host cell functions via cAMP-mediated cell signalling. The symptoms are typically very strong and may even be deadly. The best-known example is *Vibrio cholerae* and its cholera toxin, which modifies Gαs into a permanently adenylyl cyclase-stimulating form. BepA, in turn, manipulates host cell signalling in a subtle sophisticated manner, which is ideal for chronic persistence of Bartonella henselae in the infected vascular endothelium.

The research has been carried out at the Universities of Basel and Turku.

**Dietary fiber alters gut bacteria, supports gastrointestinal health**

**URBANA** – A University of Illinois study shows that dietary fiber promotes a shift in the gut toward different types of beneficial bacteria. And the microbes that live in the gut, scientists now believe, can support a healthy gastrointestinal tract as well as affect our susceptibility to conditions as varied as type 2 diabetes, obesity, inflammatory bowel disease, colon cancer, and autoimmune disorders such as rheumatoid arthritis.

As these microbes ferment fiber in the intestine, short-chain fatty acids and other metabolites are produced, resulting in many health benefits for the host, said Kelly Swanson, a U of I professor of animal sciences.

"When we understand what kinds of fiber best nurture these health-promoting bacteria, we should be able to modify imbalances to support and improve gastrointestinal health," he said.

This research suggests that fiber is good for more than laxation, which means helping food move through the intestines, he added.

"Unfortunately, people eat only about half of the 30 to 35 grams of daily fiber that is recommended. To achieve these health benefits, consumers should read nutrition labels and choose foods that have high fiber content," said Swanson.

In the placebo-controlled, double-blind intervention study, 20 healthy men with an average fiber intake of 14 grams a day were given snack bars to supplement their diet. The control group received bars that contained no fiber; a second group ate bars that contained 21 grams of polydextrose, which is a common fiber food additive; and a third group received bars with 21 grams of soluble corn fiber.
On days 16-21, fecal samples were collected from the participants, and researchers used the microbial DNA they obtained to identify which bacteria were present. DNA was then subjected to 454 pyrosequencing, a "fingerprinting" technique that provides a snapshot of all the bacterial types present.

Both types of fiber affected the abundance of bacteria at the phyla, genus, and species level. When soluble corn fiber was consumed, Lactobacillus, often used as a probiotic for its beneficial effects on the gut, increased. Faecalibacterium populations rose in the groups consuming both types of fiber.

According to Swanson, the shifts in bacteria seen in this study—which occurred when more and differing types of fiber were consumed—were the opposite of what you would find in a person who has poor gastrointestinal health. That leads him to believe that there are new possibilities for using pre- and probiotics to promote intestinal health.

"For example, one type of bacteria that thrived as a result of the types of fiber fed in this study is inherently anti-inflammatory, and their growth could be stimulated by using prebiotics, foods that promote the bacteria's growth, or probiotics, foods that contain the live microorganism," he said.

New Role for RNAi Discovered: Epigenetic Memory May Pass RNA Silencing from One Generation to the Next
ScienceDaily (June 26, 2012) — Organisms employ a fascinating array of strategies to identify and restrain invasive pieces of foreign DNA, such as those introduced by viruses. For example, many viruses produce double-stranded (ds)RNA during their life cycle and the RNA interference (RNAi) mechanism is thought to recognize this structural feature to initiate a silencing response.

Now, UMass Medical School researchers have identified a mechanism related to RNAi that scans for intruders not by recognizing dsRNA or some other aberrant feature of the foreign sequence, but rather by comparing the foreign sequences to a memory of previously expressed native RNA. Once identified, an "epigenetic memory" of the foreign DNA fragments is created and can be passed on from one generation to the next, permanently silencing the gene.

A remarkable feature of this RNAi-related phenomenon (referred to as RNA-induced epigenetic silencing, or RNAe), is that the animal carries a memory of previous gene expression. This memory of active genes serves as an "anti-silencing" signal, which protects native genes from RNAe and under some circumstances appears to adopt foreign genes as self. These findings, described in three studies (including a study by Eric Miska and colleagues of the Gurdon Institute, University of Cambridge and Wellcome Trust, UK) published online June 25 and to appear in the July 6 issue of Cell, provide new insights into how identical organisms can have the same DNA sequence but opposite patterns of gene expression and thus dramatically different phenotypes.

"If a worm modulates gene expression by carrying a memory of the genes it expressed in previous generations, perhaps other organisms (including humans) can as well. If so, mechanisms of this type could have an important impact on evolution," said Craig C. Mello, PhD, Howard Hughes Medical Institute Investigator, Blais University Chair in Molecular Medicine and distinguished professor of molecular medicine and cell biology. "The RNAe mechanism could accelerate evolutionary change by increasing heritable phenotypic variation (without the need for DNA mutations). There is growing evidence that many organisms can track and respond epigenetically to gene expression patterns. Our findings provide insight into a whole new level of sophistication in the recognition and memory of gene expression programs."

Dr. Mello and colleagues knew that when a foreign piece of DNA encoding the green fluorescent protein, or GFP, was inserted into the small roundworm C. elegans, some of the worms would silence the newly introduced DNA while others would express the GFP gene. They then explored a role for RNAi in the decision to silence or express GFP. RNAi is a process whereby cells modulate the activity of their genes. In RNAi-related phenomena, Argonaute proteins interact with and use small RNAs as little genetic guides to recognize target nucleic acids through base-pairing interactions.

Based on their findings, Mello and colleagues posit a model composed of three separate Argonaute systems that work together to scan, identify and silence foreign DNA, while protecting the expression of normal genes. In this system, an Argonaute called PRG-1 (Piwi) bound to piwi-interacting RNA (piRNA) is responsible for scanning molecules of RNA as they leave the nucleus of the cell and determining if they are indigenous to the organism or foreign. If PRG-1 and its piRNA cofactors identify a foreign sequence, it initiates (or activates) the second Argonaute system, known as WAGO, which turns the genetic material off so it can’t be expressed.
Once the DNA is identified as foreign and silenced, an epigenetic memory is created that silences the foreign gene from one generation to the next. While the inheritance of this memory requires further exploration, the authors showed that successive generations of C. elegans are unable to express the foreign DNA even if the corresponding piRNA is absent.

"It appears that piRNAs are responsible for the initial scanning and identification of foreign nucleic acids," said Darryl Conte Jr., PhD, research assistant professor of molecular medicine and one of the co-authors on the Cell papers. "Because the foreign DNA in successive generations is being silenced, even in worms that don't have the piRNA, the information necessary for silencing is being passed on epigenetically and independently of the initial scanning done by the piRNA complex in the previous generations."

Originating from clustered regions of the genome, piRNA are diverse and abundant small non-coding RNA molecules in animals, numbering in the millions in mammals. For the most part, piRNAs in worms—and many piRNAs in mammals—lack obvious complementary targets and their function is not clearly understood. It's possible that piRNAs act as a genetic security system, using imperfect base pairing to help identify foreign nucleic acids, said Dr. Conte.

So what prevents piRNAs from recognizing and permanently silencing a gene that the worm identifies as its own? Remarkably, the authors found that such "self" transcripts are somehow protected from entering the WAGO system and that some active genes can actually turn on silent genes. Because the self transcripts are associated with a third Argonaute known as CSR-1, the authors propose that CSR-1 provides an anti-silencing or protective function, which licenses the expression of genes that the worm recognizes as its own.

"This is one of the truly unique findings of these studies," said Conte. "Before, we knew that the RNAi process could be used to regulate genes or to turn them off completely. In this case, what we see is an RNAi mechanism that appears to prevent a gene from being silenced by the piRNA pathway. It works almost as a form of protection that allows the gene to be expressed."

"Taken together, these studies posit a surprisingly complex role for small-RNA systems in epigenetic programming," said Mello. "It shows how piRNAs continuously scan all the genes expressed in the germline, constantly comparing each sequence to a memory of previous gene expression. When foreign genes are recognized and silenced, this new epigenetic knowledge can be passed down to successive generations. On the other hand, occasionally new genes are expressed, apparently stochastically, and this active state too can be passed on as a stable epigenetic memory, thus the organism effectively adopts the foreign gene as self."

Journal Reference:
Masaki Shirayama, Meetu Seth, Heng-Chi Lee, Weifeng Gu, Takao Ishidate, Darryl Conte, Craig C. Mello. piRNAs Initiate an Epigenetic Memory of Nonself RNA in the C. elegans Germline. Cell, 2012; DOI: 10.1016/j.cell.2012.06.035

Scientists Detect New Immune Alert Signal
ScienceDaily (June 22, 2012) — New discovery expands our knowledge as to when the mammalian cell detects an incoming viral attack—and what the cell does to protect the body: The new finding may improve vaccine efficiency and could provide better treatment of recurrent infections.

Researchers from Aarhus University have now located the place in the human body where the earliest virus alert signal triggers the human immune system. They have also discovered a new alarm signal, which is activated at the very first sign of a virus attack.

"We have detected a new immune alarm signal, which helps the cells realize that they may soon get infected with virus," says Søren Riis Paludan, professor of immunology and virology at Aarhus University, who has completed the study together with Christian Holm, postdoc at Aarhus University.

Cell membrane triggers the alarm
Recent research indicates that our immune system is alerted about a threatening virus infection when genomic material from the virus enters the cell. Researchers from Aarhus University have revealed a process which is triggered already before the foreign genomic material enters the cell, i.e. in the membrane surrounding the cell.

"It may turn out that patients suffering from frequent infections actually have problems with activating the mechanism that we have now detected," says Søren Riis Paludan, professor of immunology and virology at Aarhus University, who has completed the study together with Christian Holm, postdoc at Aarhus University.
**Alarm signals in two directions**

"The cellular membranes are in this situation comparable to a borderline territory in looming war—and this is the place to put an outpost," says Christian Holm.

The 'outpost' will send alarm signals in two directions when danger is detected. One signal (outbound) will prepare the body for a possible attack, whereas the other signal (inbound) will make the cell investigate the threat.

"In the present study, we have revealed that this happens—and what this process means. In future studies, we will investigate how this happens," the researchers say.

They add that this new knowledge could also lead to development of more efficient vaccines.

Article: "Virus-cell fusion as a trigger of innate immunity dependent on the adaptor STING"

Journal Reference:
Christian K Holm, Søren B Jensen, Martin R Jakobsen, Natalia Cheshenko, Kristy A Horan, Hanne B Moeller, Regina Gonzalez-Dosal, Simon B Rasmussen, Maria H Christensen, Timur O Yarovinsky, Frazer J Rixon, Betsy C Herold, Katherine A Fitzgerald, Søren R Paludan. **Virus-cell fusion as a trigger of innate immunity dependent on the adaptor STING**. Nature Immunology, 2012; DOI: 10.1038/ni.2350

**S.C. House Upholds Haley Veto on HPV Vaccine**


In a 54-47 vote on Tuesday, the state House failed to override Gov. Nikki Haley’s veto of a bill intended to boost vaccination against the STD human papillomavirus, which causes most cases of cervical cancer. A two-thirds majority vote would have overridden the veto.

Rep. Bakari Sellers (D-Denmark), sponsor of the bill, said he plans to re-introduce it next year. The measure would have provided informational brochures about HPV to the parents of sixth-graders; the parents could then choose to have their children receive the vaccine without cost in the seventh grade. It specified those provisions depended on state budget support.

Haley’s veto message called the measure unnecessary and a suspended unfunded mandate. The Republican governor said HPV vaccination needs to be discussed among parents, their children and their doctor. Government health agencies should not play a role in telling parents whether to go ahead with vaccination. “I don’t want a leaflet going out making any parent think their child has to have it,” she said.

“The governor’s veto message sounded like it was written by a political consultant rather than a former sponsor of an HPV mandate,” said Sellers. Haley was co-sponsor of a 2007 bill calling for mandatory HPV vaccinations for seventh-grade girls, unless parents opted out. That measure was defeated unanimously in the House, and Haley has since said her support of it was a mistake.

Sellers said poor parents in rural areas especially need the facts about HPV.

Dr. Andrew Kraft, director of the Hollings Cancer Center at the Medical University of South Carolina, supported Sellers’ bill. The state ranks ninth for cervical cancer deaths, and African-American women are three times more likely to die from it than white women.

**Disparities in Sexually Transmitted Disease Rates Across the 'Eight Americas'**

Sexually Transmitted Diseases Vol. 39; No. 6: P. 458-464, (06..2012) Harrell W. Chesson; and others

The research team set out to examine rates of three bacterial STDs—syphilis, gonorrhea, and chlamydia—in eight US subpopulations defined by race and a small number of county-level sociodemographic and geographical characteristics.

Referred to as the “eight Americas,” the subpopulations are: 1) Asians and Pacific Islanders in certain counties; 2) Northland low-income rural white; 3) Middle America; 4) low-income whites in Appalachia and the Mississippi Valley; 5) Western Native American; 6) black middle America; 7) Southern low-income rural black; and 8) high-risk urban black.

The corresponding author of the original eight Americas project, which examined disparities in mortality rates, provided a list of the counties comprising each of the eight Americas. The authors used county-level surveillance data to determine rates of new cases per 100,000 population for the three STDs in the eight Americas.

The results showed that across the eight Americas, rates of reported STDs “varied substantially.” These were generally lowest in Americas 1 and 2, while they were highest in Americas 6, 7, and 8.

“Although disparities in STDs across the eight Americas are generally similar to the well-established disparities in STDs across race/ethnicity, the grouping of counties into the eight Americas does offer additional insight into disparities in STDs in the United States,” the team concluded. “The high STD rates
we found for black Middle America are consistent with the assertion that sexual networks and social factors are important drivers of racial disparities in STDs."
asymmetric cellular division seemed uncertain. Meyer-Hermann's analyses suggest that one of the two daughter cells leaves the germinal center and starts producing antibodies while the other stays behind and undergoes another round of mutation and selection inside the germinal center. The mathematical model illustrates the advantage of this type of set-up. While one fairly specialized daughter cell is already making antibodies, its clone, which can be further optimized in the next round, stays behind. Compared with symmetric division, in asymmetric division there is a tenfold increase in the number of antibodies produced. In addition, the cell that stays behind in the germinal center stores information regarding a successful antibody it has produced, and the optimization process thus concludes more quickly. "This kind of time-saving in antibody production can be a real life-saver in the case of a dangerous infection," explains Michael Meyer-Hermann.

**Both innate and adaptive immune responses are critical to the control of influenza**

Both innate and adaptive immune responses play an important role in controlling influenza virus infection, according to a study, published in the Open Access journal *PLoS Computational Biology*, by researchers from Oakland University, Michigan, and Los Alamos National Laboratory, New Mexico, USA.

Influenza, as a contagious respiratory illness remains a major public health problem worldwide. Seasonal and pandemic influenza results in approximately 3 to 569 million cases of severe illness and approximately 250,000 to 500,000 deaths worldwide. Although most infected subjects with intact immune systems are able to clear the virus without developing serious flu complications, the biological factors responsible for viral control remain unclear.

To investigate the factors for viral control, the researchers developed mathematical models that included both innate and adaptive immune responses to the virus. These models were used to study the viral dynamics of the influenza virus infection in horses. After infection, viral levels rise rapidly, reach a peak and fall, then they attain a low plateau that can be followed in some animals by a second peak. Ultimately, viral levels decline and the infection is cleared. By comparing modeling predictions with experimental data, researchers examined the relative roles of availability of cells susceptible to infection, so-called target cells, and innate and adaptive immune responses in controlling the virus.

The research showed that the two-part innate immune response, generated by natural killer cells, and the antiviral effect caused by interferon, a naturally produced protective molecule, can explain the first rapid viral decline and subsequent second viral peak. The second peak comes about because as the viral level falls, the immune response also falls allowing the virus the opportunity to grow back before the adaptive ultimately clears it.

However, for eventual viral clearance it is the body's adaptive immune response that is needed. The data analyzed were from equine influenza virus infection in horses. However, similar viral kinetic profiles have been observed in humans infected with the influenza virus. The authors conclude that the study can be used to explain the viral and interferon kinetics observed during a typical influenza virus infection.


**Gene discovery helps explain how flu can cause severe infections**

Scientists have discovered a new gene in the influenza virus that helps the virus control the body's response to infection.

Although this control is exerted by the virus, surprisingly it reduces the impact of the infection. The findings will help researchers better understand how flu can cause severe infections, as well as inform research into new treatments.

Researchers found when the virus gene – called PA-X – was active, mice infected with flu subsequently recovered. When the PA-X gene did not work properly, the immune system was found to overreact. This made the infection worse, and did not help destroy the virus any quicker.

The study looked at how the gene affected the behaviour of "Spanish flu", a virulent strain of influenza that caused a pandemic in 1918.

It was carried out by the Universities of Cambridge, Cork, Edinburgh and Utah, the Institute of Systems Biology in Seattle and the United States National Institutes of Health.

Scientists discovered the PA-X gene some 30 years after flu genome was first decoded.
Professor Paul Digard, of The Roslin Institute at the University of Edinburgh, said: "Just finding this gene in the first place is important, but the find is even more significant because of the role it seems to play in the body's response to flu."

The researchers, whose study is published online in the journal Science, found the hidden gene by analysing patterns of changes in the genetic information of thousands of different flu strains.

Dr Andrew Firth, of the University of Cambridge, said: "The flu virus has a very, very small genome—just 12 genes. Finding a new gene makes a pretty significant change to our understanding of this virus."

**Flu immunity is affected by how many viruses actually cause the infection**

*New research published in the Journal of Leukocyte Biology suggests that the immune response differs depending on the amount of virus received during infection*

Bethesda, MD—Not only does the type of flu virus affect a patient's outcome, but a new research report appearing in the *Journal of Leukocyte Biology* suggests that the number of viruses involved in the initial infection may be important too. Scientists from Canada found that when mice were infected by relatively high concentrations of the flu virus, they not only developed immunity against the virus that infected them, but this also promoted the generation of a type of immune cell in the lungs poised to rapidly react against infections with other strains of the flu, as well. Mice that were infected with a relatively low concentration of the virus developed weaker immunity against the strain that infected them, did not build up this crucial population of immune cells in the lungs, and showed only delayed immunity toward other flu strains. This discovery could pave the way for new prophylactic strategies to fight flu infections and provides a novel basis for vaccine design.

"Hopefully, the findings of our study will help to develop better vaccine preparations that will be more effective in inducing protective cellular immunity to fight against infectious pathogens such as bacteria, viruses and fungi," said Martin V. Richter, Ph.D., the lead researcher involved in the work from the Department of Medicine at the Université de Sherbrooke and Centre de Recherche Clinique Étienne-Le Bel in Québec, Canada.

To make this discovery, scientists infected two groups of mice with two different infectious doses of influenza A (H3N2) and analyzed several aspects of inflammation and immunity during the initial infection as well as during reinfection with a different strain of virus. The first group was infected with a low dose of the virus whereas the second group was infected with a high dose of the same virus. Mice infected with the high dose showed increased morbidity, a greater degree of lung inflammation, but also a greater recruitment of influenza-specific immune cells (CD8+ T cells) into their lungs, and a better generation of long-lived respiratory CD8+ T cells called memory CD8+ T cells. In contrast, the mice infected with the low dose of virus suffered less from primary infection but all of the immune responses were induced to lower levels. Consequently, reinfection of mice, 60 days after primary infection, revealed that mice previously infected with a higher dose showed increased protection due to greater magnitude of the memory CD8+ T cell pool present in their lungs before reinfection. This is the first demonstration that the initial infectious dose has an important impact on the generation of specific types of immune memory cells and on the degree of immune protection against reinfection.

"Recent experience with emerging and mutating strains of influenza virus highlight how very few changes in this virus could lead to a catastrophic flu crisis," said John Wherry, Ph.D., Deputy Editor of the *Journal of Leukocyte Biology*. "While considerable efforts have been invested in predicting new emerging flu strains for our yearly vaccines, it is impossible to prepare for every possible way the flu can mutate. This new research shows that it may be possible to enhance current vaccines to offer broader protection against different flu strains, known and unknown."

**Details:** Isabelle Marois, Alexandre Cloutier, Émilie Garneau, and Martin V. Richter. Initial infectious dose dictates the innate, adaptive, and memory responses to influenza in the respiratory tract. J. Leukoc Biol. July 2012 92:107-121; doi:10.1189/jlb.1011490; [http://www.jleukbio.org/content/92/1/107.abstract](http://www.jleukbio.org/content/92/1/107.abstract)
Programmable DNA scissors: A double-RNA structure in the bacterial immune system has been discovered that directs Cas9 protein to cleave and destroy invading DNA at specific nucleotide sequences. This same dual RNA structure should be programmable for genome editing. (Credit: Image by H. Adam Steinberg, artforScience.com)

ScienceDaily (June 28, 2012) — Genetic engineers and genomics researchers should welcome the news from the Lawrence Berkeley National Laboratory (Berkeley Lab) where an international team of scientists has discovered a new and possibly more effective means of editing genomes. This discovery holds potentially big implications for advanced biofuels and therapeutic drugs, as genetically modified microorganisms, such as bacteria and fungi, are expected to play a key role in the green chemistry production of these and other valuable chemical products.

Jennifer Doudna, a biochemist with Berkeley Lab's Physical Biosciences Division and professor at the University of California (UC) Berkeley, helped lead the team that identified a double-RNA structure responsible for directing a bacterial protein to cleave foreign DNA at specific nucleotide sequences. Furthermore, the research team found that it is possible to program the protein with a single RNA to enable cleavage of essentially any DNA sequence.

"We've discovered the mechanism behind the RNA-guided cleavage of double-stranded DNA that is central to the bacterial acquired immunity system," says Doudna, who holds appointments with UC Berkeley's Department of Molecular and Cell Biology and Department of Chemistry, and is an investigator with the Howard Hughes Medical Institute (HHMI). "Our results could provide genetic engineers with a new and promising alternative to artificial enzymes for gene targeting and genome editing in bacteria and other cell types."

Doudna is one of two corresponding authors of a paper in the journal Science describing this work titled "A programmable dual RNA-guided DNA endonuclease in adaptive bacterial immunity." The second corresponding author is Emmanuelle Charpentier of the Laboratory for Molecular Infection Medicine at Sweden's Umeå University. Other co-authors of the paper were Martin Jinek, Krzysztof Chylinski, Ines Fonfara and Michael Hauer.

Bacterial and archaeon microbes face a never-ending onslaught from viruses and invading circles of nucleic acid known as plasmids. To survive, the microbes deploy an adaptive-type nucleic acid-based immune system that revolves around a genetic element known as CRISPR, which stands for Clustered Regularly Interspaced Short Palindromic Repeats. Through the combination of CRISPRs and associated endonucleases, called CRISPR-associated—"Cas"—proteins, bacteria and archaeons are able to utilize small customized crRNA molecules (for CRISPR-derived RNA) to target and destroy the DNA of invading viruses and plasmids.
There are three distinct types of CRISPR/Cas immunity systems. Doudna and her colleagues studied the Type II system which relies exclusively upon one family of endonucleases for the targeting and cleaving of foreign DNA, the Cas9 proteins.

"For the Type II CRISPR/Cas system, we found that crRNA connects via base-pairs with a transactivating RNA (tracrRNA), to form a two-RNA structure," Doudna says. "These dual RNA molecules (tracrRNA:crRNA) direct Cas9 proteins to introduce double-stranded DNA breaks at specific sites targeted by the crRNA-guide sequence."

Doudna and her colleagues demonstrated that the dual tracrRNA:crRNA molecules can be engineered as a single RNA chimera for site-specific DNA cleavage, opening the door to RNA-programmable genome editing.

"Cas9 binds to the tracrRNA:crRNA complex which in turn directs it to a specific DNA sequence through base-pairing between the crRNA and the target DNA," Doudna says. "Microbes use this elegant mechanism to cleave and destroy viruses and plasmids, but for genome editing, the system could be used to introduce targeted DNA changes into the genome.

Doudna notes that the "beauty of CRISPR loci" is that they can be moved around on plasmids.

"It is well-established that CRISPR systems can be transplanted into heterologous bacterial strains," she says. "Also, there is evidence to suggest that CRISPR loci are horizontally transferred in nature."

Doudna and her colleagues are now in the process of gathering more details on how the RNA-guided cleavage reaction works and testing whether the system will work in eukaryotic organisms including fungi, worms, plants and human cells.

"Although we've not yet demonstrated genome editing, given the mechanism we describe it is now a very real possibility," Doudna says.

New Mechanism of Bacterial Pathogenesis Discovered

ScienceDaily (June 27, 2012) — Scientists have identified a new mechanism of bacterial pathogenesis. The results of the research project, partly funded by the Academy of Finland, have been published in the journal Proceedings of the National Academy of Sciences of the United States of America (PNAS).

Bacteria that cause chronic infections have an amazing but yet poorly known ability to subvert immune response, live and produce offspring, enter and wake up from a dormant phase to cause, in some instances, deadly complications.

Bartonella bacteria cause chronic infections in mammals (incl. humans), and are typically transmitted to new hosts mainly by arthropod vectors such as fleas, lice and ticks, but also via direct tissue trauma (e.g. cat scratches).

One very notable feature of these bacteria is their ability to cause vasoproliferative tumours that resemble Kaposi’s sarcoma in patients suffering from immunodeficiency (e.g. AIDS, aggressive cancer treatments, organ transplantation). If left untreated, these foci of inflammation maintain a chronic infection and contribute to transmitting bacteria to new hosts.

In his research, biologist Arto Pulliainen (University of Turku) has demonstrated that Bartonella henselae injects a protein called BepA into vascular endothelial cells and that this protein manipulates cAMP-mediated cell signalling using a previously unknown mechanism.

BepA directly binds the host cell adenylyl cyclase, which is an enzyme responsible for the production of cAMP. However, the binding of BepA to the adenylyl cyclase does not activate cAMP production per se, but the adenylyl cyclase rather becomes more sensitive to its natural activator, stimulatory G-protein (Gαs). The cellular concentration of cAMP increases and prevents the death of the host cell. BepA significantly prolongs the lifespan of the host cell and partly contributes to the formation of vasoproliferative tumours.

Several bacterial species are known to manipulate host cell functions via cAMP-mediated cell signalling. The symptoms are typically very strong and may even be deadly. The best-known example is Vibrio cholerae and its cholera toxin, which modifies Gα into a permanently adenylyl cyclase-stimulating form. BepA, in turn, manipulates host cell signalling in a subtle sophisticated manner, which is ideal for chronic persistence of Bartonella henselae in the infected vascular endothelium.

Journal Reference:
PLoS Pathogens

**Broad Spectrum Pro-Quorum-Sensing Molecules as Inhibitors of Virulence in Vibrios**

**Abstract**

Quorum sensing (QS) is a bacterial cell-cell communication process that relies on the production and detection of extracellular signal molecules called autoinducers. QS allows bacteria to perform collective activities. *Vibrio cholerae*, a pathogen that causes an acute disease, uses QS to repress virulence factor production and biofilm formation. Thus, molecules that activate QS in *V. cholerae* have the potential to control pathogenicity in this globally important bacterium. Using a whole-cell high-throughput screen, we identified eleven molecules that activate *V. cholerae* QS: eight molecules are receptor agonists and three molecules are antagonists of LuxO, the central NtrC-type response regulator that controls the global *V. cholerae* QS cascade. The LuxO inhibitors act by an uncompetitive mechanism by binding to the pre-formed LuxO-ATP complex to inhibit ATP hydrolysis. Genetic analyses suggest that the inhibitors bind in close proximity to the Walker B motif. The inhibitors display broad-spectrum capability in activation of QS in *Vibrio* species that employ LuxO. To the best of our knowledge, these are the first molecules identified that inhibit the ATPase activity of a NtrC-type response regulator. Our discovery supports the idea that exploiting pro-QS molecules is a promising strategy for the development of novel anti-infectives.

**Author Summary**

The disease cholera, caused by the pathogenic bacterium *Vibrio cholerae*, is a major health concern in developing regions. In order to be virulent, *V. cholerae* must precisely control the timing of production of virulence factors. To do this, *V. cholerae* uses a cell-cell communication process called quorum sensing to regulate pathogenicity. In the current work, we identify and characterize new classes of small molecules that interfere with quorum-sensing-control of virulence in multiple *Vibrio* species. The molecules target the key quorum-sensing regulator LuxO. These molecules have the potential to be developed into new anti-infectives to combat infectious diseases of global importance.

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**Could Stem Cells Cure MS?**

A growth factor isolated from human stem cells shows promising results in a mouse model of multiple sclerosis.

**By Megan Scudellari | May 23, 2012**

Human mesenchymal stem cells (hMSCs) have become a popular potential therapy for numerous autoimmune and neurological disorders. But while these bone marrow-derived stem cells have been studied in great detail in the dish, scientists know little about how they modulate the immune system and promote tissue repair in living organisms.

Now, one research team has uncovered a molecular mechanism by which hMSCs promote recovery in a mouse model of multiple sclerosis (MS).

According to research, published online Sunday (May 20) in *Nature Neuroscience*, a growth factor produced by hMSCs fights MS in two ways: blocking a destructive autoimmune response and repairing neuronal damage. The finding could help advance ongoing clinical trials testing hMSCs as a therapy for MS.

The researchers have identified “a unique factor that has surprisingly potent activity mediating neuron repair,” said Jacques Galipeau, a cell therapy researcher at Emory University in Atlanta, Georgia, who was not involved in the research. “The magnitude of the effect on a mouse model of MS is a big deal.”

MS is an autoimmune disease in which the immune system attacks myelin sheaths that surround and protect nerve cells. The attack leaves nerves exposed and unable to send signals to the brain and back, resulting in the loss of motor skills, coordination, vision, and cognitive abilities. There is no cure for MS, and most current therapies work to simply suppress the immune system, preventing further neuronal damage. None have demonstrated an ability to also repair damaged myelin and promote recovery.

In 2009, Robert Miller and colleagues at Case Western Reserve University in Cleveland, Ohio, demonstrated that hMSCs dramatically reversed the symptoms of multiple sclerosis in a mouse model of...
the disorder. “The animals got better,” recalled Miller. The team hypothesized that the stem cells suppress the immune response and promote remyelination.

But Miller wanted to know exactly what the cells were doing. To find out, his team isolated the medium on which the hMSCs were grown to determine if the cells or something they secreted was responsible for the observed recovery. The medium alone was enough to induce recovery in mice, pointing to the latter.

To find out exactly which molecule or molecules in the medium were responsible, the researchers separated the proteins in the fluid based on the molecular weight and injected each isolate into mice exhibiting symptoms of MS. The mid-weight solution, of proteins with masses between 50 and 100 kilodaltons (kDa), caused recovery. “That eliminated a huge number of potential candidates,” said Miller.

The researchers then narrowed the field again with a literature search for a molecule that fit their criteria: secreted by hMSCs, 50-100 kDa in size, and involved in tissue repair. They identified hepatocyte growth factor (HGF), a cytokine made by mesenchymal cells that has been shown to promote tissue regeneration and cell survival in numerous experiments. Sure enough, HGF alone was enough to promote recovery in the MS mouse models, and blocking the receptor for HGF in those mice blocked recovery. The team also demonstrated that HGF suppresses immune responses in vivo and accelerates remyelination of neurons in vitro. Finally, they saw that HGF causes remyelination in rats with a lesion on their spinal cord.

“I feel quite confident that HGF suppresses the immune response and also drives myelin repair,” said Miller. There are likely other hMSCs-produced factors that contribute to the cells’ beneficial effect, but HGF is certainly critical, he said. “The data are compelling,” added Galipeau.

There are currently several clinical trials testing hMSCs in MS patients around the world, including a phase I trial at the Cleveland Clinic in Ohio that emerged from the work in Miller’s lab. The new mechanistic information could help researchers designing those therapies to select cells that produce high levels of HGF, said Miller, which should promote remyelination and maximize symptom reversal.

But the research begs a question: why not simply forgo the cells altogether? That point is up for debate. Miller argues that stem cells act as vehicles to transport HGF, and other potential factors, directly to the central nervous system and maintain production there. But a single protein is a far more practical therapy—cheaper and easier to produce—than a cell therapy, countered Galipeau. “The best cell therapy is one done without a cell,” he said. “Identifying these factors and testing them as single agents is an important short-term deliverable of stem cell science.”

To find out more about which cell therapies are in clinical trials, stay tuned for the July issue of The Scientist, featuring an analysis of the growing cell therapy industry.


Jumping Genes a Cause of Cancer?
Genome sequence analysis confirms mobile genetic elements are a mutagenic mechanism in a variety of cancers.
By Ruth Williams | June 28, 2012

Within the human genome, small DNA elements called retrotransposons have the potential to wreak mutational havoc by copying themselves and reinserting into the genome at multiple locations. Normal adult cells have suppressive mechanisms to stop these elements from jumping about, but according to a report published today (June 28) in Science, those mechanisms can break down in certain cancers. The findings suggest that, in some cases, jumping genes might even cause cancer or contribute to its progression.

“The paper is very important,” said Keith Slotkin a molecular geneticist at Ohio State University in Columbus, who did not participate in the study. “There has long been a weak association between cancer and transposable element activity, but this paper now categorically shows that transposable element activation is a source of new mutations in cancer cells.”
Retrotransposons are common in eukaryotic genomes and, thanks to repeated rounds of copying and inserting themselves over the course of evolution, they generally comprise a significant fraction of a species’ DNA. Indeed, they make up a whopping 45 percent of the human genome.

“Most are molecular fossils—dead pieces of DNA,” explained John Moran a human geneticist at the University of Michigan Medical School in Ann Arbor, who did not participate in the research. That is, they have accumulated so many mutations over the course of evolution that they are now merely inactive remnants. “But,” he said, “Some are actively mobilizing.

Normal adult cells keep these mobile elements under control using a number of mechanisms including epigenetic suppression to prevent their expression, and mRNA degradation to catch those that are transcribed, explained Slotkin.

But a handful of reports documenting retrotransposon insertions in tumor cells suggest that these suppressive mechanisms might go awry in some cancers. Peter Park of Harvard Medical School in Boston wanted to know just how common such cancer-related retrotransposon activation was. “Whole genome sequencing technologies have now allowed us to look at this in a very comprehensive way,” he said.

There was one complication, however: traditional sequencing software programs are designed to specifically omit repeated DNA elements like transposons, explained co-author Peter Kharchenko, also of Harvard Medical School. So Kharchenko and Park designed a new program called TEA, transposable element analyzer.

The team used TEA to compare the whole genome sequence data of tumors and normal tissues taken from 43 cancer patients. TEA searched the genomic sequence fragments for ones containing both repeat elements and unique sequence data to determine the exact position of transposable elements in the genomes, and it found nearly 200 novel insertions in the tumor genomes. Sixty-four of these occurred in genes, many of which are commonly mutated in cancer. The insertions often affected expression of those genes, suggesting a causative or contributing role in the cancer.

Interestingly, while insertions were relatively common in cancers of epithelial origin, such as colorectal and ovarian, not one was detected in tumors of the blood or brain. “Understanding why there may be cell-type-specific differences that provide more permissive environments for retrotransposition would be very interesting to follow up,” said Moran.

“Retrotransposition is clearly not the only mechanism contributing to mutagenesis and cancers,” said Kharchenko “but it is an option that hasn’t been considered previously.”

The team now plans to extend their analysis, and apply the TEA software to as many cancer genomes as possible. “If it is prevalent enough,” said Kharchenko, and if it does appear to contribute to cancer pathology, “then you can start thinking about ways to target it.” A lot of these elements behave like retroviruses, he added, so research on suppressing retroviruses might be equally useful for designing therapies to keep retrotransposons in place.


Literature Review Examines Incidence of MRSA Infections Among HIV-Infected People

“Despite the rise of methicillin-resistant Staphylococcus aureus (MRSA) skin and soft tissue infections (SSTIs) among HIV-infected persons during the era of highly active antiretroviral therapy (HAART), the precise relationship between these two infections has not been fully elucidated. Therefore, we provide a comprehensive, literature-based review of MRSA infections among HIV-infected persons. ...

“A systematic search of MEDLINE using the search terms 'HIV' and 'MRSA' identified references published during the HAART era (January 1996 to January 2011). ...

“The most common type of MRSA infection among HIV-infected persons is SSTI caused by USA300, Panton-Valentine leukocidin (PVL)-positive strains. HIV-infected persons have an increased risk for both initial MRSA infections and recurrent infections compared with the general population. Risk factors for MRSA infections in this population include immunosuppression, comorbid conditions and certain lifestyle behaviours such as high-risk sexual behaviours and illicit drug use. Further research is needed on the optimal treatment and prevention strategies for MRSA infections among HIV-infected persons. ...

“HIV-infected persons have a propensity for MRSA SSTI and a high rate of recurrent disease. The reasons for the elevated rates of MRSA infections among HIV-infected persons appear to be multifactorial, but may be mitigated with optimized HIV control and reductions in associated risk factors.”
Four-in-One AIDS Drug Gets the OK in Clinical Trial
Agence France Presse, (06.28.2012)
A potential new once-daily HIV treatment is as safe and effective as traditional combination therapies, according to two clinical trials reported on Friday. Researchers tested Quad—an experimental pill made by Gilead Sciences and comprising emtricitabine (FTC), tenofovir (TDF), elvitegravir, and a booster called cobicistat—against two other treatment combinations.

In the first study, Quad was matched against the three-in-one pill Atripla, which has been a standard HIV therapy since 2006. After 48 weeks, 88 percent of patients taking Quad had undetectable viral loads, compared with 84 percent of Atripla patients. Side effects were infrequent among the North American trial’s 700 participants. Mild nausea was the most common adverse event for Quad patients, and the Atripla group was more likely to experience dizziness, unusual dreams or insomnia, and skin rashes.

The second trial compared Quad with a widely recommended therapy, ritonavir-boosted atazanavir, FTC, and TDF. After 48 weeks, 90 percent taking Quad had undetectable viral loads, compared with 87 percent of those who took the other combination. Just 3.7 percent of patients taking Quad had to stop because of side effects, compared with 5.1 percent of those taking the other drug combination. However, reported kidney complications were relatively higher in the Quad group. The trial involved 708 patients at study sites in Australia, North America, and Europe.

In May, a Food and Drug Advisory panel recommended the agency approve Quad for previously untreated adult patients with HIV. The agency’s decision is expected by August.

[PNU editor’s note: The studies, “Co-Formulated Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Versus Co-Formulated Efavirenz, Emtricitabine, and Tenofovir for Initial Treatment of HIV-1 Infection: A Randomized, Double-Blind, Phase 3 Trial, Analysis of Results After 48 Weeks” and “Co-Formulated Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate Versus Ritonavir-Boosted Atazanavir Plus Co-Formulated Emtricitabine and Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: A Randomized, Double-Blind, Phase 3, Non-Inferiority Trial,” were published in the Lancet (2012;9835:2439-2448 and 2429-2438, respectively).]