December 2012 Epidemics and AIDS Update

1. The South Responds to Its Surging HIV Epidemic
2. Indonesia’s Fastest Growing HIV Demographic? Housewives
3. Childhood HIV Risks Becoming Neglected Disease As Fewer Children Born With HIV, Experts Warn
4. Genome of the Black Death Reveals Evidence for an Antique Bubonic Plague Pandemic
5. Fat’s Immune Sentinels
6. Virus Monopolizes Host’s Repairmen
7. Architecture Reveals Genome’s Secrets
8. Viral Skeleton
9. Crucial Step in AIDS Virus Maturation Simulated for First Time
10. A leap forward for red blood cell formation
11. Why Some Strains of Lyme Disease Bacteria Are Common and Others Are Not
12. 'Transport Infrastructure' Determines Spread of HIV Subtypes in Africa, Study Finds
13. Couples HIV Testing and Counselling Prompts Rapid Switch to Consistent Condom Use in South African Study
14. Gladstone scientists discover novel mechanism by which calorie restriction influences longevity
15. Rilpivirine for HIV: added benefit for single agent proven
16. In Girl’s Last Hope, Altered Immune Cells Beat Leukemia
17. Electrically spun fabric offers dual defense against pregnancy, HIV
18. Botswana: Public health bill shocking and regressive
19. Many U.S. Children with TB Have International Connections
20. Six Promising HIV Drugs in the Pipeline
21. Outrage sparked by Brighton University film showing
22. BBC News Examines HIV Microbicide Research
23. Uganda’s Proposed Anti-Homosexuality Legislation Would Inhibit Health Care Access
25. Epigenetics May Be a Critical Factor Contributing to Homosexuality, Study Suggests
26. Experiment Finds Achilles’ Heel of Ulcer Bug, H. Pylori
27. People Lack Knowledge About Link Between Oral Cancer, Sexual Health
28. More South African pregnant women contracting HIV
29. Namibia: No Change in Behaviour Despite HIV/AIDS
30. Doctors force headbands onto HIV patients
31. Brighton university cancels screening of AIDS denialist film
32. Syphilis and HIV: A Dangerous Duo Affecting Gay and Bisexual Men
33. CDC: Chlamydia, Gonorrhea Cases Increasing
34. Global Burden Of Disease Study Finds People Worldwide Living Longer, But With More Illness, Disability
35. WHO Releases New Guidelines For Interventions Aimed At Protecting Sex Workers From HIV
36. New findings on killer bacteria’s defence
37. A drug used to treat HIV might defuse deadly staph infections
38. Aerobic exercise trumps resistance training for weight and fat loss
39. Dead Guts Spill History of Extinct Microbes: Fecal Samples from Archeological Sites Reveal Evolution of Human Gut Microbes
40. Rich Kenyans hardest hit by HIV, says study
41. Tackling HIV and AIDS through taxation in Uganda
42. New Guidelines to Better Prevent HIV in Sex Workers
43. Experts Warn Banning Thimerosal From Use In Vaccines Would Harm Immunization Campaigns In Developing World
44. Immune cells use tethered slings to avoid being swept away
45. Mayo Clinic-led Study Unravels Biological Pathway That Controls the Leakiness of Blood Vessels
46. Chances seen rising for chikungunya outbreaks in NYC, Atlanta, Miami
47. Plumes Across the Pacific Deliver Thousands of Microbial Species to North American West Coast
48. People With HIV Hospitalized Less Often Since Combination Antiretroviral Drug Therapy Introduced
49. Autoimmune Disease: Retraining White Blood Cells
50. Drug Used to Treat HIV Might Defuse Deadly Staph Infections
51. Treatment with a protease inhibitor during the first trimester of pregnancy increases the risk of pre-term birth
52. Major Breakthrough in HIV Research: Study Published Today Online in The Journal of Experimental Medicine Identifies Population of Cells Serving as the Major Reservoir for HIV ****
53. ViiV Healthcare announces regulatory submissions for dolutegravir in the EU, US and Canada
The South Responds to Its Surging HIV Epidemic

*American Medical News*, (12.03.2012) Christine S. Moyer

The American South is having an HIV/AIDS epidemic which did not receive attention until recently. The release of new HIV data in July has helped raise awareness of the epidemic’s shift from cities such as New York and San Francisco to the rural South. According to a July report by the Southern AIDS Coalition, approximately 37 percent of the nation’s population lives in the South, but half of the new HIV diagnoses and 46 percent of the new AIDS cases occur there each year. Southern health professionals and community members are implementing programs that target access to health care, low education rates, and the stigma of HIV/AIDS.

In Alabama, there are only five credentialed HIV medicine physicians. As a result, patients travel more than an hour to reach a treatment center, and those without transportation often go without care as there is no public transit in rural areas. To correct this problem, staff at Medical AIDS Outreach of Alabama used to drive 50 miles once a week from Montgomery to Selma to treat patients. In 2012, the organization introduced telemedicine as a more efficient way to reach patients in some of the state’s poorest and most rural communities. There are several remote sites where patients can meet virtually with their physicians in a one-to-one, real-time interaction. With a Bluetooth stethoscope and digital dermascope, doctors examine virtually a patient’s heart, lung, and abdominal sounds as well as flushed skin, lesions, and thrush. A pharmacist is also available one a week through telemedicine to discuss adherence to prescribed medications. In Birmingham, Ala., cosmetology students learn basic information about the disease, its stigma, and prevention methods as part of Beauty in Knowing, a five-session program.
Experts Warn Childhood HIV Risks Becoming Neglected Disease As Fewer Children Born With HIV,

"The success in reducing the number of children born with HIV is in danger of leaving children who already have the disease with poor access to treatment, experts in HIV and AIDS have warned," BMJ reports. "Denis Broun, executive director of UNITAID, a not-for-profit organization that purchases drugs for the treatment of HIV and AIDS and other diseases, has welcomed news that the number of new infections among children worldwide had fallen from 560,000 in 2003 to 330,000 in 2011," BMJ notes. "However, it said that only 28 percent of children who needed antiretrovirals got them, whereas the proportion in adults is 50 percent," the journal adds. "Kate Iorpenda, senior adviser on HIV and children at the International HIV and AIDS Alliance, said that, in the worldwide push to stop transmission from mothers to their babies—the mantra of the AIDS-free generation—children already infected with HIV were in danger of being forgotten," BMJ writes, noting, "She said that pediatric HIV infections in children is falling," the journal writes, adding, "But he said that because fewer children are already infected people to medical care, and reduce stigma about the disease.

Indonesia’s Fastest Growing HIV Demographic? Housewives

According to the Surabaya Aids Prevention Commission, which monitors the spread of HIV in Indonesia, housewives in parts of Indonesia now outnumber prostitutes for new cases of HIV. The Bernama news outlet reports that 60 percent of new HIV cases in Bogor, West Java, are housewives, while HIV among sex workers is leveling out. The commission encourages all pregnant women to get tested for HIV; however, the Jakarta Globe reports that less than 1 in 10 consent to testing, adding that those who do test positive blame their husbands. The commission sees husbands who travel across provinces for work and spend long periods away from home as the top offenders. The HIV-positive women feel that their own communities will not support them even if they became HIV-positive by an unfaithful husband, as Indonesia’s newspapers still tout headlines about HIV-positive couples being run out of villages and children being expelled from schools because they have HIV-positive fathers.

Childhood HIV Risks Becoming Neglected Disease As Fewer Children Born With HIV,

"A report by UNAIDS... released a week before World AIDS Day on 1 December, said that the annual number of new HIV infections among children worldwide had fallen from 560,000 in 2003 to 330,000 in 2011," BMJ notes. "The success in reducing the number of children born with HIV is in danger of leaving children who already have the disease with poor access to treatment, experts in HIV and AIDS have warned," BMJ reports. "Denis Broun, executive director of UNITAID, a not-for-profit organization that purchases drugs for the treatment of HIV and AIDS and other diseases, has welcomed news that the number of new infections among children is falling," the journal writes, adding, "But he said that because fewer children are born with the virus, drug companies would no longer have an incentive to manufacture treatments and that childhood HIV might become a neglected disease."

"The success in reducing the number of children born with HIV is in danger of leaving children who already have the disease with poor access to treatment, experts in HIV and AIDS have warned," BMJ reports.
drugs were not a profitable market for drug companies and that there was a lack of drugs that were 'appropriate, affordable, and palatable’” (Gulland, 11/30).

**Genome of the Black Death Reveals Evidence for an Antique Bubonic Plague Pandemic**

ScienceDaily (Nov. 29, 2012) — In a comparison of more than 300 contemporary strains of *Yersinia pestis*, the bacterium that causes bubonic plague, with ancient bacterial DNA isolated from victims of the Black Death (1347–1351), a team led by researchers at University of Tuebingen obtained evidence suggestive of a bubonic plague outbreak in the late antique period (8th to 10th centuries AD). The study published online November 30 in *PLoS ONE* raises strong suspicion that the plague of Justinian, a massive pandemic that is thought to be in part responsible for the collapse of the East Roman Empire, may have been caused by the same bacterium implicated in the Black Death.

After the initial reconstruction of the complete medieval genome of *Y.pestis* from a Black Death cemetery in London last year, the researchers from the University of Tuebingen used a published genome dataset from more than 300 modern *Y.pestis* strains to reconstruct the relationship of ancient and modern plague bacteria. Due to the well-established age of the ancient remains they were able to date major radiation events in the history of this pathogen that are likely linked to major pandemics in the human population.

The **comparison of modern and ancient genomes revealed that of the 311 *Y.pestis* strains analyzed, 275 trace their ancestry back to the medieval Black Death pandemic in the mid of the 14th century, confirming a previous analysis of 21 complete plague genomes by the same authors in 2011.** In the new larger dataset, however, the authors identified an additional cluster of 11 contemporary bacterial strains that branch in the *Y.pestis* phylogeny between the 7th and 10th centuries, thus suggesting a radiation event of *Y.pestis* bacteria during a major outbreak. This time period roughly coincides with the Justinian plague, which historical sources suggest took place between the 6th and 8th centuries AD.

Historians have long suspected that the plague of Justinian was a pandemic of bubonic plague but until now little empirical evidence existed. The suggestion that this pandemic was likely also caused by bubonic plague was rather unexpected for the researchers as their previous analysis published in 2011 revealed no evidence for major outbreaks of bubonic plague before the Black Death. "Our new analysis implies that bubonic plague may have been a major killer already in the late Roman Empire." explains Krause, a Juniorprofessor at the University of Tuebingen specializing in Palaeogenetics. "The plague of Justinian seems like the best candidate for this earlier pandemic."

**Journal Reference:**

**Fat's Immune Sentinels**

Certain immune cells keep adipose tissue in check by helping to define normal and abnormal physiological states

By Justin Odegaard and Ajay Chawla | December 1, 2012

Obesity and associated health consequences are the greatest public-health challenges of our time. Worldwide, an estimated 1.5 billion people tip the scales as overweight—300–500 million of whom are obese—placing nearly a quarter of humanity at dramatically increased risk for diabetes, cardiovascular disease, and many types of cancer. While considerable scientific investments have barely begun to slow the expansion of our waistlines, they have yielded unexpected physiologic insights, perhaps the greatest of which is the discovery that proper metabolic function requires a previously unsuspected level of cooperation between the cells that make up each internal organ and that organ's resident leukocytes.

For almost 2 centuries, the stereotypical appearance of basic human tissues—muscles with their long, cabled cells; kidneys with their cauliflower floret–shaped structures—have been a familiar staple of medical textbooks. But this depiction has proven to be deceptive. Only recently has cellular inventory of these tissues revealed remarkable numbers of macrophages—whose main function is to ingest and degrade dead cells and pathogens—and other leukocytes tucked away among the more familiar tissue cells. Researchers had seen these immune cells with simple stains, but had always assumed they were transient, rather than permanent residents. Now, it’s clear that rather than being randomly distributed, these leukocytes are arranged in reproducible patterns that are tissue-specific. For example, liver samples consistently harbor similar numbers of macrophages (known as Kupffer cells) lining the ducts and
channels between liver cells, whereas brain tissues have a similarly constant complement of microglia, the resident macrophages of the central nervous system, located around blood vessels and near synapses, as well as in other areas. Indeed, macrophage representation is significant and similar—around 5 to 15 percent—across nearly every tissue type, and is remarkably well conserved across vertebrate species. Perhaps most interesting of all, however, is that depletion of macrophages from any given tissue does not result in permanent loss, haphazard recolonization, or encroachment by other leukocyte lineages, but in rapid and precise restoration of the original macrophage complement in both spatial and numerical terms. If macrophages had only been present transiently, such precise recolonization would not occur.

Metabolic function requires a previously unsuspected level of cooperation between the cells that make up each internal organ and that organ’s resident leukocytes. While macrophages’ role in inflammation following infection or injury has long been appreciated, the strict precision and temporal stability of their arrangements in healthy tissues, the conservation of these patterns across vertebrate species, and their rapid and precise reestablishment following depletion all suggest that active mechanisms exist to maintain the specific number and activation status of tissue macrophage populations at set points that ensure an appropriate complement of leukocytes at all times. Indeed, recent work has begun to unearth the complex recruitment and retention networks dedicated to the maintenance and survival of resident leukocyte/macrophage populations. For example, many organs continually release chemokines that attract monocytes—macrophage precursor cells—and promote their survival. Needless to say, such sophisticated arrangements—especially in tissues where there is little risk of infection, such as the brain—are not easily explained by traditional theories of host defense. Why, then, would organs go to such lengths to outfit themselves with macrophages?

Studies are beginning to reveal that resident macrophages shoulder critical, nonimmunologic tissue functions in the brain, gut, and bone marrow. In the brain, microglia are required for the development and function of neuronal synapses, for pruning synapses, clearing superfluous newborn hippocampal cells, mediating extracellular matrix remodeling, and directing synapse firing. Resident intestinal macrophages are necessary for the maintenance of gut epithelial integrity. They receive signals from damaged epithelial cells and release activation factors to nearby regenerative colon stem cells. Similarly, bone marrow macrophages act as critical components of the hematopoietic—or blood-cell forming—stem cell niche, retaining the stem cells in the marrow, preventing their inappropriate mobilization, and releasing them into circulation in times of need. Together, these observations suggest that, as a general principle, vertebrate tissues are critically dependent on resident tissue macrophages to perform their primary functions. Macrophages are also present at the same unchanging percentages in healthy adipose tissue, both the white variety that stores globules of excess fat, and the brown, which burns fat stores in order to generate heat. Researchers are only just beginning to understand the role of resident macrophages in adipose tissue, but the concept of leukocyte set points—defined as a specific state observed in vivo to which the system returns following perturbation—could be useful in explaining the maintenance of healthy adipose tissue metabolism and its dysregulation in obese adipose tissue when the set point changes.

**Macrophages and healthy fat metabolism**

White adipose tissue is the primary site of long-term nutrient storage in vertebrates. It is also the largest endocrine organ in humans, secreting a variety of hormones termed “adipokines” that regulate systemic metabolism. Healthy white adipose tissue is characterized histologically by a predominance of adipocytes
mixed with a smattering of adipose-tissue macrophages, eosinophils, and regulatory T cells (T regs). In nonobese individuals, interleukin 4 (IL-4) secreted by eosinophils maintains adipose tissue macrophages in an activation state that promotes and maintains proper adipocyte function.

However, there are several modes of macrophage activation. The cells comprise a heterogeneous and plastic leukocyte lineage. While their physiologic roles are diverse and, in many instances, poorly understood, their activation states may be broadly divided into two categories: classical (M1) and alternative (M2). Classical M1 activation is an aggressive state in which macrophages attack and engulf bacteria or bacterially infected cells and secrete cytokines that promote inflammation, such as interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α). M1 is the state most commonly associated with macrophages during infection. Alternative M2 activation describes the behavior of macrophages reacting to parasitic infection, but is also associated with wound healing, and results in the production of anti-inflammatory cytokines such as IL-10. However, when macrophages are present as normal tissue constituents, they are not activated by either bacteria or parasites, nor, once active, do they seek out these pathogens. The M1 and M2 classifications are useful in that they describe pro- (M1) or anti-inflammatory (M2) states.

Although we know that pro-inflammatory M1 activated macrophages are present in obese fat tissue, and anti-inflammatory M2 activated macrophages are present in lean fat tissue, the exact nature of the macrophage-adipocyte signaling mechanism is unclear. Nor do we know what stimulates the eosinophils to release macrophage-supporting IL-4 in lean tissue or what makes eosinophil numbers diminish in obese tissues. However, the fact that these two states appear to be preserved in obese and lean adipose tissue points to the intimate interdependence between adipocytes and leukocytes for proper tissue function and, importantly, shows that disruptions in the tissue set point results in significant functional consequences for both the tissue and the organism as a whole.

In contrast to white adipose tissue, brown adipose tissue has little role in long-term storage of energy but is critically required for acclimation to cold temperatures via a process termed adaptive thermogenesis. This stems from brown adipose tissue’s ability to oxidize fatty acids via uncoupled respiration, which generates heat rather than ATP in the mitochondria. Indeed, active brown adipose tissue is capable of impressive metabolic feats: the 63 g of brown adipose tissue present in a typical adult human has been estimated, if fully activated, to be capable of catabolizing 4.1 kg of white adipose tissue each year. Until recently, it was believed that sympathetic nerves, which innervate both brown and white adipose tissues, detect dropping temperatures and coordinate the metabolic response to cold exposure. However, my (Chawla’s) research group at the University of California, San Francisco, has shown that the signal for the thermogenic response to cold is, in part, transmitted to brown adipocytes by alternatively activated M2 macrophages. Importantly, exposure of animals to progressively colder temperatures induces alternative activation of macrophages resident in both brown and white adipose tissue. As a result, these macrophages synthesize catecholamines and release norepinephrine, which causes white fat to convert its fat stores into metabolically accessible fatty acids and activates brown adipose tissue’s thermogenic capacity. In one final experiment, we artificially manipulated the
macrophage set point in brown and white adipose tissues by injecting IL-4 or genetically reducing the macrophages’ ability to respond to the cytokine. Simply changing the levels of this one immune cytokine was enough to ramp up thermogenesis when more IL-4 was present, or to impair it when the response to the cytokine was diminished. While using IL-4 to activate brown fat may seem an attractive approach to shedding excess weight, cytokines are prohibitively expensive to make for long term use and difficult to deliver (they must be injected), and they may exacerbate or cause allergies.

**Obesity**

While the rigidity and precision of tissue set points are regulated by tight physiologic constraints, an organism’s survival under varying environmental influences necessitates constant adaptation. Tissue equilibria must then counteract these influences to restore homeostasis. With obesity now an omnipresent global concern, the influence of environmental stress—particularly in the form of nutrient excess—on white adipose tissue set points is an object of intense scrutiny. As nutrient levels exceed homeostatic requirements, adipocytes respond by increasing in number and in size. This nutrient excess, however, eventually causes cellular stress, which changes the leukocyte set point from around 10 percent macrophages in lean white adipose tissue to as much as 50–60 percent in the adipose tissue of obese mice. The percentage of protective M2 pathway-activating eosinophils also dramatically decreases in obese white adipose tissue. In turn, macrophages in obese mice are classically (M1) activated, swapping the anti-inflammatory M2 phenotype for one that is pro-inflammatory.

To highlight the downstream physiological effects of such inflammation, one recent study showed that severe inflammation, as usually caused by pervasive bacterial or viral infection, results in a departure from the homeostatic set point in order to most effectively combat the disease. The immune system produces, mobilizes, and supports an impressive arsenal of immune cells, the majority of which rely on glucose for their energy requirements. To supply this high demand for glucose, an organism-wide signal is sent to all nonessential tissues to dampen their insulin sensitivity, thus making glucose more available in circulation where it can be prioritized for use by the immune system. Because of any given pathogen’s inevitable proliferative advantage, the speed and responsiveness of this reaction is of the utmost importance. Therefore, predetermined set points allow both rapid and accurate tissue recalibration and nutrient reprioritization after the infection has been cleared. This mechanism helps explain why chronic, low-level inflammation in adipose tissue results in permanent insulin resistance in many tissues of the body. When engorged and stressed fat cells begin to apoptose, they attract classically activated macrophages to remove cell debris. These cells activate and recruit more macrophages and other inflammatory immune cells, reinforcing the new numerical and phenotypic set point of leukocytes in the stressed fat tissue. As a result, adipocytes, in addition to liver and muscle cells, become resistant to insulin and no longer respond properly to the hormone, which normally initiates uptake of excess glucose from the bloodstream. This occurs in an effort to limit storage of excess nutrients and relieve cellular stress.

Disruptions in the tissue set point results in significant functional consequences for both the tissue and the organism as a whole.

If nutrient intake returns to homeostatic levels—or metabolic demand increases proportionately—the original tissue equilibrium is reestablished. If nutrient intake and expenditure are mismatched over a long period of time, however, a new set point is established in white adipose tissue, characterized by a chronic low-grade inflammation (mediated by the classically activated M1 macrophage population) and insulin resistance. This set point emerges as the key pathophysiological nexus responsible for the adverse health consequences of the new obese white adipose tissue set point.

**Tissue set points**

The wealth of literature on macrophages and other leukocytes in adipose tissue clearly defines functional roles for these cells in adipose tissue biology and establishes them as bona fide tissue constituents rather than immunologic transients. The physiologically normal set points in fat tissue can be shifted by chronic overnutrition; the pro-inflammatory obese adipose tissue itself, once established, demonstrates temporal
stability and resistance to change. As in lean adipose tissue, any perturbation of leukocyte set points, whether numeric or phenotypic, disrupts the tissue’s new functional parameters.2

While significant progress has been made in defining leukocyte set points within adipose tissue with respect to obesity and insulin signaling, our understanding of leukocyte populations, phenotypes, and functional contributions in other tissues remains rudimentary. Indeed, our understanding remains incomplete even within adipose tissue: what defines a stable set point? How are predefined set points encoded? How can equilibria be manipulated to combat maladaptive shifts? Addressing these questions within adipose tissue offers the prospect of understanding how other complex tissues may adapt to changing environmental demands. The therapeutic implications of an improved understanding are profound because they suggest that pharmacologic targeting of macrophage activation, rather than simply inflammation, might be efficacious in treating the global obesity epidemic.

Justin Odegaard is a molecular pathology fellow at Stanford University School of Medicine, and Ajay Chawla is an associate professor at the University of California, San Francisco.

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References

Virus Monopolizes Host’s Repairmen

Human cytomegalovirus fixes its broken DNA by exclusively co-opting its host’s repair proteins

By Ed Yong | November 29, 2012

Human cells have several pathways for repairing damage to DNA, but those infected by human cytomegalovirus (HCMV) have no such recourse. Researchers at the University of Idaho have found that this virus can monopolize its host’s repair proteins, so they exclusively fix damage to the virus’s genome but not the host’s.

“If the virus co-opts the repair machinery for its own good, a cell’s normal capacity to repair itself might be disabled,” said Lee Fortunato from the University of Idaho, who led the new study, published today (29 November) in PLOS Pathogens. And that’s exactly what she and her colleagues found.

HCMV can itself damage host DNA, breaking both strands of the double helix at specific points. Although the cell responds by mobilizing repair proteins, most of these repairs are never finished.

This is partly because, as Fortunato showed in earlier studies, HCMV impounds some repair proteins in its replication centers—large structures within the host nucleus where the virus reproduces itself. “I started thinking about whether the virus was absconding with what it needed for its own ends, perhaps leaving the host genome vulnerable in the process,” she said.

To test that idea, Fortunato’s team exposed infected skin cells to ultraviolet (UV) radiation to inflict DNA damage. Specifically, UV radiation is known to fuse adjacent thymine bases together into dimers,
which are then cut out and replaced through a pathway called nucleotide excision repair (NER). Using antibodies that recognize the fused bases, the team showed that they had disappeared from the viral replication centers after a day, but still remained in the rest of the cell’s nucleus, where host DNA resides. The researchers also DNA from infected cells through gel electrophoresis, to separate large fully-repaired pieces from smaller unrepaired fragments. They treated the gels with fluorescent molecules that recognise viral DNA and host DNA, and glow in different colours. Sure enough, viral DNA was efficiently repaired, but host DNA was not.

“Our study is the only one to date that has looked separately at the viral and host genomes,” said Fortunato. “If we had just looked at the entire DNA of these cells, we would have concluded that NER was decreased in HCMV infected cells—true for the host genome, but not for the viral one.”

 “[The finding] suggests that the viral genome is perhaps more accessible to being repaired,” said Matt Weitzman, a virologist from the University of Pennsylvania, who was not involved in the study. However, he added, “the mechanism through which this happens still need to be addressed.” Fortunato suspects that viral proteins could interact with the host’s repair proteins and actively shuttle them into the replication centers. “My hope is that we might be able to find the viral proteins responsible for sequestering the repair machinery in the infected cells,” Fortunato said. Developing drugs that block these proteins might allow infected cells to repair their genome more efficiently, which could be useful for people with suppressed immune systems.

Regardless of the mechanism, the results might help to explain one of the more severe consequences of HCMV infection—birth defects. Although most US adults have been infected by HCMV at some point in their lives, they usually suffer little more than a mild cold, unless they have weakened immune systems. But if the virus infects a pregnant woman, it can cross the placenta into the fetus. Around 1 percent of fetuses are infected in this way, and between 10 and 25 percent of them develop neurological problems, such as small heads (microcephaly) and problems with hearing and vision.

Fortunato suspects that HCMV’s ability to damage DNA, while preventing cells from repairing it, might be involved in these birth defects. Damaged fetal cells that are not killed by the virus “might not function properly in a developing brain, migrate to [their] correct position, or interact properly with neighboring cells,” she said. Since a fetus only has a small number of cells, problems in any one of them may have serious consequences.

J. M. O’Dowd et al., “HCMV-infected cells maintain efficient nucleotide excision repair of the viral genome while abrogating repair of the host genome,” PLOS Pathogens, 8: e1003038, 2012.

Architecture Reveals Genome’s Secrets

Three-dimensional genome maps are leading to a deeper understanding of how the genome’s form influences its function

By Sabrina Richards | November 25, 2012

Genome sequencing projects have provided rich troves of information about stretches of DNA that regulate gene expression, as well as how different genetic sequences contribute to health and disease. But these studies misses a key element of the genome—its spatial organization—which has long been recognized as an important regulator of gene expression. Regulatory elements often lie thousands of base pairs away from their target genes, and recent technological advances are allowing scientists to begin examining how distant chromosome locations interact inside a nucleus. The creation and function of 3-D genome organization, some say, is the next frontier of genetics.

Genome spatial organization is critical for gene regulation, explained Job Dekker, a molecular geneticist at the University of Massachusetts Medical School, and “everything else chromosomes do involves three dimensions,” as well. Chromosomes have to replicate, separate properly during division, and change shape during the cell cycle—all without tangling. The genome is “rebuilt entirely after cell division,” Dekker said.

The mechanisms for such delicate orchestration have remained unclear, however. About 10 years ago—just as the human genome project was completing its first draft sequence—Dekker pioneered a new
In addition to better understanding cancer, chromosome folding may help predict it. As normal cells transition into tumor cells, genes can change their spatial organization in characteristic ways, said Tom Mistel, a cell biologist at the National Cancer Institute at the National Institutes of Health who is using the genome’s 3-D architecture to develop diagnostic tools. His team has shown that in breast cancer, certain genes “change position dramatically as their cells transform into cancer cells,” allowing Mistel
and his colleagues to “look at an unknown tissue biopsy, localize genes, and with high accuracy determine whether its cancer or normal,” he said.

**Comments**

*Roy Niles*, November 26, 2012

Forms only seem to influence functions. Influence requires some form of intelligent intent or purpose. A form’s intelligence is in its function, so in the end it’s the function that does the influencing of anything that forms. Unless you have an accidental form with no function at all of course—which is likely to be impossible in a functionally formed universe.

*John Edser*, November 26, 2012

What concerns me is how modern genome analysis effects evolutionary theory. Darwin’s pioneering work remains in a Hamilton and Dawkins inspired, gene centric dark age. Modern research is pointing one way: organism gene combinations code for phenotypes not individual genes such that each coding combination must include one non coding control gene. This strictly disallows genes their own individual fitness. Yet, Hamilton’s model, which demands independent in fitness gene centricity in order to power a proposed evolution of organism fitness altruism, continues to underwrite modern evolutionary theory. Models cannot validly replace the theory they were simplified/oversimplified from yet this was and remains the case. Hamilton et al deleted all genetic epistasis from their proposed gene centric model. Hamilton’s Rule which remains the basis of Dawkins “selfish gene” centricity: rb>c provides no variable to represent genetic epistasis. I corrected this amazing omission via including the variable e allowing gene combinations to code for phenotypes: \((r^e)b>c\). Fact: no organism in nature is comprised of just a single locus with two alleles. Thus J.B.S Haldane who inspired Hamilton et al cannot claim to lay down his life for just 2 brothers related 0.5 or eight cousins related 0.125 but minimally, 4 brothers or 64 cousins related 0.25 and 0.015625 respectively since e=2 as a minimum. As e increases above 2 the rule becomes inoperable disallowing gene centricity. Humans have 23 chromosome pairs so a minimal human model requires \(e=23\) putting Hamilton’s c cost into the billions! Hamilton’s modelling unreality has never been addressed. John Edser  
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**Viral Skeleton**

A newly discovered family of tubulins—members of the cytoskeleton—encoded by bacteriophages plays a role in arranging the location of DNA within virus’s bacterial host

By Kerry Grens | November 1, 2012
**PhuZed Phage**: When phage infect bacteria, host proteins begin transcribing a viral gene to produce PhuZ proteins (1), which form tubulin-like polymers that elongate from each pole of the cell (2). The filaments position replicating viral DNA at the cell’s center (3). Newly made viral DNA is encased in capsids (4), and released by lysis from the cell after final assembly (5) to infect other bacteria.

**EDITOR’S CHOICE IN STRUCTURAL BIOLOGY**

**THE PAPER**


Until a few years ago, the cytoskeleton was thought to be a structure unique to eukaryotes, but a stream of discoveries in the past decade has shown that prokaryotes also have actin- and tubulin-like components. Tubulins are proteins that form microtubules, which manage everything from sorting genetic material during cell division to supporting cell shape and assisting in cell motility. A collaboration between David Agard’s group at the University of California, San Francisco, and Joe Pogliano’s lab at UC San Diego has now shown that a bacteriophage virus also encodes a family of tubulin-like proteins, which appear to determine the location of phage’s DNA in the host cell. “This points to the fact that phage too have their own very sophisticated cell biology,” says Agard.

The initial discovery relied on a simple database search for tubulin-resembling genes in the genome of a bacteriophage that infects *Pseudomonas chlororaphis* bacteria. The team named the family PhuZ for phage tubulin/FtsZ—FtsZ being a bacterial tubulin. In characterizing the structure of PhuZ, the researchers found that it forms filaments like other tubulins, but in a unique way. Individual monomers of tubulin proteins typically connect with one another longitudinally to form filaments, but Agard and his colleagues found that the distance between PhuZ monomers in this chain is much greater than that among any other tubulins known. “To me, that hints at unexpected properties, and unexpected properties are always good!” says Agard. Instead of having more robust longitudinal contacts, monomers of PhuZ have an extension at one end—the carboxy terminus—that acts like a bridge to span and strengthen the links of the PhuZ filament.

To examine the novel protein’s function, the group tagged PhuZ with green fluorescent protein. They observed that PhuZ formed filaments that extended across the host cell, from pole to pole, and that also touched the phage DNA clustered in the middle of the cell.

The researchers also studied a mutant form of PhuZ, which lacked the protein’s ability to assemble and disassemble dynamically, and instead assembled permanently into a polymer. They found that in most cases, the DNA cluster no longer localized to the middle of the cell. And a third of cells infected with mutant-PhuZ phages had more than one viral DNA cluster. The mutant...
protein also reduced the replication capacity of the phage by about half. The results led Agard’s group to suspect that because DNA positioning affected replication numbers, the PhuZ protein could be critical to the phage’s overall ability to infect its bacterial host.

Jan Löwe at the MRC Laboratory of Molecular Biology says that the findings add to the growing expanse of research on non-eukaryotic cytoskeletons. “I think this is a great example of what’s still to come,” he says.

**Crucial Step in AIDS Virus Maturation Simulated for First Time**

ScienceDaily (Dec. 4, 2012) — Using computational techniques, researchers in Spain have shown how a protein responsible for the maturation of the virus releases itself to initiate infection.

Bioinformaticians at IMIM (Hospital del Mar Medical Research Institute) and UPF (Pompeu Fabra University) have used molecular simulation techniques to explain a specific step in the maturation of the HIV virions, i.e., how newly formed inert virus particles become infectious, which is essential in understanding how the virus replicates. These results, which have been published in the latest edition of PNAS, could be crucial to the design of future antiretrovirals.

HIV virions mature and become infectious as a result of the action of a protein called HIV protease. This protein acts like a pair of scissors, cutting the long chain of connected proteins that form HIV into individual proteins that will form the infectious structure of new virions. According to the researchers of the IMIM-UPF computational biophysics group, “One of the most intriguing aspects of the whole HIV maturation process is how free HIV protease, i.e. the ‘scissors protein,’ appears for the first time, since it is also initially part of the long poly-protein chains that make up new HIV virions.”

Using ACEMD a software for molecular simulations and a technology known as GPUGRID.net, Gianni De Fabritiis’ group has demonstrated that the first “scissors proteins” can cut themselves out from within the middle of these poly-protein chains. They do this by binding one of their connected ends (the N-terminus) to their own active site and then cutting the chemical bond that connects them to the rest of the chain. This is the initial step of the whole HIV maturation process. If the HIV protease can be stopped during the maturation process, it will prevent viral particles, or virions, from reaching maturity and, therefore, from becoming infectious.

This work was performed using GPUGRID.net, a voluntary distributed computing platform that harnesses the processing power of thousands of NVIDIA GPU accelerators from household computers made available by the public for research purposes. It’s akin to accessing a virtual supercomputer. One of the benefits of GPU acceleration is that it provides computing power that is around 10 times higher than that generated by computers based on CPUs alone. It reduces research costs accordingly by providing a level computational power that previously was only available on dedicated, multi-million dollar supercomputers.

Researchers use this computing power to process large numbers of data and generate highly complex molecular simulations. In this specific case, thousands of computer simulations have been carried out, each for hundreds of nanoseconds (billions of a second) for a total of almost a millisecond.

According to researchers, this discovery in the HIV maturation process provides an alternative approach in the design of future pharmaceutical products based on the use of these new molecular mechanisms. For now, this work provides a greater understanding of a crucial step in the life cycle of HIV, a virus that directly attacks and weakens the human immune system, making it vulnerable to a wide range of infections, and which affects millions of people around the world.

**Journal Reference:**
A leap forward for red blood cell formation

Researchers have identified 75 genetic regions that influence red blood cell formation

New research is revealing how red blood cells are made and how the body regulates the amount of haemoglobin that is packaged in red blood cells at any time. Genomic analysis techniques have doubled the number of genetic regions that are likely to be involved in red blood cell formation and subsequent study using fruit flies has given insights into what these regions do.

Haemoglobin is the protein which captures oxygen from the lungs for transport and delivery to tissues. It colours blood cells red and each day hundreds of millions of fresh red blood cells have to be formed by blood stem cells to replace the ones which come to the end of their life cycle. Anaemia, one of the most common disorders for which people visit their surgery, ensues if the production of new red blood cells is insufficient or their lifespan is shortened. The new genetic information is laying the foundations for future studies into the roots of anaemia by uncovering new biological pathways and mechanisms involved in controlling the size and number of red blood cells and the levels of haemoglobin.

The researchers used genome-wide association studies to identify genetic regions that appeared to influence the formation of red blood cells and their haemoglobin content.

"We studied the genetic influences behind six different physical parameters of red blood cells that reflect the volume and number of red blood cells and the levels of haemoglobin," says Dr John Chambers, lead author from Imperial College, London. "Our initial genetic association study looked into the genomes of 135,367 people and identified 75 genetic regions that directly influence these different traits of red blood cells. More than half – 43 – of these discoveries are new in people."

The team then closely examined using computational biology approaches the 75 genetic regions and the more than 3,000 genes responsible for protein production lie close to these regions. They prioritised 121 'candidate' genes or genes that are likely to regulate a trait in red blood cells from this list and investigated their function using information on model systems like from public databases as well as newly-generated data for fruit fly.

"Our work shows how model systems like fruit fly and mice can be used to provide insights into human genetics," says Professor Willem Ouwehand, lead author from the University of Cambridge and NHS Blood and Transplant. "We searched through a Mouse Genome database and found that 29 of our 121 candidate genes are linked to red blood cell formation in mice.

"These previous studies revealed that—when the function of these genes was switched off- the mice frequently developed reduced numbers of red blood cells, and anaemia. These observations made in mice make it highly likely that the remaining candidate genes, about which there is no knowledge yet, are also important regulators of red blood cell formation in people."

To investigate further, the team then reduced or 'silenced' the activity of the candidate genes in fruit flies. Although fruit flies do not have red blood cells, they share some of the gene functions leading to the formation of blood elements. These studies confirmed that sets of genes involved in controlling human red blood cell traits in people were also important for the formation of blood cells in fly.

"These results support the view that genetic association studies identify sets of genes that are conserved in evolution across a wide range of species," says Dr Nicole Soranzo, lead author from the Wellcome Trust Sanger Institute. "This is exciting because it means that we can obtain extensive new insights into the genetics and biological pathway of human health by studying model organisms."

"Although the underlying mechanisms for the majority of genes we've identified still need to be elucidated, our research is opening many doors for future studies on the generation of red blood cells for clinical use in the laboratory and may also provide insights which may lead to improvements in the treatment of patients with inherited anaemias."

Why Some Strains of Lyme Disease Bacteria Are Common and Others Are Not

ScienceDaily (Dec. 4, 2012) — New clues about the bacteria that cause Lyme disease could lead to a novel strategy to reduce infections, according to a study to be published in mBio®, the online open-access journal of the American Society for Microbiology, on Dec. 4.

The study reveals that the immune system of the white-footed mouse, a very common reservoir for Borrelia burgdorferi (the bacterium that causes the disease), responds differently to different strains of the bacterium, a finding that will help scientists tweak the animals' immune systems to prevent infection. A vaccine that keeps these wild mice free of the pathogen could significantly curb the spread of the disease from mice to ticks to humans.
"There's no human vaccine, and there's not likely to be one," says Alan Barbour of the University of California, Irvine, the lead author of the study. "We have to focus on lowering the risk. One way to do that is by treating the animals that carry the disease." Rabies offers a good example of how this might be accomplished, says Barbour. By deploying vaccine-laced food bait, public health officials have managed to lower the rabies infection rate in wildlife and significantly limited the spread of the disease to pets and humans.

Although Lyme disease only emerged in the U.S. in the past 40 years or so, around 25,000 cases are now reported every year in this country and the medical costs of these cases are estimated to range in the billions of dollars. Despite the growing importance of the disease, little is known about the evolution and ecology of the bacterium that causes the illness.

Barbour and his colleagues sought to understand why as many as 15 different strains of B. burgdorferi exist in the wild at differing degrees of prevalence. In the parts of the country where Lyme disease is most common, the majority of white-footed mice are infected with B. burgdorferi during the course of the year. Unlike humans and lab mice, white-footed mice don't get sick when they're infected so the bacteria grow and multiply within them, and when a deer tick bites it sucks up the bacteria along with its blood meal.

In the lab, the group at UC Irvine exposed white-footed mice to various strains of B. burgdorferi and tracked the course of the infection. All the B. burgdorferi strains infected the white-footed mice, but some strains managed to grow to high densities in various mouse tissues while others did not. Barbour says the immune reactions the mice mounted against the various strains explain these discrepancies: the greater the immune response, the fewer bacteria found in a mouse's tissues and vice-versa. Importantly, the strains that grew to greatest densities within the mice are also the strains that are most prevalent in the wild.

When they looked at the immune reaction to individual B. burgdorferi proteins the authors found a complex interplay of reactivities. The mice reacted in different degrees to the various proteins present in a single bacterial strain, which could explain why such a great diversity of B. burgdorferi strains are sustained in the wild, say the authors.

Barbour says knowing more about how the white-footed mouse reacts to all the various B. burgdorferi strains and immunogenic proteins will help vaccine developers select the best proteins to put in a vaccine. "The best candidate for the mouse vaccine is something that's the same in all the [B. burgdorferi] strains," he says.

Once a vaccine for the white-footed mouse is developed, it will need to be tested by exposing immunized mice to a selected set of diverse B. burgdorferi strains, says Barbour, and the results of this study can help make that selection. "If we can find five that are representative, that would be an advantage."

This study, he says, "is going to provide a foundation for future studies in understanding the infection in these animals as we proceed with developing vaccines."

**Journal Reference:**
Elisabeth Baum, Fong Hue, and Alan G. Barbour. *Experimental Infections of the Reservoir Species Peromyscus leucopus with Diverse Strains of Borrelia burgdorferi, a Lyme Disease Agent.* mBio, 2012; DOI: [10.1128/mBio.00434-12](https://doi.org/10.1128/mBio.00434-12)

**'Transport Infrastructure' Determines Spread of HIV Subtypes in Africa, Study Finds**

ScienceDaily (Dec. 4, 2012) — Road networks and geographic factors affecting "spatial accessibility" have a major impact on the spread of HIV across sub-Saharan Africa, according to a study published online by the journal AIDS, official journal of the International AIDS Society. AIDS is published by Lippincott Williams & Wilkins, a part of Wolters Kluwer Health.

Using sophisticated mapping techniques and detailed databases, Dr Andrew J. Tatem of the University of Florida and colleagues have found "coherent spatial patterns in HIV-1 subtype distributions" across Africa. The researchers write, "A comprehensive understanding and evidence-base on accessibility, travel and mobility in resource poor settings would...provide a valuable resource for the strategic planning of disease control." The article is available on the AIDS journal homepage and in the November 28 print edition.

**Molecular HIV Data Overlaid on Spatial Accessibility Maps...**

Dr Tatem and his team performed a spatial analysis of the distribution of HIV for the years 1998 to 2008 to explore the impact of transportation networks and geography on the spread of HIV. Molecular data on specific HIV subtypes were obtained and analyzed in relation to "detailed and complete" spatial datasets on Africa-wide road networks.
In addition to roads, the data included a wide range of factors affecting "spatial accessibility," such as land cover, settlement locations, bodies of water, and topography. Sophisticated models were used to calculate not just the distance between locations, but also the ease of traveling from one place to another. Even simply laying a chart of HIV subtypes over a map of travel times between settled areas makes the link between spatial accessibility and HIV subtype "clearly evident." Dr Tatem and coauthors write, "[C]lusters of similar subtype distributions are well connected and easily accessible from one another, whereas regions of low accessibility separate groupings of similar subtype distributions."

**...Show Role of Travel in Spread of HIV Subtypes**

Transport networks and ease of travel—rather than the straight-line distances between locations—provided a much better explanation for the distribution of HIV subtypes. The data showed clustering of certain subtype distributions in well-connected regions—such as the western, eastern, and southern Africa and Ethiopia—that are separated by areas of "limited connectivity."

In contrast, the difficulty of travel in certain areas of central Africa likely restricted the spread of HIV, the researchers suggest. "The relatively poor connectivity in central Africa likely contributed to the slow initial growth of the epidemic in the first half of the 20th century," according to Dr Tatem and colleagues. The same factor may explain why HIV rates remained relatively low in central Africa, while soaring elsewhere.

Although the study has some important limitations, it adds important evidence for understanding how transport infrastructure and geography have affected—and will continue to affect—the spread of HIV. The authors hope that the modeling techniques used can be extended to map cultural and other factors affecting HIV subtype distribution and transmissibility. More accurate data on "actual volumes and flows of human travel" could also lend new insights.

"The increased travel and mobility of people may lead to the accelerated spread of new variants and the further diversification of the global HIV epidemic," Dr Tatem and coauthors write. They believe that ongoing efforts to monitor the spread of HIV subtypes could have important implications for developing effective prevention and treatment strategies.

**Journal Reference:**
Andrew J. Tatem, Joris Hemelaar, Rebecca R. Gray, Marco Salemi. *Spatial accessibility and the spread of HIV-1 subtypes and recombinants. AIDS, 2012; 26 (18): 2351 DOI: 10.1097/QAD.0b013e328359a904*

**Couples HIV Testing and Counseling Prompts Rapid Switch to Consistent Condom Use in South African Study**

*AI IDSMAP* @, (12.05.2012) Carole Leach-Lemens

Researchers report that HIV testing and counseling of couples resulted in consistent condom use among sero-discordant couples in stable relationships in South Africa. The study determined whether HIV testing and counseling (HTC)—with ongoing counseling and condom distribution—resulted in reduced unprotected sex in HIV-discordant couples who are in stable relationships.

Participants were part of the Partners in Prevention HSV/HIV transmission study to assess acyclovir as a secondary prophylaxis in HIV/HSV-2 co-infected persons to prevent transmission to their uninfected partner. The 508 HIV-infected participants self-reported behavioral data. They were from three South African sites: Gugulethu, Orange Farm, and Soweto. Most of the couples were in long-term relationships with low levels of intimate partner violence. The HIV-positive participants were predominantly female (77 percent), with a mean age of 33 years.

The important factor in the study was the timing of HTC for the HIV-positive participant: 0?7 days after testing positive, 8?14, 15–30, and more than 30 days. The primary outcome was unprotected sex reported by the person with HIV. Predicted probabilities of unprotected sex in the last month were calculated at baseline, at one month, and at 12 months. Of the participants, 71 percent who recently learned their HIV status reported having unprotected sex as compared to 25 percent who knew their status for a month. One month later, after all the couples had received HIV testing and counseling and were aware of the discordant relationship, the proportion of participants reporting unprotected sex was reduced from 71 percent to 8 percent.

Monthly counseling for the sero-positive partner, quarterly individual or couples’ testing, counseling for the uninfected partner, and condom provision resulted in the couples maintaining low levels of unprotected sex for one year. The authors conclude that the findings provide evidence that couples HTC is effective at rapidly increasing condom uptake, facilitating on-going condom use, and lowering rates of transmission. They advise caution in generalizing the findings to other than stable relationships.
**Gladstone scientists discover novel mechanism by which calorie restriction influences longevity**

**Breakthrough suggests way to protect cells from damage caused by chronic disease**

SAN FRANCISCO, CA—December 6, 2012—Scientists at the Gladstone Institutes have identified a novel mechanism by which a type of low-carb, low-calorie diet—called a "ketogenic diet"—could delay the effects of aging. This fundamental discovery reveals how such a diet could slow the aging process and may one day allow scientists to better treat or prevent age-related diseases, including heart disease, Alzheimer’s disease and many forms of cancer.

As the aging population continues to grow, age-related illnesses have become increasingly common. Already in the United States, nearly one in six people are over the age of 65. Heart disease continues to be the nation’s number one killer, with cancer and Alzheimer’s close behind. Such diseases place tremendous strain on patients, families and our healthcare system. But today, researchers in the laboratory of Gladstone Senior Investigator Eric Verdin, MD, have identified the role that a chemical compound in the human body plays in the aging process—and which may be key to new therapies for treating or preventing a variety of age-related diseases.

In the latest issue of the journal *Science*, available online today, Dr. Verdin and his team examined the role of the compound β-hydroxybutyrate (βOHB), a so-called "ketone body" that is produced during a prolonged low-calorie or ketogenic diet. While ketone bodies such as βOHB can be toxic when present at very high concentrations in people with diseases such as Type I diabetes, Dr. Verdin and colleagues found that at lower concentrations, βOHB helps protect cells from “oxidative stress”—which occurs as certain molecules build to toxic levels in the body and contributes to the aging process.

"Over the years, studies have found that restricting calories slows aging and increases longevity—however the mechanism of this effect has remained elusive," Dr. Verdin said. Dr. Verdin, the paper’s senior author, directs the Center for HIV & Aging at Gladstone and is also a professor at the University of California, San Francisco, with which Gladstone is affiliated. "Here, we find that βOHB—the body’s major source of energy during exercise or fasting—blocks a class of enzymes that would otherwise promote oxidative stress, thus protecting cells from aging."

Oxidative stress occurs as cells use oxygen to produce energy, but this activity also releases other potentially toxic molecules, known as free radicals. As cells age, they become less effective in clearing these free radicals—leading to cell damage, oxidative stress and the effects of aging.

However, Dr. Verdin and his team found that βOHB might actually help delay this process. In a series of laboratory experiments—first in human cells in a dish and then in tissues taken from mice—the team monitored the biochemical changes that occur when βOHB is administered during a chronic calorie-restricted diet. The researchers found that calorie restriction spurs βOHB production, which blocked the activity of a class of enzymes called histone deacetylases, or HDACs.

Normally HDACs keep a pair of genes, called Foxo3a and Mt2, switched off. But increased levels of βOHB block the HDACs from doing so, which by default activates the two genes. Once activated, these genes kick-start a process that helps cells resist oxidative stress. This discovery not only identifies a novel signaling role for βOHB, but it could also represent a way to slow the detrimental effects of aging in all cells of the body.

"This breakthrough also greatly advances our understanding of the underlying mechanism behind HDACs, which had already been known to be involved in aging and neurological disease," said Gladstone Investigator Katerina Akassoglou, PhD, an expert in neurological diseases and one of the paper’s co-authors. "The findings could be relevant for a wide range of neurological conditions, such as Alzheimer’s, Parkinson’s, autism and traumatic brain injury—diseases that afflict millions and for which there are few treatment options."

"Identifying βOHB as a link between caloric restriction and protection from oxidative stress opens up a variety of new avenues to researchers for combating disease," said Tadahiro Shimazu, a Gladstone postdoctoral fellow and the paper’s lead author. "In the future, we will continue to explore the role of βOHB—especially how it affects the body’s other organs, such as the heart or brain—to confirm whether the compound’s protective effects can be applied throughout the body."
Rilpivirine for HIV: added benefit for single agent proven
Contents of the dossier for the fixed combination product incomplete: existing study data not adequately analysed
Since the start of 2012, a new drug called rilpivirine has been available for adult patients infected with the human immunodeficiency virus type 1 (HIV-1). It is marketed by two different pharmaceutical companies, by one as a single agent (trade name Edurant®) and by the other as a fixed combination with other HIV drugs (trade name Evipler®). In two early benefit assessments pursuant to the “Act on the Reform of the Market for Medicinal Products” (AMNOG), the Institute for Quality and Efficiency in Health Care (IQWiG) has investigated whether the two new drugs have advantages over current standard therapies. According to IQWiG, there is proof that rilpivirine as a single agent offers a considerable added benefit to men infected with HIV-1. For women, the available studies provide corresponding "indications" of considerable added benefit.

On the other hand, no added benefit can be derived from the manufacturer’s dossier for the fixed combination—although precisely the same studies were available to the two pharmaceutical companies. This is because, unlike the manufacturer of the single agent, the company making the fixed combination product did not analyse the study data in a suitable way. Hence the contents of its dossier are incomplete.

G-BA specifies efavirenz as the appropriate comparator therapy
Two pharmaceutical companies introduced the new drug onto the market in Germany at the same time; one as a single agent and one in a fixed combination with emtricitabine and tenofovir. Both products are approved for adults who are beginning a treatment directed at stopping the multiplication of the virus for the first time and in whom not more than 100,000 viral components can be detected per millilitre of blood.

The Federal Joint Committee (G-BA) has in each case specified efavirenz-based therapy in combination with other drugs as the appropriate comparator therapy.

Studies on the single agent also relevant for the fixed combination
Results from a total of 3 studies were available. Since, at the time of the assessment, only analyses after 48 weeks were fully available for the two largest studies, IQWiG’s assessment is based on these analyses.

In all 3 studies, rilpivirine was tested as a single agent. Nevertheless, the results are also relevant for the assessment of the combination product, because the dosage of rilpivirine, emtricitabine and tenofovir administered in these studies corresponds exactly to the dosage in the fixed combination.

Viral load is a sufficiently valid surrogate parameter
In its dossier, the manufacturer of the single agent did not submit any data on the patient-relevant outcome "AIDS-defining diseases/death", i.e. on the outbreak of AIDS and on survival. Instead, the manufacturer used results of "viral load" in order to prove the added benefit. The viral load denotes the number of components of a virus present in the blood and it shows how active HIV is.

In principle, IQWiG considers this "surrogate parameter" as valid, i.e. meaningful, because patients in whom the number of viruses can be persistently suppressed below the limit of detection have, according to the current state of knowledge, a lower risk of developing AIDS or of dying. However, it is unclear whether a treatment has just as great an effect on the patient-relevant outcome as on the surrogate parameter.

Effect depends on gender
As regards the reduction in viral load, the 3 studies showed a statistically significant difference in favour of rilpivirine. However, as shown by the data on subgroups presented in this dossier [on the single agent], this only applies to male patients. This means that gender is here an "effect modifier". IQWiG therefore determines that there is proof of an added benefit in HIV-1-infected men, but not in women. Because of the described uncertainty concerning the size of the effect on the patient-relevant outcome, the extent of this added benefit cannot be quantified (is "non-quantifiable").

Fewer neurological side effects
Rilpivirine as a single agent also has advantages in terms of side effects: "neurological events" such as headaches or insomnia occurred less frequently. However, the analysis presented by the manufacturer contains a few uncertainties, which is why IQWiG considers there is no proof here, but only an "indication" of a lesser harm with rilpivirine compared to efavirenz.

Based on the overall results on side effects and viral load, the Institute considers that for male patients, there is proof of a considerable added benefit and for female patients a corresponding "indication".
No proof of added benefit of the fixed combination
In contrast to the single agent, there is no proof of an added benefit for the fixed combination of rilpivirine, emtricitabine and tenofovir. In its dossier the manufacturer did not analyse the available data in a suitable way.

Subgroup analyses (age, gender, severity of disease etc.) are routinely required in every dossier. However in this case the manufacturer did not carry these out, despite the fact that its dossier refers to the same studies reported in the dossier submitted by the manufacturer of the rilpivirine single agent, in which gender had been identified as an effect modifier. It is, however, precisely under these circumstances that such subgroup analyses are essential. The necessary data that the manufacturer should have analysed in an appropriate manner were indeed available. The pharmaceutical company also gives no reasons why the subgroup analyses were not provided.

In addition, the company excluded one study although it contained relevant information. The manufacturer of the single agent product accordingly included this study in its dossier.

In view of these deficiencies, IQWiG considers itself compelled to declare the contents of the dossier as "incomplete".

Dossiers are of a widely differing quality
"What is immediately striking in the assessment of rilpivirine, is the widely differing quality of the two dossiers—although the data on which they are based are practically identical", commented Institute Director Jürgen Windeler. "Whereas one manufacturer has used and suitably processed all the available data, the other has completely excluded one relevant study and has also not properly analysed the two other studies". The motives remain obscure.

G-BA decides on the extent of added benefit
The dossier assessment is part of the overall procedure for early benefit assessment conducted by the G-BA. After publication of the manufacturer's dossier and its assessment by IQWiG, the G-BA initiates a formal commenting procedure which provides further information and can result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

An overview of the results of the two benefit assessments by IQWiG is given by the following extract: rilpivirine (PDF, 541 kB) and rilpivirine/emtricitabine/tenofovir (PDF, 131 kB). You can also find easily understandable and brief German-language information about rilpivirine and rilpivirine/emtricitabine/tenofovir on the website gesundheitsinformation.de, published by IQWiG.

NYTimes, December 9, 2012
In Girl’s Last Hope, Altered Immune Cells Beat Leukemia
By Denise Grady
PHILIPSBURG, Pa. — Emma Whitehead has been bounding around the house lately, practicing somersaults and rugby-style tumbles that make her parents wince.

It is hard to believe, but last spring Emma, then 6, was near death from leukemia. She had relapsed twice after chemotherapy, and doctors had run out of options.

Desperate to save her, her parents sought an experimental treatment at the Children’s Hospital of Philadelphia, one that had never before been tried in a child, or in anyone with the type of leukemia Emma had. The experiment, in April, used a disabled form of the AIDS virus to reprogram Emma’s immune system genetically to kill cancer cells.

The treatment very nearly killed her. But she emerged from it cancer-free, and seven months later is still in complete remission. She is the first child and one of the first humans ever in whom new techniques have achieved a long-sought goal — giving a patient’s own immune system the lasting ability to fight cancer.

Emma had been ill with acute lymphoblastic leukemia since 2010, when she was 5, her parents, Kari and Tom, said. She is their only child.

She is among just a dozen patients with advanced leukemia to have received the experimental treatment, which was developed at the University of Pennsylvania. Similar approaches are also being tried at other centers, including the National Cancer Institute and Memorial Sloan-Kettering Cancer Center in New York.

“Our goal is to have a cure, but we can’t say that word,” said Dr. Carl June, who leads the research team at the University of Pennsylvania. He hopes the new treatment will eventually replace bone-marrow
transplantation, an even more arduous, risky and expensive procedure that is now the last hope when other treatments fail in leukemia and related diseases.

Three adults with chronic leukemia treated at the University of Pennsylvania have also had complete remissions, with no signs of disease; two of them have been well for more than two years, said Dr. David Porter. Four adults improved but did not have full remissions, and one was treated too recently to evaluate. A child improved and then relapsed. In two adults, the treatment did not work at all. The Pennsylvania researchers are presenting their results on Sunday and Monday in Atlanta at a meeting of the American Society of Hematology.

Despite the mixed results, cancer experts not involved with the research say it has tremendous promise, because even in this early phase of testing it has worked in seemingly hopeless cases.

“I think this is a major breakthrough,” said Dr. Ivan Borrello, a cancer expert and associate professor of medicine at the Johns Hopkins University School of Medicine.

Dr. John Wagner, director of pediatric blood and marrow transplantation at the University of Minnesota, called the Pennsylvania results “phenomenal,” and said they were “what we’ve all been working and hoping for but not seeing to this extent.”

A major drug company, Novartis, is betting on the Penn team, and has committed $20 million to building a research center on the Penn campus to bring the treatment to market.

Hervé Hoppenot, president of Novartis Oncology, called the research “fantastic” and said it had the potential — if the early results hold up — to revolutionize the treatment of leukemia and related blood cancers. Researchers say the same approach, reprogramming the patient’s immune system, may also be used eventually against tumors like breast and prostate cancer.

To perform the treatment, doctors remove millions of the patient’s T-cells — a type of white blood cell — and insert new genes that enable the T-cells to kill cancer cells. The new genes program the T-cells to attack B-cells, a normal part of the immune system that turns malignant in leukemia.

The altered T-cells — called chimeric antigen receptor cells — are then dripped back into the patient’s veins, and if all goes well they multiply like crazy and start destroying the cancer.

The T-cells home in on a protein called CD-19 that is found on the surface of most B-cells, whether they are healthy or malignant.

A sign that the treatment is working is that the patient becomes terribly ill, with raging fevers and chills — a reaction that oncologists call “shake and bake,” Dr. June said. Its medical name is cytokine-release syndrome, or cytokine storm, referring to the natural chemicals that pour out of cells in the immune system as they are being activated, causing fevers and other symptoms. The storm can also flood the lungs and cause perilous drops in blood pressure — effects that nearly killed Emma.

Steroids sometimes ease the reaction, but did not help Emma. Her temperature hit 105. She wound up on a ventilator, unconscious and swollen almost beyond recognition, surrounded by friends and family who had come to say goodbye.

But at the eleventh hour, a battery of blood tests gave the researchers a clue as to what might help save Emma: Her level of one of the cytokines, interleukin-6 or IL-6, had shot up a thousandfold. Doctors had never seen such a spike before and thought it might be what was making her so sick. Dr. June knew that a drug could lower IL-6 — his daughter takes it, for rheumatoid arthritis. It had never been used for a crisis like Emma’s, but there was little to lose. Her oncologist, Dr. Stephan A. Grupp, ordered the drug. The response, he said, was “amazing.”

Within hours, Emma began to stabilize. She woke up a week later, on May 2, the day she turned 7; the intensive-care staff sang “Happy Birthday.”

Since then, the research team has used the same drug, tocilizumab, in several other patients.

In patients with lasting remissions after the treatment, the altered T-cells persist in the bloodstream, though in smaller numbers than when they were fighting the disease. Some patients have had the cells for years.

Dr. Michel Sadelain, who conducts similar studies at the Sloan-Kettering Institute, said: “These T-cells are living drugs. With a pill, you take it, it’s eliminated from your body and you have to take it again.”

But T-cells, he said, “could potentially be given only once, maybe only once or twice or three times.”

Penn researchers said they were surprised to find any big drug company interested in their work, because a new batch of T-cells must be created for each patient — a far cry from the familiar commercial strategy of developing products like Viagra or cholesterol medicines, in which millions of people take the same drug.

But Mr. Hoppenot said Novartis was taking a different path with cancer drugs, looking for treatments that would have a big, unmistakable impact on a small number of patients. Such home-run drugs can be
approved more quickly and efficiently, he said, with smaller studies than are needed for drugs with less obvious benefits.

“The economic model is totally acceptable,” Mr. Hoppenot said.

But such drugs tend to be hugely expensive. A prime example is the Novartis drug Gleevec, which won rapid approval in 2001 for use against certain types of leukemia and gastrointestinal tumors. It can cost more than $5,000 a month, depending on the dosage.

Dr. June said that producing engineered T-cells costs about $20,000 per patient — far less than the cost of a bone-marrow transplant. Scaling up the procedure should make it even less expensive, he said, but he added, “Our costs do not include any profit margin, facility depreciation costs, or other clinical care costs, and other research costs.”

The research is still in its early stages, and many questions remain. The researchers are not entirely sure why the treatment works, or why it sometimes fails. One patient had a remission after being treated only twice, and even then the reaction was so delayed that it took the researchers by surprise. For the patients who had no response whatsoever, the team suspects a flawed batch of T-cells. The child who had a temporary remission apparently relapsed because not all of her leukemic cells had the marker that was targeted by the altered T-cells.

It is not clear whether a patient’s body needs the altered T-cells forever. The cells do have a drawback: they destroy healthy B-cells as well as cancerous ones, leaving patients vulnerable to certain types of infection. So, Emma and the other patients need regular treatments with immune globulins to prevent illness.

So far, her parents say, Emma seems to have taken it all in stride. She went back to school this year with her second-grade classmates, and though her grades are high and she reads about 50 books a month, she insists impishly that her favorite subjects are lunch and recess.

“It’s time for her to be a kid again and get her childhood back,” Mr. Whitehead said.

November 30, 2012

**Electrically spun fabric offers dual defense against pregnancy, HIV**

By Hannah Hickey

The only way to protect against HIV and unintended pregnancy today is the condom. It’s an effective technology, but not appropriate or popular in all situations.

A University of Washington team has developed a versatile platform to simultaneously offer contraception and prevent HIV. Electrically spun cloth with nanometer-sized fibers can dissolve to release drugs, providing a platform for cheap, discrete and reversible protection.

The electrospun fibers can release chemicals or they can physically block sperm, as shown here.

The research was published this week in the Public Library of Science’s open-access journal *[PLoS One](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3754617/)*. The Bill & Melinda Gates Foundation last month awarded the UW researchers almost $1 million to pursue the technology.

“Our dream is to create a product women can use to protect themselves from HIV infection and unintended pregnancy,” said corresponding author *[Kim Woodrow](https://www.piw.org/staff/kim-woodrow)*, a UW assistant professor of
bioengineering. “We have the drugs to do that. It’s really about delivering them in a way that makes them more potent, and allows a woman to want to use it.”

Electrospinning uses an electric field to catapult a charged fluid jet through air to create very fine, nanometer-scale fibers. The fibers can be manipulated to control the material’s solubility, strength and even geometry. Because of this versatility, fibers may be better at delivering medicine than existing technologies such as gels, tablets or pills. No high temperatures are involved, so the method is suitable for heat-sensitive molecules. The fabric can also incorporate large molecules, such as proteins and antibodies, that are hard to deliver through other methods.

At a lab meeting last year, Woodrow presented the concept, and co-authors Emily Krogstad and Cameron Ball, both first-year graduate students, pursued the idea.

Fibers stick to a hard surface (top) and then can be removed to create a hollow ring (bottom left). Bottom right shows a closeup of the tiny fibers.

They first dissolved polymers approved by the Food and Drug Administration and antiretroviral drugs used to treat HIV to create a gooey solution that passes through a syringe. As the stream encounters the electric field it stretches to create thin fibers measuring 100 to several thousand nanometers that whip through the air and eventually stick to a collecting plate (one nanometer is about one 25-millionth of an inch). The final material is a stretchy fabric that can physically block sperm or release chemical contraceptives and antivirals.

“This method allows controlled release of multiple compounds,” Ball said. “We were able to tune the fibers to have different release properties.”

One of the fabrics they made dissolves within minutes, potentially offering users immediate, discrete protection against unwanted pregnancy and sexually transmitted diseases.

Another dissolves gradually over a few days, providing an option for sustained delivery, more like the birth-control pill, to provide contraception and guard against HIV.

The fabric could incorporate many fibers to guard against many different sexually transmitted infections, or include more than one anti-HIV drug to protect against drug-resistant strains (and discourage drug-resistant strains from emerging). Mixed fibers could be designed to release drugs at different times to increase their potency, like the prime-boost method used in vaccines.

The electrospun cloth could be inserted directly in the body or be used as a coating on vaginal rings or other products.

Electrospinning has existed for decades, but it’s only recently been automated to make it practical for applications such as filtration and tissue engineering. This is the first study to use nanofibers for vaginal drug delivery.

While this technology is more discrete than a condom, and potentially more versatile than pills or plastic or rubber devices, researchers say there is no single right answer.

“At the time of sex, are people going to actually use it? That’s where having multiple options really comes into play,” Krogstad said. “Depending on cultural background and personal preferences, certain populations may differ in terms of what form of technology makes the most sense for them.”

The team is focusing on places like Africa where HIV is most common, but the technology could be used in the U.S. or other countries to offer birth control while also preventing one or more sexually transmitted diseases.

The research to date was funded by the National Institutes of Health and the UW’s Center for AIDS Research. The other co-author on the paper is Thanyanan Chaowanachan, a UW postdoctoral researcher and longtime HIV expert.

The team will use the new Gates Foundation grant to evaluate the versatility and feasibility of their system. The group will hire more research staff and buy an electrospinning machine to make butcher-paper sized sheets. The expanded team will spend a year testing combinations that deliver two antiretroviral drugs used to treat HIV and a hormonal contraceptive, and then six months scaling up production of the most promising materials.
Botswana: Public health bill shocking and regressive
7 Dec 2012

Media release issued by BONELA, the Alliance’s linking organisation in Botswana.

The Botswana Network on Ethics, Law and HIV/AIDS (BONELA), is shocked by the introduction of a Public Health Bill which our Parliament is currently debating. This Bill has some provisions that have no place in a democratic and modern day Botswana. It has provisions that are counter-productive, discriminatory, unconstitutional and barbaric. In a nutshell, this is what the Bill seeks:

1. To empower medical practitioners to force clients (you and I) to undergo HIV tests without their consent. The rationale for this is not provided for in the Bill. Despite it being unacceptable, it can be abused by curious doctors. See clause 104 (3) b

2. Also empowers doctors to test clients without their knowledge. In essence, doctors can just test a client for HIV without informing them that they are being tested and without any counselling. The wisdom of that is unknown. See clause 105 (2) b

Essentially, the two foregoing provisions throw the right to privacy which is entrenched in our constitution out of the window.

3. Clients due for surgical or dental procedure can be required to undergo an HIV test before the procedure. In other words, your dentist may refuse to remove your tooth before you test for HIV. Is there a medical justification for this? NO!!!! See clause 109 (3)

4. Force doctors to report HIV cases to Director of Health Services in the same breath as TB, smallpox, cholera and yellow fever. We understand why some diseases such as TB are notifiable but we do not understand why the Director has to know that so and so has HIV unless they sleep with them without protection. This will certainly push clients away from health facilities for fear of their HIV status becoming a public knowledge. See clause 52 as read with the definition of notifiable diseases under clause 2.

5. To force people living with HIV to tell whomsoever they have sexual relations with to tell them of their HIV status. This provision is regressive in that it undermines the value of knowing ones status. People are better off not knowing their status if knowledge of one’s status forces one to tell whoever they have sex with. Furthermore, not knowing one’s status can be a good line of defence in a court of law if one is charged with infecting another person with HIV. Emphasise should be on promoting safe sex by all, irrespective of whether one knows their status or not. Women, who are normally the first to test, will be hard done by this law because an assumption will be created that since they came to know of their status first, then they infected their male partners who ordinarily test through their partners, or after their partners or never test at all. See clause 116

6. To empower doctors to tell one’s sexual partner of their HIV status without their consent. The checks and balances put in place are not pragmatic and can be susceptible to abuse.

7. To limit the right to freedom of movement for HIV positive persons. For instance an HIV infected person may be detained and isolated if there is evidence that they are likely to infect other persons. How is that going to be assessed? Why emphasis can’t be put on providing whoever is exposed to the virus with PEP? Clause 116

8. To take away the parental consent and guardianship and place them in the hands of doctors. This is unconstitutional and unlawful as the upper guardian of all children is the High Court and not doctors. Doctors’ duty is to treat and not to make decisions about the interests of the children when they have legal guardians. If the legal guardians unreasonably withhold their consent then we have the High Court to intervene. See clause 151

Remarkable provisions

9. Allows any person from the age of 16 to test for HIV. As BONELA we have long pushed for this and we are excited about it. Clause 105 (1) b

10. We are more delighted that the Bill seeks to expressly prohibit pre-employment HIV testing. See clause 104 (2)

Lastly, we are concerned by government attitude and tendency of introducing Bills in Parliament and debate them before engaging all stakeholders including the civil society and Batswana as a whole. We know that the Botswana Health Professions Council is not aware of this Bill for they have not been consulted on it. As custodians of health we expect them to be intimately involved as this Bill is going to affect the way they work. This bill is significant in the lives of all of us and we therefore call upon
Reverend Dr. John G.N. Seakgosing to withdraw it and if he refuses to, we urge MPs to reject it.
Participatory democracy is about engaging communities.

**Many U.S. Children with TB Have International Connections**
*Healio*, (12.07.2012)
National Surveillance System data analyzed by Centers for Disease Control and Prevention’s (CDC) Division of Tuberculosis Prevention indicated that 75 percent of the 2,660 children diagnosed with TB in the United States from 2008 to 2012 were either born outside the United States or had travelled outside the US borders. More than half of these cases were adolescents or older. The report also included data from 2009 on parents or guardians who had international ties. Many of the children with TB—66 percent—had parents who were born outside of the United States. CDC’s report emphasized the effects of the global epidemic of TB on children and adolescents within the United States.

The report emphasized the cost-effectiveness and prevention benefits of TB screening. CDC researchers, Carla A. Winston, PhD, MA, and Heather J. Menzies, MD, MPH, recommended that health care providers assess children’s risk for TB during routine care visits. In addition, as children enter a low-prevalence area, they should be screened for latent TB infection to prevent acute TB infections, advised Andrea T. Cruz, MD, of the TB Initiative of Texas Children’s Hospital in Houston.


**Six Promising HIV Drugs in the Pipeline**
By Warren Tong
December 5, 2012

*Table of Contents*
- **Introduction**
- **GS-7340 (Also Known as Tenofovir Alafenamide, or TAF)**
- **Dolutegravir (DTG)**
- **S/GSK-1265744 (or simply “744”)**
- **HIV Entry Inhibitors**
- **New Fixed-Dose Combination and Antiretroviral Formulations**

*Introduction*
What new HIV medications do we have to look forward to over the next few years? How will these newer drugs improve upon the older ones? To shed some light on these questions, Roy Gulick, M.D., provided an overview at ID Week 2012 of drugs in development.

Since the first HIV medication, zidovudine (AZT, Retrovir), was approved in 1987, 26 other antiretrovirals have been made available in the U.S. for treating HIV—a history that Gulick recapped in *song* during this conference. Our best regimens today are potent, convenient and relatively non-toxic.

However, according to Gulick, there is potential to make medications even better than those we have today. Newer drugs should build upon some of these aspects, he said:
- Improve convenience (reduce dosage frequency, less than once a day).
- Improve tolerability and reduce toxicity (even the best drugs today still have some of these issues).
- Penetrate reservoirs more effectively (such as the genital tract and central nervous system).
- Exploit new targets, thereby improving activity (particularly against drug-resistant viruses).
- Improve formulation.

The list of drugs in the pipeline continues to be full of antiretroviral agents, whether they are in early development or undergoing clinical trials. Gulick highlighted six of the most promising drugs.

*GS-7340 (Also Known as Tenofovir Alafenamide, or TAF)*
GS-7340 is an investigational nucleoside agent that is a prodrug of the approved formulation of tenofovir (TFV, Viread). A prodrug is a medication that, when metabolized in the blood, breaks down into the active form of the compound. The NRTI sold under the brand name Viread is actually tenofovir disoproxil fumarate (TDF), a prodrug that breaks down into tenofovir.

GS-7340’s antiretroviral activity was first presented in a study by Martin Markowitz, M.D., and others at CROI 2011. In a small, 14-day study, Markowitz and his team found that GS-7340 performed slightly better than the "old" TDF, with greater decreases in HIV RNA at lower dosages (GS-7340 at 50 or 150 mg vs. TDF at 300 mg).
These findings were further supported by study results from Peter Ruane, M.D., and others at CROI 2012. Ruane and his team compared GS-7340 (at dosages of 8, 25 and 40 mg) with TDF (at 300 mg) in 38 treatment-naive patients over 10 days of monotherapy. GS-7340 again performed better than TDF, showing 0.76, 0.94 and 1.08 log reductions in HIV RNA, respectively, while TDF only showed a 0.48 log reduction in HIV RNA. The findings were statistically significant for the 25-mg ($P = .017$) and 40-mg ($P = .01$) dosages.

Ruane and his group also found that the plasma concentrations of tenofovir, when the prodrugs were metabolized, were 10 to 100 times higher for TDF than for any of the three dosages of GS-7340. This finding suggests that, because GS-7340 delivers less compound to target tissues, it could reduce toxicity levels in the organs, Gulick said.

On the other hand, when comparing intracellular concentrations of tenofovir in peripheral mononuclear cells like lymphocytes (which is where we want the drugs to be), GS-7340 achieved up to 20 times higher levels than TDF, Gulick noted.

In both of these studies, GS-7340 was generally well tolerated and no serious adverse events were reported.

A third study of GS-7340 was presented at ICAAC 2012. It found that GS-7340 had high potency against 26 HIV-1 isolates representing 7 subtypes. The drug also showed high potency against three HIV-2 isolates. In addition, GS-7340 maintained its viral potency longer than TDF, showing its better stability.

Further GS-7340 studies are in progress. Particularly because of its low dosage and high potency, it can be readily co-formulated with other agents. Gulick pointed out two studies exploring such coformulations. The first study will compound GS-7340 with emtricitabine (FTC, Emtriva) plus elvitegravir (EVG) plus cobicistat, and compare that to elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild). The second study will compound GS-7340 with emtricitabine, darunavir (Prezista) and cobicistat (which would be the first one-pill, once-a-day protease inhibitor-based regimen), and compare that to tenofovir/emtricitabine (Truvada) plus darunavir plus cobicistat.

**Dolutegravir (DTG)**

Of the six highlighted compounds, Gulick stated that dolutegravir is the furthest along in development. Dolutegravir is an investigational integrase inhibitor, but it has distinguished itself from the two approved integrase inhibitors, raltegravir (Isentress) and elvitegravir. Dolutegravir has a long half-life of 15 hours, indicating it can be taken once a day. Gulick emphasized that it does not require pharmacokinetic boosting. He noted that resistance does occur, but that dolutegravir showed activity against raltegravir- and elvitegravir-resistant viral strains.

Its antiviral potency was shown in a phase-2a study by Sherene Min, M.D., and others. In 28 treatment-naive patients receiving either 2, 10 or 50 mg of dolutegravir, there was an average of a 1.51 to 2.46 log reduction in viral load after only 10 days of once-daily dosing. Seven of the 10 patients receiving 50 mg dosages achieved a viral load less than 50 copies/mL. Min and her team reported low pharmacokinetic variability and good short-term tolerability (the most common side effects were diarrhea, fatigue, and headache; adverse events were mild to moderate in severity).

According to Gulick, phase-3 results are complete and will be submitted to the U.S. Food and Drug Administration by the end of the year.

One of the phase-3 studies, known as SPRING 2, found dolutegravir to be non-inferior to raltegravir. The study followed 827 treatment-naive patients with a viral load above 1,000 copies/mL over 48 weeks. They were given either 50 mg of dolutegravir or 400 mg of raltegravir. Both groups were successful at achieving viral loads below 50 copies/mL (88% for dolutegravir and 85% for raltegravir). Both drugs were also very well tolerated, with only 2% in each group having to discontinue treatment because of adverse events.

Furthermore, a dolutegravir-based regimen consisting of abacavir/lamivudine (Epzicom, Kivexa) plus dolutegravir was actually found to be superior to tenofovir/emtricitabine plus efavirenz (Sustiva, Stocrin), according to the results of a companion phase-3 study by Sharon Walmsley, M.D., and others. In 822 treatment-naive patients studied over 48 weeks, 88% of the dolutegravir group achieved a viral load below 50 copies/mL, compared to 81% of the efavirenz group. Gulick pointed out that the difference was because of tolerability: 10% of the efavirenz group discontinued treatment because of adverse events, compared to just 2% of the dolutegravir group. He commented that this would mark the first real challenger to efavirenz’s long-held dominance in treatment-naive studies with a 48-week primary endpoint.

In terms of renal safety, the study found dolutegravir did interfere with tubular secretion of creatinine. However, Gulick noted, the increase in creatinine was only about .1 to .15 mg/dL, and occurred
only within the first two weeks after starting dolutegravir, then stabilized over the rest of the 48-week study. As the Walmsley study noted, dolutegravir does not affect actual glomerular filtration rate. In terms of resistance, dolutegravir appears to have a higher barrier to resistance than the other integrase inhibitors. In the Walmsley study, among both the dolutegravir and efavirenz groups, only 4% experienced virologic failure (18 and 17 individuals, respectively). Of the nine in each group that had genotypic test results available, "You see no nucleoside and no integrase mutations in the dolutegravir group. And as you would expect in the efavirenz [regimen], there were some nucleoside and non-nucleoside mutations detected," Gulick stated.

Because dolutegravir showed activity against elvitegravir- and raltegravir-resistant viral strains, as shown in a study by Masanori Kobayashi and others, Joseph Eron, M.D., and others studied the use of dolutegravir for patients who had developed resistance to raltegravir. Their pilot study, known as VIKING, followed 51 patients with three or more class resistances, including demonstration of raltegravir mutations. The patients were given 50 mg of dolutegravir, either once or twice a day, for 10 days. A virologic response was defined as either a viral load below 400 copies/mL or a 0.7 log reduction. As Gulick explained, "The best responses were in the twice-a-day group. Whether you looked at all patients, those with the specific Q148 or other mutations, you can see response rates, over a short 10 days of therapy, exceeding 90%.”

The VIKING study went on to follow the patients over 24 weeks. After the initial two weeks, the patients added an optimized background regimen. These follow-up results were presented by Vincent Soriano, M.D., Ph.D., at the 2011 European AIDS Conference. Soriano and his team found that by the end of the 24-week period, 41% of the once-a-day group and 75% of the twice-a-day group were able to re-suppress their viral load below 50 copies/mL.

Further studies of dolutegravir in the setting of other integrase inhibitor resistance are ongoing. S/GSK-1265744 (or simply "744")
S/GSK-1265744 is an integrase inhibitor, similar to dolutegravir. Results from two studies presented at ICAAC 2012 found that 744 had high potency and an exceedingly long half-life. When given orally at once-daily doses of 30 mg, patients showed a median 2.6 log reduction in viral load. More impressive, when using nanotechnology to formulate 744 to be injected subcutaneously or intramuscularly, a single dose showed a half-life between 21 and 50 days. Remarkably, after a single dose, patients still had detectable levels of 744 up to 48 weeks after injection.

Similar to dolutegravir, 744 seems to have a high barrier to drug resistance. According to Gulick, using site-directed molecular clones (molecules created with specific mutations) associated with integrase inhibitor resistance, these mutations showed high levels of resistance to raltegravir and elvitegravir, but remained susceptible to 744 and dolutegravir.

In terms of safety, there were some injection site reactions and nodules associated with subcutaneous dosing. But conceivably, 744 could be taken as infrequently as every three months for treatment, or even as PrEP (pre-exposure prophylaxis). Research is ongoing.

HIV Entry Inhibitors
HIV entry inhibitors block HIV at the point at which they attach to CD4 cells. Many of the other classes of drugs, including protease inhibitors, NRTIs and NNRTIs, fight HIV after it has infected a CD4 cell.

Among the entry inhibitors, there are presently three sub-classes. We already have approved drugs in the first two sub-classes: CCR5 antagonists and fusion inhibitors. In the CCR5 antagonist sub-class, we already have maraviroc (Selzentry, Celsentri), and a new drug called cenicriviroc is being investigated. The fusion inhibitor class has long featured only enfuvirtide (Fuzeon), but a new drug called albuviride is being studied.

The third sub-class is an investigational one: CD4 attachment inhibitors. These new drugs are being developed to either bind at the location of HIV’s gp120 protein (such as BMS-663068) or on the CD4 receptor itself (such asibalizumab, a once- or twice-a-day drug that’s still under investigation for both treatment and prevention).

Gulick offered a closer look at a few of these drugs in his overview.

Cenicriviroc (CVC)
Cenicriviroc is an investigational CCR5 antagonist. Not only does it antagonize CCR5 binding, it also antagonizes CCR2 binding. CCR2 is a receptor that sits on the surface of macrophages and may be involved in inflammation.

Cenicriviroc showed potent antiretroviral activity in a small study by Jacob Lalezari, M.D., and others. They followed treatment-experienced patients who had not been on treatment for at least six weeks, had a CD4+ cell count above 250 and a viral load above 5,000 copies/mL. They were randomized to receive
either 25, 50, 75, 100 or 150 mg of once-daily cenicriviroc. At the highest doses, after 10 days, patients showed a 1.5 log reduction in viral load.

An update on the follow-up study was discussed by David Martin, M.D., at CROI 2012. In Martin et al’s phase-2b study, they randomized 150 treatment-naive patients into three groups to receive tenofovir/emtricitabine with either cenicriviroc (at 100 or 200 mg) or efavirenz. Cenicriviroc was administered using a new, 50-mg formulation. In preliminary data from 18 patients, cenicriviroc was found to be well-absorbed and within the expected therapeutic range of potency. Further study will assess the safety, efficacy and effect of CCR2 inhibition on inflammatory biomarkers.

Albuvirtide

The only approved fusion inhibitor, enfuvirtide, offers a lot of activity against HIV, but the obvious downside is that it requires twice-daily injections. Albuvirtide, on the other hand, is an investigational fusion inhibitor that when given intravenously has a long average half-life of 11 days, warranting weekly dosing.

Albuvirtide has a similar design to enfuvirtide. It is a peptide that is an analogue of gp41, one of the envelope proteins on HIV's surface, and thereby blocks HIV through CD4 membrane fusion.

Two proof-of-concept studies by Dong Xie and others were presented at ICAAC 2012. In the first study, albuvirtide was given to 54 treatment-naive patients in a single dose; doses ranged from 20 to 640 mg. They found that albuvirtide’s half-life ranged between 10 and 13 days, and that the drug suppressed plasma viremia for between 6 and 10 days. Albuvirtide was generally well tolerated, with no injection-site reactions and no serious adverse events.

In the second study, albuvirtide was given to 12 treatment-naive patients in multiple doses of either 160 or 320 mg. Doses were given on days 1, 2, 3, 8 and 15. The participants averaged viral load decreases of 0.68 log copies/mL (at 160 mg) and 1.05 log copies/mL (at 320 mg). Similar to the first study, there were no injection-site reactions and no serious adverse events. No anti-albuvirtide antibodies were detected in patients for up to 42 days.

BMS-663068 (a.k.a. BMS-068)

BMS-068 is an HIV attachment inhibitor. It is an oral prodrug that breaks down into the active compound BMS-626529 (a.k.a. BMS-529). It inhibits CD4 binding by specifically binding to gp120, one of HIV’s envelope proteins that binds to CD4 cells. Gulick stated BMS-068 could be taken once or twice a day without boosting, but noted, "There is decreased baseline susceptibility in some patients due to envelope polymorphisms."

BMS-068 taken over 8 days with or without ritonavir (Norvir) resulted in substantial declines in plasma HIV RNA levels and was generally well tolerated, according to a study by Richard Nettles, M.D., and others. The study followed 50 patients with a CD4+ cell count above 200 cells/mL and a viral load above 5,000 copies/mL. They were either treatment-naive or not taking any treatment. The median change in viral load ranged from a 1.21 to a 1.73 log reduction, demonstrating that CD4 attachment inhibition can be quite potent and effective.

In terms of resistance, a study presented by Neelanjana Ray, M.D., at CROI 2012, found little resistance after the eight days of monotherapy. Ray and his team analyzed the changes in phenotypic susceptibility and known attachment inhibitor resistance substitutions that may have occurred during the Nettles study. Of the 48 patients that completed the study, 42 had at least a 1 log drop in viral load, showing that BMS-068 was effective. However, the other six (about 12%) had no virologic response, even though their baseline IC50 (a measure of the effectiveness of a compound in inhibiting a biochemical function) levels were quite high.

"When they took a close look and they sequenced gp160, which is broken down into gp120, they showed that a mutation (M426L) was associated with resistance," explained Gulick. "You can see that in patients with virologic response, very few (only 6%) have this mutation, whereas in those without virologic response, 5 of the 6 had this mutation. So it looks like this will be important in screening for activity of this compound as its development moves forward."

New Fixed-Dose Combination and Antiretroviral Formulations

Gulick pointed out three one-pill, once-a-day formulations being developed:

- GS-7340/FTC/elvitegravir/cobicistat.
- GS-7340/FTC/darunavir/cobicistat.
- Abacavir/lamivudine (3TC, Epivir)/dolutegravir.
- In addition, three other in-development formulations that Gulick mentioned were:
- Lopinavir/ritonavir/lamivudine.
- Atazanavir (Reyataz)/cobicistat and darunavir/cobicistat (both in clinical trials).
- Rilpivirine long-acting (RPV-LA).

Regarding the last drug in those lists, a small pilot study presented at CROI 2012 found that RPV-LA could potentially be given once a month in its long-acting nano-formation. It would likely need to be paired with other drugs, but research is ongoing for its use in treatment and prevention.

**Outrage sparked by Brighton University film showing**

6:20pm Monday 10th December 2012
By Bill Gardner

A university professor has been criticised for suggesting to his students that HIV does not cause Aids.

Activists are planning to protest against the screening of a controversial film at University of Brighton on Wednesday, December 12.

Hundreds of students were invited to the event by Dr Karl Cox, who invited them to “find out the truth about HIV”.

The film, House of Numbers, suggests the virus does not cause the killer disease Aids. It has been widely discredited by the scientific community.

Among a number of claims, it suggests blood tests are unreliable, HIV diagnoses are wrong and that the virus is a work of fiction created to sell more medicines.

In Dr Cox’s email invitation, he asked students: “How accurate are HIV tests? Is HIV fact or fiction?”

More than 100 people have signed an online petition calling for the film’s screening to be cancelled. On Facebook, students have organised a non-violent protest to take place during the showing.

'Dangerous'

Jesse Laffan, a 23-year-old student from Portslade, said the film was “completely misleading”.

He said: “I find this quite affronting, with World Aids Day having been so recent and living in a city where HIV transmission is a real issue.

“I think promoting this is dangerous, especially to young students.”

The film is being shown on University of Brighton premises in conjunction with a charity called the World Foundation for Natural Science.

On its website, the organisation describes its mission as, “healing this world in accord with Natural Law, thus restoring Divine Order on this precious Planet Earth. For only this way real solutions for the challenges man and nature are facing can be found”.

One Aids sufferer from Brighton said Brighton University’s decision to allow Dr Cox to screen the film was “unbelievable”.

'Gobsmacked'

Andy – not his real name – said: “Why would they want to teach their students dangerous nonsense which teaches them not to bother taking precautions?

“I’m gobsmacked, to be honest. It’s hard enough to get the message through to young people without them being exposed to stupid films like this.

“The university should cancel the showing immediately.”

A spokesperson for HIV and sexual health charity Terrence Higgins Trust, said: “We have always had serious concerns about this inaccurate, misleading and irresponsible film.

“That’s why, as the leading HIV and sexual health charity, staff from Terrence Higgins Trust will be on hand after any screening of this film at the university to ensure that the students have access to the facts about HIV.”

A University of Brighton spokesperson said: “Our position is absolutely clear. We regard HIV and Aids as extremely serious matters of concern and we provide our students with advice and we support research into these issues.”

The spokesperson said the university would be reviewing whether or not to allow the film to be shown on university premises.

**BBC News Examines HIV Microbicide Research**

BBC News examines ongoing efforts to develop a female-controlled microbicide to prevent HIV infection. But so far, “efforts ... have presented a great deal of frustration in the fight against this global epidemic,” the news service writes, detailing the history of some failed experiments. "According to the Microbicide Trials Network, there are currently nine different microbicide products in clinical trials," BBC notes.

Angela Obasi of the Liverpool School of Tropical Medicine said, "In many parts of the world — especially in
the parts of the world where HIV is most prevalent—there are gender status issues that make it very tricky for a woman to control the circumstances under which she is exposed to HIV. ... So methods that are controlled by women give them a critically important power over the safety of their own bodies," according to the news service (Gill, 12/8).

**Uganda's Proposed Anti-Homosexuality Legislation Would Inhibit Health Care Access**

The Center for Global Health Policy's "Science Speaks" blog examines the potential impacts of a proposed anti-homosexuality bill in Uganda, writing that the bill "would stand as an obstacle to both access to health care and to the ability of health care providers to even offer services," making prevention of "the bill's passage a matter of life and death, as well as of rights and dignity." According to the blog, "The record of Uganda's HIV fight, once hailed as a model and a success story, now showing the most alarming reverses in Africa, stands as testament to what happens to health responses in a setting where science, human rights, and the realities of the impact of discriminatory laws are ignored. In all of those, of course, Uganda is far from alone, raising the question of what the world's greatest united humanitarian effort, the work to treat and prevent the spread of HIV, could achieve when those issues are addressed." The blog briefly examines other countries' anti-sodomy laws and proposed anti-homosexuality legislation (Barton, 12/10).

**Potent Antibodies Neutralize HIV and Could Offer New Therapy, Study Finds ***

Dec. 10, 2012 — Having HIV/AIDS is no longer a death sentence, but it's still a lifelong illness that requires an expensive daily cocktail of drugs—and it means tolerating those drugs' side effects and running the risk of resistance. Researchers at The Rockefeller University may have found something better: they've shown that a **therapeutic approach harnessing proteins from the human immune system can suppress the virus in mice without the need for daily application** and could one day be used in humans to treat the disease.

Florian Klein and colleagues in Michel Nussenzweig's Laboratory of Molecular Immunology found that a **combination of five different antibodies**—proteins the immune system uses to fight infection—**effectively suppressed HIV-1 replication and kept the virus at bay for a 60 day period after termination of therapy thanks to their longer half-life, while current antiretroviral drugs require daily intake.***

These especially potent antibodies were only recently discovered, some of them by several of Klein's colleagues in the Nussenzweig laboratory. Called **broadly-neutralizing antibodies**, they were identified and cloned from HIV-infected patients whose immune systems showed an unusually high ability to neutralize HIV. In recent years the potent antibodies were found to prevent HIV from infecting non-human primates, demonstrating the possibility for a vaccine in humans. But they were thought to have little or no effect on established infections.

"Antibodies had been written off as a treatment for HIV/AIDS because previous studies showed only a limited effect on controlling the virus," says Klein. "But that was before these more potent antibodies were discovered. We wanted to readdress this question using these new tools."

HIV-1 is notorious for evading the immune system's attacks by constantly mutating, but the new antibodies are able to throw a wrench in that strategy. The key is in the combination. The **antibodies target HIV-1's surface protein gp160, a large molecule that forms a spike that seeks out host cells and attaches to them. One antibody alone wasn't enough to quell the virus; neither was a mix of three. But five of them in unison proved too complicated for gp160 to mutate its way out of.***

The researchers used "humanized" mice for the study, provided by Alexander Ploss in the Laboratory of Virology and Infectious Disease, because normal mice don't have the right receptors to be infected with HIV-1.

"Although HIV-1 infection in humanized mice differs in many important aspects from infection in humans, the results are encouraging to investigate these antibodies in clinical trials," says Klein. "It also may be that a combination of antibodies and the already established antiretroviral therapy is more efficacious than either alone," says Klein.

"If this could be used as a treatment one day, it is conceivable that patients would only need to take traditional drugs until the virus is controlled, and then receive antibodies every two to three months to maintain that control. We're eager to explore if a benefit in HIV-1-treatment can be achieved in humans."
**Journal Reference:**

**Epigenetics May Be a Critical Factor Contributing to Homosexuality, Study Suggests**
Dec. 11, 2012 — Epigenetics—how gene expression is regulated by temporary switches, called epi-marks—appears to be a critical and overlooked factor contributing to the long-standing puzzle of why homosexuality occurs.

According to the study, published online today in *The Quarterly Review of Biology*, sex-specific epi-marks, which normally do not pass between generations and are thus "erased," can lead to homosexuality when they escape erasure and are transmitted from father to daughter or mother to son.

From an evolutionary standpoint, homosexuality is a trait that would not be expected to develop and persist in the face of Darwinian natural selection. Homosexuality is nevertheless common for men and women in most cultures. Previous studies have shown that homosexuality runs in families, leading most researchers to presume a genetic underpinning of sexual preference. However, no major gene for homosexuality has been found despite numerous studies searching for a genetic connection.

In the current study, researchers from the Working Group on Intragenomic Conflict at the National Institute for Mathematical and Biological Synthesis (NIMBioS) integrated evolutionary theory with recent advances in the molecular regulation of gene expression and androgen-dependent sexual development to produce a biological and mathematical model that delineates the role of epigenetics in homosexuality.

Epi-marks constitute an extra layer of information attached to our genes' backbones that regulates their expression. While genes hold the instructions, epi-marks direct how those instructions are carried out—when, where and how much a gene is expressed during development. Epi-marks are usually produced anew each generation, but recent evidence demonstrates that they sometimes carry over between generations and thus can contribute to similarity among relatives, resembling the effect of shared genes.

Sex-specific epi-marks produced in early fetal development protect each sex from the substantial natural variation in testosterone that occurs during later fetal development. Sex-specific epi-marks stop girl fetuses from being masculinized when they experience atypically high testosterone, and vice versa for boy fetuses. Different epi-marks protect different sex-specific traits from being masculinized or feminized—some affect the genitals, others sexual identity, and yet others affect sexual partner preference. However, when these epi-marks are transmitted across generations from fathers to daughters or mothers to sons, they may cause reversed effects, such as the feminization of some traits in sons, such as sexual preference, and similarly a partial masculinization of daughters.

The study solves the evolutionary riddle of homosexuality, finding that "sexually antagonistic" epi-marks, which normally protect parents from natural variation in sex hormone levels during fetal development, sometimes carryover across generations and cause homosexuality in opposite-sex offspring. The mathematical modeling demonstrates that genes coding for these epi-marks can easily spread in the population because they always increase the fitness of the parent but only rarely escape erasure and reduce fitness in offspring.

"Transmission of sexually antagonistic epi-marks between generations is the most plausible evolutionary mechanism of the phenomenon of human homosexuality," said the study's co-author Sergey Gavrilets, NIMBioS' associate director for scientific activities and a professor at the University of Tennessee-Knoxville.

**Journal Reference:**
William R. Rice, Urban Friberg, and Sergey Gavrilets. *Homosexuality as a Consequence of Epigenetically Canalized Sexual Development. The Quarterly Review of Biology, 2012; 87 (4) [link]*
Experiment Finds Achilles' Heel of Ulcer Bug, H. Pylori

Dec. 10, 2012 — Experiments at the U.S. Department of Energy’s (DOE) SLAC National Accelerator Laboratory have revealed a potential new way to attack common stomach bacteria that cause ulcers and significantly increase the odds of developing stomach cancer.

The breakthrough, made using powerful X-rays from SLAC’s Stanford Synchrotron Radiation Lightsource (SSRL), was the culmination of five years of research into the bacterium Helicobacter pylori, which is so tough it can live in strong stomach acid. At least half the world’s population carries H. pylori and hundreds of millions suffer health problems as a result; current treatments require a complicated regimen of stomach-acid inhibitors and antibiotics.

"We were looking for a means to disrupt H. pylori's own mechanism for protecting itself against stomach acid," said Hartmut "Hudel" Luecke, a researcher at the University of California, Irvine, and principal investigator on the paper, published online Dec. 9 in Nature. With this study, he said, "We have deciphered the three-dimensional molecular structure of a very promising drug target."

Luecke and his team zeroed in on tiny channels that H. pylori uses to allow in urea from gastric juice in the stomach; it then breaks this compound into ammonia, which neutralizes stomach acid. Blocking the channels would disable this protective system, leading to a new treatment for people with the infection.

Solving the structure of the protein to find the specific area to target wasn’t easy. The channels are formed by the protein embedded in the bacterium’s cell membrane, and membrane proteins are notoriously difficult to crystallize, which is a prerequisite for using protein crystallography, the main technique for determining protein structures. This technique bounces X-rays off of the electrons in the crystallized protein to generate the experimental data used to build a 3-D map showing how the protein’s atoms are arranged.

The challenge with membrane proteins is that they are especially hard to grow good quality crystals of, and for this experiment, said Luecke, "We needed to grow and screen thousands of crystals."

"We collected over 100 separate data sets and tried numerous structural determination techniques," said Mike Soltis, head of SSRL’s Structural Molecular Biology division, who worked with Luecke and his team to create the 3-D map of the atomic structure. The final data set was measured at SSRL’s highest brightness beam line (12-2), which produced the critical data that met the challenge.

"This is the hardest structure I’ve ever deciphered, and I’ve been doing this since 1984," Luecke said. "You have to try all kinds of tricks, and these crystals fought us every step of the way. But now that we have the structure, we’ve reached the exciting part—the prospect of creating specific, safe and effective ways to target this pathogen and wipe it out."

Journal Reference:
David Strugatsky, Reginald McNulty, Keith Munson, Ching-Kuang Chen, S. Michael Soltis, George Sachs, Hartmut Luecke. Structure of the proton-gated urea channel from the gastric pathogen Helicobacter pylori. Nature, 2012; DOI: 10.1038/nature11684

An isolated look at the structure of the six-molecule ring of urea channels embedded in the membrane of Helicobacter pylori. Urea passes through the center of each of the six channel molecules. The center of the ring is filled with a lipid bilayer plug. (Credit: Hartmut Luecke / UC Irvine)
People Lack Knowledge About Link Between Oral Cancer, Sexual Health

*Dentistry Today*, (12.11.2012)

According to recent reports, although general awareness about sexually transmitted disease has risen in recent years, most individuals do not know that the human papillomavirus (HPV) can cause oral cancer. Recent data suggests that only one in four people can identify HPV as a cause for oral cancer, and that approximately half of the population do not know that HPV can be spread through sexual activity. Research has shown that HPV may play a larger role in individuals developing oral cancers in the future, and may even rival smoking as a risk factor. Oral cancer cases have increased significantly, with one of the reasons being the lack of awareness about the impact of sexual activity on oral health.

More South African pregnant women contracting HIV

Wednesday, December 12, 2012

JOHANNESBURG — A new study on Monday showed increased HIV infection rates among pregnant women living in areas with high migrant labour in South Africa, the country with one of the world’s highest caseloads.

Infections in the eastern province of Mpumalanga jumped from 34.7 per cent in 2009 to 36.7 per cent.

Health Minister Aaron Motsoaledi said some of the districts in these areas had rates above the national antenatal HIV prevalence rate of 29.5 per cent.

"In areas where we see new mining operations, new towns, constructions and new people coming in, we expect something like this higher prevalence rate to happen," said Motsoaledi.

"It needs our attention," he added.

The farming and mining provinces of Free State, North West, Limpopo also recorded increases.

The study was conducted in 2011 on some 33,446 women who attended antenatal clinics for the first time.

The semi-arid Namaqua district in the sparsely inhabited region of Northern Cape recorded the lowest prevalence rate at 6.2 percent. However, the country’s economic hub, Gauteng province, which includes Johannesburg and the capital Pretoria showed a slight decrease from 30.4 percent in 2010 to 28.7 percent in 2011.

In South Africa six million people currently live with the virus that causes AIDS.

After years of refusing to roll out drugs, the country now runs the world’s largest treatment programme, serving 1.3 million people.

Health officials plan to step up awareness campaigns to fight the scourge.

Namibia: No Change in Behaviour Despite HIV/Aids

*By Lorraine Kazondovi, 12 December 2012*

Windhoek — Despite the numerous information dissemination drives and campaigns to raise awareness about HIV/AIDS, very little in terms of behavioural change can be observed among Namibians.

This was the general sentiment when the Ministry of Education commemorated World AIDS Day during the period December 5-7 last week under the theme—"Getting to Zero". It also came to light that in 2007, 70 percent of teacher absenteeism was attributed to sick leave, which has a negative impact on the education sector.

According to the Director of Programme Quality Assurance at the Ministry of Education, Edda Bohn, education can be the most powerful force in combating the spread of HIV and AIDS, however the epidemic can weaken an education system’s ability to function.

"Teachers and other educators are dying in increasing numbers and at comparatively young ages, it taking time before they can be replaced. This affects the ability to supply education of good quality. Teachers who are ill are often absent and there is nobody to take over the affected classes. Rural posting of teachers is becoming more difficult because teachers who are ill want to be near health facilities," she said.

The major outcomes of the education system are threatened by frequent teacher and learner absenteeism; dropping out of school; concern for the sick at home, which interferes with the ability to concentrate on teaching and learning; repeated occasions of mourning in schools, families and communities, as well as unhappiness and fear of stigmatization on the part of teachers and learners who have been affected by HIV and AIDS, according to Bohn.

With approximately 60 000 employees and engaging about 650 000 learners, the education sector has an immense responsibility to ensure the preservation of its human capital if national and
international development targets such as the Millennium Development Goals are to be met, according to Bohn.

"Given the current national prevalence rate of 18.8 percent, concerted measures need to be put in place to invest in HIV prevention, care, support and impact mitigation programmes within the workplace and learning institutions to address the socio-economic impacts currently being felt through reduced service delivery. If this scenario is allowed to continue, it will have an adverse effect on productivity and delivery on the core mandate of the education sector, which will in turn affect the targets set in NDP4 and Vision 2030," she explained.

As a result, policies and strategies have been put in place, of which the first to be developed was the National HIV and AIDS Policy for the education sector in 2003. The HIV and AIDS Workplace Policy for the education sector was developed in 2007, while the strategic plan for the Workplace Wellness Programme was developed in 2006.

A relief teacher strategy drafted in 2008 has now been printed and is expected to be launched today. "The challenges that we are facing are the implementation of the existing policies and the mainstreaming of HIV and AIDS in all our daily routines," said Bohn.

There is a need to integrate in the curriculum campaigns such as My Future Is My Choice and Window of Hope that are geared to empowering learners, according to Bohn.

**Doctors force headbands onto HIV patients**

TNN Dec 14, 2012, 06.42AM IST

AHMEDABAD: AIDS patients at Jamnagar’s general hospital are made to wear headbands which proclaim their HIV positive status. The Gujarat high court (HC) on Thursday issued notices to concerned authorities after this issue was brought to its notice in a public interest litigation (PIL).

The PIL was filed by advocate Vijay Nangesh highlighting the "improper" practice in G G Hospital in Jamnagar. The lawyer submitted that the patients infected with HIV are given a band to be tied on their heads so that others could identify them and keep distance from them. He also produced photographs of patients carrying tags of HIV on their heads.

The petition claims that such a branding of HIV infected people is inhuman treatment to them, for this marking leads to isolation of these patients as other patients and their relatives maintain a "safe distance" from them. The petitioner also pointed out that this inhuman practice also causes panic among other patients who are in the hospital.

The PIL cited a guideline given by the Supreme Court saying that the identity of such people must not be disclosed . The lawyer also cited rules framed by the Medical Council of India in this regard . The PIL has demanded immediate restriction on this practice of disclosing AIDS patients’ identity. It has also sought action against responsible officials. After hearing the case, a bench of Chief Justice Bhaskar Bhattacharya and Justice J B Pardiwala sought reply from the state health department secretary, Jamnagar collector and the medical superintendent of the GG Hospital. Further hearing on this issue is kept next week.

Meanwhile, other PILs are also being heard by the HC on the issue of HIV infected people . The high court has ordered CBI probe in the incident of HIV infection among thalassemic kids in Junagadh .

**Brighton university cancels screening of AIDS denialist film**

by Scott Roberts , 12 December 2012, 6:01pm

The University of Brighton has cancelled the screening of a film which claims the HIV virus does not cause AIDS after a student backlash.

The documentary, House of Numbers, has been dismissed by academics and health experts worldwide as AIDS denialist propaganda.

According to the Argus newspaper, University of Brighton computing and mathematics lecturer Dr Karl Cox suggested to his students that HIV does not lead to AIDS, and invited them to “find out the truth about HIV” by watching the 2009 film directed by Brent Leung.

In the film, Leung interviews a range of scientists and AIDS denialists.

Among a number of false claims, it suggests blood tests are unreliable, HIV diagnoses are wrong and that the virus is a work of fiction created to sell more medicines.

Jesse Laffan, a 23-year-old University of Brighton student, said the film, which was due to be screened today (12 December), is “completely misleading”.
He said: “I find this quite affronting, with World AIDS Day having been so recent and living in a city where HIV transmission is a real issue”.

In a statement, HIV and sexual health charity Terrence Higgins Trust, said: “We have always had serious concerns about this inaccurate, misleading and irresponsible film”.

A spokesman for the University of Brighton said: “The screening of this film was organised by an individual member of university staff who has no academic or professional expertise in health sciences.

“Our position is clear: We regard HIV and AIDS as extremely serious matters of concern; we provide our students with advice and we support research concerning these issues.”

A person with AIDS has an immune system so weakened by HIV that the person usually becomes sick from one of several opportunistic infections or cancers.

**Syphilis and HIV: A Dangerous Duo Affecting Gay and Bisexual Men**

*BLOG.AIDS.GOV* ©, (12.13.2012)  Gail Bolan

A blog by Gail Bolan, M.D., Director of the Division of STD Prevention, Centers for Disease Control and Prevention (CDC), discusses surveillance data released in CDC’s 2011 STD Surveillance Report. Bolan draws attention to the increase in primary and secondary syphilis rates among gay and bisexual men— who account for more than 70 percent of all infections—and what can be done to reverse the high rates of infection among this sector of society. She notes that a large number of these infections are among young men who have sex with men (MSM), with the highest rates among 20–29 year olds.

Annual surveillance data in the report emphasize the disproportionate burden of disease among gay and bisexual men. Bolan explains that the genital sores caused by syphilis make sexual transmission and acquisition of HIV even easier. Hence, there is an estimated two-to-fivefold increased risk of HIV if persons with syphilis are exposed to the virus. Also, studies show that syphilis increases the viral load of persons with HIV infection. These facts increase Bolan’s concern, since data show that four of every 10 MSM with syphilis is co-infected with HIV. Bolan argues that the stakes are too high to ignore these health disparities and emphasizes the importance of promptly diagnosing and treating syphilis infections among MSM to decrease their chances for HIV infection.

Bolan stated that to fight the root causes of health disparities among gay and bisexual men involves confronting the underlying conditions that place the group at greater risk of STDs. She contends that risk behavior alone does not explain the disproportionate STD burden of MSM, but that complex issues such as homophobia and stigma are responsible to some extent for these infections. She discusses how CDC is working with program partners to take action to confront the underlying causes of STD disparities and provides the example of the more comprehensive holistic sexual healthcare through CDC’s program collaboration and service integration. Also, action plans guided by the best available science and input from partners are being implemented to help individuals and communities overcome environmental forces that increase the risk of acquiring an STD.

Bolan is aware that government cannot do it alone and that more broad-based action is needed by all involved. She envisages that working together, government and individuals can face sexual health issues. The blog concludes with Bolan’ suggestions for what health care providers, individuals, and community leaders should do to create greater awareness and openness about sexual health issues, to help end the disparity, and to ensure good health for gay and bisexual men who are disproportionately impacted by STDs and HIV.

To read the blog visit: http://blog.aids.gov.

**CDC: Chlamydia, Gonorrhea Cases Increasing**

*USA Today* ©, (12.13.2012)  Cathy Payne

The Centers for Disease Control and Prevention shared new data on December 13 that indicates the number of infections from the sexually transmitted diseases chlamydia and gonorrhea increased from 2010 to 2011 in the United States. “Sexually Transmitted Disease Surveillance 2011” reported the incidence of these and other STDs among the US population. Hillard Weinstock, an author of the report, stated that the groups most affected include “gay and bisexual men as well as young people.”

The number of gonorrhea cases reported in 2011 totaled 321,849, which represents a 4 percent increase over 2010. Women who have gonorrhea may develop pelvic inflammatory disease that can cause infertility. The rate of chlamydia in the United States rose by 8 percent, with a total of 1.4 infections in 2011. Seventy-two percent of the nation’s 13,970 syphilis cases in 2011 occurred among men who have sex
with men. Syphilis can result in paralysis, dementia, and death. The incidence of syphilis remained unchanged from 2010 to 2011.


Global Burden Of Disease Study Finds People Worldwide Living Longer, But With More Illness, Disability

"A sharp decline in deaths from malnutrition and infectious diseases like measles and tuberculosis has caused a shift in global mortality patterns over the past 20 years, according to a study released on Thursday, with far more of the world's population now living into old age and dying from diseases mostly associated with rich countries, like cancer and heart disease," the New York Times reports (Tavernise, 12/13). The Global Burden of Disease Study 2010, "published in the Lancet, has taken more than five years and involves 486 authors in 50 countries," the Guardian's Poverty Matters blog notes (Mead, 12/13). Researchers worldwide "drew conclusions from nearly 100,000 data sources, including surveys, censuses, hospital records and verbal autopsies," NPR's Shots blog writes (Doucleff, 12/13). The Global Burden of Disease (GBD) Study 2010 consists of "seven separate reports conducted by researchers at the University of Washington, the Harvard School of Public Health, and elsewhere [that] gauged people's health in 187 countries and determined that developing countries are looking more like richer Westernized countries in terms of the health problems that pose the biggest burden: high blood pressure, diabetes, cancer, and heart disease," according to the Boston Globe (Kotz, 12/13).

"The report represents the biggest systematic effort to portray the world's distribution and causes of a wide range of major diseases, injuries, and health risk factors, and the first since a 1990 GBD study was commissioned by the World Bank, according to a Lancet press release," CIDRAP notes (Schnirring, 12/13). "Since then, campaigns to vaccinate kids against diseases like polio and measles have reduced the number of children dying to about seven million" from more than 10 million in 1990, the Associated Press writes (Cheng, 12/13). "The risk of dying prematurely from many 'adult' diseases (such as heart attacks and cancer) has also fallen because of better treatment and prevention," the Washington Post reports, noting, "Soon after 2015, for the first time in history, there will be more people older than 65 than younger than five" (Brown, 12/13). However, the study "finds that countries face a wave of financial and social costs from rising numbers of people living with disease and injury," Reuters writes (Kelland, 12/13). "The [study] should help the world's medical authorities direct their fire more effectively," according to the Economist, which notes "the time may have come for a review of the world's approach to public health, for vaccination, antibiotics, insecticides and the like are useless against heart disease, diabetes and cancer" (12/15). The Guardian's Data Blog presents data from the study using two interactive infographics (Rogers, 12/13). The blog EpiAnalysis provides highlights from the report along with a number of infographics (12/13).

WHO Releases New Guidelines For Interventions Aimed At Protecting Sex Workers From HIV

The WHO on Wednesday "released new guidelines [.pdf] providing technical recommendations on effective interventions for the prevention and treatment of HIV and other sexually transmitted infections (STIs) among sex workers and their clients," New Europe Online reports. "The guidelines were developed in cooperation with the United Nations Population Fund (UNFPA) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) and are directed, in particular, to national public health officials and managers of HIV/AIDS and STI programs, non-governmental organizations and health workers," the news service notes (Gaydazhieva, 12/13).

"The new WHO guidelines recommend that countries work towards decriminalization of sex work and urge countries to improve sex workers' access health services," UNAIDS writes in an article on its webpage, noting "Sex workers in many places are highly vulnerable to HIV and other sexually transmitted infections (STIs) due to multiple factors, including large numbers of sex partners, unsafe working conditions and barriers to the negotiation of consistent condom use" (12/12). According to a WHO press release, the guidelines "also outline a set of interventions to empower sex workers and emphasize that correct and consistent condom use can reduce transmission between female, male and transgender sex workers and their clients" (12/12)
**New findings on killer bacteria’s defence**

14 December 2012

New research from Lund University casts new light on the interaction between the immune system and streptococcus bacteria, which cause both mild tonsillitis and serious infections such as sepsis and necrotising fasciitis. The way in which antibodies attach to the bacteria is linked to how serious the disease is.

Antibodies are key to the recognition and neutralisation of bacteria by our immune system. The most common antibodies have the shape of a Y, and the two prongs fasten to molecules that belong to the bacteria. The cells in the immune system recognise the shaft and can then attack the bacteria.

Since the 1960s, it has been known that certain bacteria have developed the ability to turn these antibodies around, which makes it more difficult for the immune system to identify them. These include streptococcus bacteria, sometimes referred to as ‘killer bacteria’, that cause both common tonsillitis and more serious diseases such as sepsis (blood poisoning) and necrotising fasciitis (flesh-eating disease). Because it has not been possible to study this phenomenon in detail, researchers have until now presumed that antibodies are always turned around in these streptococcal infections.

Now researchers at Lund University have shown that this is not the case. In less serious conditions, such as tonsillitis, the antibodies are back-to-front, but in more serious and life-threatening diseases such as sepsis and necrotising fasciitis, the antibodies are the right way round. These findings have now been published in the *Journal of Experimental Medicine* and completely alter the understanding of bacterial infections with several of our most common pathogenic bacteria.

“This information is important and fundamental to improving our understanding of streptococcal infections, but our results also show that the principle described could apply to many different types of bacteria”, says Pontus Nordenfelt, who is currently conducting research at Harvard Medical School in Boston.

The present study shows that it is the concentration of antibodies in the local environment in the body that controls how the antibodies sit on the surface of the bacteria. In the throat, for example, where the concentration is low, the antibodies sit the wrong way round, but in the blood, where the concentration is high, the antibodies are the right way round. This explains why the most serious infections are so rare in comparison to the common and often mild cases of throat and skin infections. The bacteria in the blood are quite simply easier for the immune system to find.

In the future, the results could have an impact on the treatment of serious infectious diseases, since a better understanding of the mechanisms behind the diseases is needed to develop new treatments.

Lars Björck, Professor of Infectious Medicine at Lund University, has discovered some of the antibody-turning proteins and has studied their structure and function for over 30 years.

“It is fantastic to have been involved in moving a major step closer to understanding the biological and medical importance of these proteins together with talented young colleagues”, he says.

**A drug used to treat HIV might defuse deadly staph infections**

New findings could potentially lead to novel approaches to treat deadly staph infections

A new study by NYU School of Medicine researchers suggests that an existing HIV drug called maraviroc could be a potential therapy for *Staphylococcus aureus*, a notorious and deadly pathogen linked to hundreds of thousands of hospitalizations each year. Their study is published online this week in *Nature*.

"What are the chances that a drug for HIV could possibly treat a virulent Staph infection?“ asks Victor J. Torres, PhD, assistant professor of microbiology, and senior author of the study. "These findings are the result of a fantastic collaboration that we hope will result in significant clinical benefit.” Staph causes toxic shock syndrome, pneumonia, and food poisoning, among other illnesses, and is becoming increasingly resistant to antibiotics.

The discovery arose from a serendipitous finding that was a part of a collaborative study between Dr. Torres, a bacteriologist, and immunologist Derya Unutmaz, MD, associate professor of microbiology and pathology and medicine, whose laboratories are adjacent to each other.

They focused on a receptor called CCR5 that dots the surface of immune T cells, macrophages, and dendritic cells. Sixteen years ago, researchers at NYU School of Medicine discovered that CCR5 is the receptor HIV uses to gain entry into T cells in order to replicate, spread, and cause an infection that can progress into AIDS.

That same receptor has now been found to be critical to the ability of certain strains of Staph to specifically target and kill cells with CCR5, which orchestrate an immune response against the bacteria.
The scientists discovered that one of the toxins the bacterium releases, called LukED, latches on to CCR5 and subsequently punches holes through the membrane of immune cells, causing them to rapidly die. The LukED toxin belongs to a family of proteins called leukotoxins, encoded and produced by Staph to fight off the immune system's defenses.

This discovery was made after Dr. Torres asked Dr. Unutmaz and fellow HIV researcher Nathaniel Landau, PhD, professor of microbiology, if he might use some of the human immune cells they had collected over the course of their HIV studies. The laboratories of all three scientists are adjacent to each other. Dr. Torres was trying to find out which immune cells were affected by different leukotoxins. Dr. Unutmaz gave him a T cell line, which they were using for their HIV infection studies and had previously engineered to express CCR5, to test the effects of these toxins.

"Within one hour flat, T cells with CCR5 all died when exposed to LukED" says Dr. Torres, whereas a similar T cell line that lacked the receptor was completely resistant to the toxin's effects. This observation quickly led to another set of experiments to determine that the LukED toxin was indeed interacting with the receptor and that its presence on the cell surface was necessary for the toxin to kill the cells.

The investigators then treated cells with CCR5 with maraviroc, a drug on the market that binds to CCR5 and blocks HIV infection, and then exposed the cells to the Staph toxin. The result, the scientists say, was astonishing. "It was remarkable. Maraviroc completely blocked the toxic effects of this leukotoxin at doses similar to those used to inhibit HIV infection" Dr. Unutmaz says.

"The goal in blocking the toxin with maraviroc or similar agents is to give the upper hand to the immune system to better control the infection," Dr. Torres adds. The researchers further corroborated the critical role of CCR5 in Staph infections using a mouse model. When they infected mice susceptible to Staph infection with strains that contain the LukED toxin, almost all the mice died. However, mice that were genetically engineered to lack CCR5 on their cells survived this lethal Staph infection.

Based on these findings, the investigators hope that future human clinical trials will determine whether drugs that block CCR5, such as maraviroc, could help the immune system to control the infection and potentially save lives.

**Aerobic exercise trumps resistance training for weight and fat loss**

DURHAM, N.C. – Aerobic training is the best mode of exercise for burning fat, according to Duke researchers who compared aerobic training, resistance training, and a combination of the two.

The study, which appears Dec. 15, 2012, in the *Journal of Applied Physiology*, is the largest randomized trial to analyze changes in body composition from the three modes of exercise in overweight or obese adults without diabetes.

Aerobic exercise – including walking, running, and swimming – has been proven to be an effective way to lose weight. However, recent guidelines have suggested that resistance training, which includes weight lifting to build and maintain muscle mass, may also help with weight loss by increasing a person’s resting metabolic rate. Research has demonstrated health benefits for resistance training, such as improving glucose control, but studies on the effects of resistance training on fat mass have been inconclusive.

"Given that approximately two-thirds of adults in the United States are overweight due to excess body fat, we want to offer clear, evidence-based exercise recommendations that will truly help people lose weight and body fat," said Leslie H. Willis, MS, an exercise physiologist at Duke Medicine and the study's lead author.

Researchers enrolled 234 overweight or obese adults in the study. Participants were randomly assigned to one of three exercise training groups: resistance training (three days per week of weight lifting, three sets per day, 8-12 repetitions per set), aerobic training (approximately 12 miles per week), or aerobic plus resistance training (three days a week, three set per day, 8-12 repetitions per set for resistance training, plus approximately 12 miles per week of aerobic exercise).

The exercise sessions were supervised in order to accurately measure adherence among participants. Data from 119 people who completed the study and had complete body composition data were analyzed to determine the effectiveness of each exercise regimen.

The groups assigned to aerobic training and aerobic plus resistance training lost more weight than those who did just resistance training. The resistance training group actually gained weight due to an increase in lean body mass.
Aerobic exercise was also a more efficient method of exercise for losing body fat. The aerobic exercise group spent an average of 133 minutes a week training and lost weight, while the resistance training group spent approximately 180 minutes exercising a week without shedding pounds.

The combination exercise group, while requiring double the time commitment, provided a mixed result. The regimen helped participants lose weight and fat mass, but did not significantly reduce body mass nor fat mass over aerobic training alone. This group did notice the largest decrease in waist circumference, which may be attributed to the amount of time participants spent exercising.

Resting metabolic rate, which determines how many calories are burned while at rest, was not directly measured in this study. While theories suggest that resistance training can improve resting metabolic rates and therefore aid in weight loss, in this study, resistance training did not significantly decrease fat mass nor body weight irrespective of any change in resting metabolic rate that might have occurred.

"No one type of exercise will be best for every health benefit," Willis added. "However, it might be time to reconsider the conventional wisdom that resistance training alone can induce changes in body mass or fat mass due to an increase in metabolism, as our study found no change."

Duke researchers added that exercise recommendations are age-specific. For older adults experiencing muscle atrophy, studies have found resistance training to be beneficial. However, younger, healthy adults or those looking to lose weight would see better results doing aerobic training.

"Balancing time commitments against health benefits, our study suggests that aerobic exercise is the best option for reducing fat mass and body mass," said Cris A. Slentz, PhD, a Duke exercise physiologist and study co-author. "It's not that resistance training isn't good for you; it's just not very good at burning fat."

Dead Guts Spill History of Extinct Microbes: Fecal Samples from Archeological Sites Reveal Evolution of Human Gut Microbes

Dec. 12, 2012 — Extinct microbes in fecal samples from archaeological sites across the world resemble those found in present-day rural African communities more than they resemble the microbes found in the gut of cosmopolitan US adults, according to research published December 12 in the open access journal *PLOS ONE* by Cecil Lewis and colleagues from the University of Oklahoma.

The researchers analyzed 1400-8000-year-old fecal samples preserved at three archaeological sites: natural mummies from Caserones in northern Chile, and samples from Hinds Cave in the southern US and Rio Zape in northern Mexico. They also used samples from Otzi the Iceman and a soldier frozen on a glacier for nearly a century. They compared the now-extinct microbes in these samples to microbes present in current-day soil and compost, as well as the microbes present in mouths, gut and skin of people in rural African communities and cosmopolitan US adults.

The authors discovered that the extinct human microbes from natural mummies closely resembled compost samples, while one sample from Mexico was found to match that from a rural African child. Overall, the extinct microbial communities were more similar to those from present rural populations than those from cosmopolitan ones. The study concludes, "These results suggest that the modern cosmopolitan lifestyle resulted in a dramatic change to the human gut microbiome."

As Lewis explains, "It is becoming accepted that modern aseptic and antibiotic practices, are often beneficial but come with a price, such as compromising the natural development of our immune system through changing the relationship we had with microbes ancestrally. What is unclear is what that ancestral state looked like. This paper demonstrates that we can use ancient human biological samples to
learn about these ancestral relationships, despite the challenges of subsequent events like degradation and contamination.”

**Journal Reference:**

**Rich Kenyans hardest hit by HIV, says study**
By EDITH FORTUNATE efortunate@ke.nationmedia.com
Posted Sunday, December 16 2012 at 00:30

HIV is most prevalent among wealthy Kenyans, according to a new study published by the government and a UN agency.

At least 7.2 per cent of Kenya’s most wealthy are infected by the virus compared to 4.6 per cent of Kenya’s poorest, the Kenya Aids Epidemic Update released this week reports.

Money, power and lifestyle are among the contributing factors leading to a high HIV prevalence rate, according to the head of the monitoring and evaluation unit at the National Aids Control Council (NACC), Dr Patrick Mureithi.

**Vulnerable**
“Educated people have a lifestyle that leaves them vulnerable to the transmission of HIV, unlike a poor, conservative, rural man or woman,” said Dr Mureithi.

Of the wealthy who are infected, the prevalence among women is 10.2 per cent against 3.9 per cent for men.

“Women, by their biological nature, are likely to be at a higher risk of contracting HIV than men. Women are recipients while for men, it is different,” said Dr Mureithi.

With a national average of 6.2 per cent of adults living with HIV/Aids, women account for 59.1 per cent of those infected, with educated, urban women more likely to contract the virus than their rural counterparts.

“Educated women are exposed; they are likely to have more than one sexual partner, they travel to more places, leaving them more vulnerable than poor women who live a more reserved life,” Dr Mureithi said.

However, despite HIV being more prevalent in women, a higher percentage of men have more than two sexual partners at 10 per cent compared to women at 1.2 per cent.

“As I said earlier, it is the biological nature of women that makes them more vulnerable,” said Dr Mureithi.

The report also notes that while HIV has historically been more prevalent among urban residents than rural ones, the gap is closing rapidly. Notably, men in rural areas are now more likely to be HIV-infected (at 4.5 per cent) than those in urban areas (at 3.7 per cent).

The report also found that the HIV prevalence among Protestant men is 4.3 per cent, 4.2 per cent among Catholics, and 3.3 per cent among Muslims.

“Religion is not a dominating factor in the study, but yes, it is still a fact. Though in the patterns you will notice Muslim women do not have a high prevalence [at 2.8 per cent],” said Dr Mureithi. Protestant women show a prevalence rate of 8.4 per cent while their Catholic counterparts have a rate of 8 per cent.

**Geographic variability**
Kenya has the third-largest population of people living with HIV in sub-Saharan Africa and the highest national HIV prevalence of any country outside southern Africa, according to a 2008 UNAids report.

The report further notes that there is considerable geographic variability in the burden of HIV in Kenya. Provincial HIV prevalence ranges from a high of 13.9 per cent in Nyanza Province to a low of 0.9 per cent in North Eastern Province.

However, the study notes that Kenya is the global leader in scaling up voluntary medical circumcision for adult males which reduces the risk of female-to-male HIV transmission by at least 60 per cent. More than 230,000 medical circumcision procedures were carried out between November 2008 and December 2010.

Further Kenyans, on average, are less likely to have multiple sexual partners than they were in the late 1990s, and condom use has more than doubled.
Tackling HIV and AIDS through taxation in Uganda

A new tax on goods and services is being proposed in Uganda to fund HIV and AIDS prevention and protection programmes. Jamie Hitchen reports on the debate from Kampala as part of our series on life and politics in Uganda.

HIV and AIDS in Uganda

In the early 1980’s Uganda had an extremely high rate of HIV and AIDS infection that was a serious social problem. President Yoweri Museveni, in power since 1986, has been applauded for his pro-active approach to HIV and AIDS and for being a leader in Africa on prevention methods. He spearheaded a mass education campaign promoting a three-pronged ‘ABC’ HIV and AIDS prevention message: Abstinence from sexual activity until marriage; Be faithful within marriage; and Condoms as a last resort.

He was ably assisted by significant foreign aid; most notably the United States President’s Emergency Plan for AIDS Relief (PEPFAR). From 2004-2011, for example, Uganda received US$1.8 billion in direct funding.

Despite the continuation of this financial support, since 2007 HIV and AIDS infection rates have stagnated and even show a small increase from 6.4% to 7.3%.

Is a fresh, more sustainable approach, now needed? And what might this look like?

Uganda

- 34.51 million – Population
- $16.81 billion – Gross Domestic Product (GDP)
- 54 years – Life Expectancy
- 24% – Percentage of Population Living Below the Poverty Line

HIV and AIDS in Numbers

- Highest Infection Rate of 18.5% of the population in 1992
- In 2005 6.4% of the population was infected but this number now stands at 7.3% (0.9% increase)
- Women (7.7%) are more infected than men (5.6%)
- 80% of new cases are transmitted heterosexually
- The Uganda Aids Commission (UAC) was established in 1992
- Currently around 248,222 people in Uganda are receiving antiretroviral treatment, an estimated 47% of those in need

Statistics on HIV and AIDS from Global Aids Response Progress Report and general data is from the World Bank (2011)

What is being proposed

A working paper released in September 2012, Justification for Increased and Sustainable Financing for HIV in Uganda, proposes the creation of a fund specifically designated to assist projects for HIV and AIDS prevention and protection.

The fund will generate cash through levies on bank transactions and interest, air tickets, beer, soft drinks and cigarettes, as well as taxes on goods and services traded within Uganda. In addition a small tax will be added to telephone calls and to each kilowatt of electricity consumed (equivalent to 1 Ugandan Shilling (0.025pence) per phone call).

The revenue generated is expected to be spent on condom distribution, reducing cases of sexually transmitted infections and in the prevention of mother to child transmission.

In discussing the thinking behind the strategy David Apuuli Kihumu, director general of the Uganda AIDS Commission outlined the need for Uganda to fund its approach to HIV and AIDS without such heavy reliance on international support:

[Currently]...68 percent of Uganda’s HIV funding comes from donors, and 20 percent from HIV-positive people and their families, while only 11 percent comes from the government and 1 percent from the private sector.

Reactions to the tax

The reactions from ordinary Ugandans have not been particularly favourable. It’s not been so much about the idea of a HIV and AIDS tax being proposed that is drawing dissent, but it is more revealing of the absence of faith held in the government not to pocket the funds.

The current scandal at the Office of the Prime Minister discovered in October by the country’s auditor general – the theft of €12 million committed by workers based at the Office of the Prime Minister, taken from joint donor funds from Ireland, Norway, Denmark and Sweden that was ear-marked for peace and
development programmes in Northern Uganda – is still fresh in the memory and has led to several international organisations and governments withholding or suspending aid.

These kinds of breaches of trust felt by Ugandans and donors provide the backdrop to nearly all political debates in Uganda. Although people I have spoken to do not necessarily think the HIV and AIDS tax idea is a bad one, there are still those who don’t support it based on “official” Uganda’s recent record. Most people believe that the practices of managing and enforcing the tax would fail to achieve the results it sets out to in the first place. Two of the most repeated questions I have heard again and again were:

Who would be in charge of dispersing the funds?

And how would accountability for the funds be created?

Citizens are also asking why the current funding, which remains high, around $400 million in 2010-11, is not preventing an increase in the rate of infection.

Three issues remain problematic:

1) There is a failure to properly engage with the root causes of the problem in rural areas.

2) Knowledge levels of prevention methods remain at just 33%.

3) Lack of trained public health officials with the outreach and equipment to have an impact.

Questions therefore need to be asked as to whether it is a shortfall in funds that is the problem or the attitude and approach to tackling the issue which needs re-thinking.

What’s happening in neighbouring countries?

Other African countries have also trialled or are considering similar measures and so this debate is not just taking place in Uganda.

In Kenya the National Aids Control Council (NACC) is proposing that the government enforce a 2 percent tax on mobile phone airtime, to raise $153 million over five years. It has even been reported that the country’s largest mobile phone network has expressed a willingness and support to participate in such a programme.

Kenya is already part of an air ticket funding scheme, whereby a small levy on airline tickets and cargo goes towards HIV and AIDS programmes. The money raised is specifically used to buy anti-retroviral drugs.

Meanwhile Zimbabwe has also a strategy which raises funds for HIV and AIDS prevention through taxation at 3%. This was a policy forced on them in 1999 by declining donor support brought about by political developments in the country. Low salaries and weak state structures have made collecting this difficult. Recent years have seen revenues of $20.5 million collected from this scheme but while it is undoubtedly an improvement more is needed to tackle the HIV and AIDS problem in Zimbabwe.

Final Comments

The idea of levying a small tax on everyday goods such as petrol and phone tariffs is an innovative, bold solution and one that, at least in theory, has merits for ensuring sustainable funding that isn’t dependent on international support.

Ugandan scepticism-at-large about the transparency of parliament and the air of resignation about official corruption held by the public and by government officials are at the core of why meaningful debates about a HIV and AIDS health tax are being held back.

Is this method of collecting revenues the right solution for Uganda?

How can the money be best spent to get Uganda reducing its HIV and AIDS infection rates?

These are just some of the questions that should be driving the debate, and hopefully will. An announcement of a renewed commitment to tackling HIV AIDS by the government on 3 December 2012 may be a start but there is a need to involve all Ugandans in a national debate. HIV and AIDS affects a huge percentage of the population, directly and indirectly, and their views cannot, and should not be ignored.

Opinions about how to tackle HIV and AIDS may differ but the ideal of a society free of the illness is a vision shared by all.

New Guidelines to Better Prevent HIV in Sex Workers


The World Health Organization (WHO), the United Nations Population Fund (UNFPA), UNAIDS, and the Global Network of Sex Work Projects have developed a set of technical recommendations for effective programs to prevent and treat HIV/AIDS and other STDs among sex workers. The complete report,
“Prevention and Treatment of HIV and Other Sexually Transmitted Infections for Sex Workers in Low- and Middle-income Countries,” was published by the WHO Department of HIV/AIDS in December 2012 at URL: http://www.who.int/hiv/pub/guidelines/sex_worker/en/index.html. The guidelines advise that nations should decriminalize sex work and increase the access of sex workers to health services. Regular, voluntary screening and treatment for sex workers and empowerment regarding condom negotiation were other key elements of the guidelines.

Factors that increase the risk of HIV and other STDs for sex workers include a larger number of sexual partners and social marginalization. Because their work is against the law, sex workers face barriers to condom negotiation. Violence and alcohol and drug use may also contribute to higher risk for sex workers.

The guidelines provide direction for national public health officials, health workers, HIV/AIDS program managers, and community organizations that serve sex workers. Brazil, India, Kenya, and Thailand have successfully implemented similar steps to improve the health of sex workers and control the epidemic of HIV and STDs among the wider population.

**Experts Warn Banning Thimerosal From Use In Vaccines Would Harm Immunization Campaigns In Developing World**

"A group of prominent doctors and public health experts warns in articles to be published Monday in the journal Pediatrics that banning thimerosal, a mercury compound used as a preservative in vaccines, would devastate public health efforts in developing countries," the New York Times reports. "Representatives from governments around the world will meet in Geneva next month in a session convened by the United Nations Environmental Program to prepare a global treaty to reduce health hazards by banning certain products and processes that release mercury into the environment ... [b]ut a proposal that the ban include thimerosal ... has drawn strong criticism from pediatricians," the newspaper writes (Tavernise, 12/17).

The compound, which prevents the growth of bacteria or fungi in multi-use vials of vaccines, is not used in the U.S., but "in countries with fewer resources—where many children still die of vaccine-preventable diseases—it’s cheaper and easier to use multi-dose vials of vaccines against diphtheria and tetanus, for example," Reuters notes. "Earlier this year, the WHO said replacing thimerosal with an alternative preservative could affect vaccine safety and might cause some vaccines to become unavailable," the news agency writes (Pittman, 12/17). "Advocacy groups have lobbied to include the substance in the ban, and some global health experts worry that because the government representatives due to vote next month are for the most part ministers of environment, not health, they may not appreciate the consequences of banning thimerosal in vaccines," the New York Times states, noting, "The Pediatrics articles are timed to raise a warning before the meeting" (12/17).

**Immune cells use tethered slings to avoid being swept away**

**High-speed lab video shows neutrophil using its long membrane tether like a sling to anchor itself during navigation**

Neutrophils, critical components of the immune system’s response to bacteria and other pathogens, throw out tube-like tethers that act as anchor points, controlling their speed as they roll along the walls of blood vessels during extremely fast blood flow en route to an infection site, according to research presented on Dec. 17 at the American Society for Cell Biology Annual Meeting in San Francisco.

To attack a bacterial infection in tissue, neutrophils have to leave the blood stream and approach the infection site through tiny venules that are part of the microcirculation system, according to Prithu Sundd, PhD, who is in the laboratory of Klaus Ley, PhD, at the La Jolla Institute for Allergy and Immunology, La Jolla, CA.

Extensions of the cell membrane, the slings turned out to be vital aids in the navigation because if neutrophils lose control while attempting to enter infected tissue, they can be swept away in the blood flow, which could delay the immune defense mechanism. Flow in these narrow venules is measured as wall shear stress. A shear stress exceeding 2 dyn/cm2 can sweep away other leukocytes, but neutrophils have a special ability to move under control at shear stress 10 times higher.

Shear-resistance in neutrophils was known to be aided by cell flattening and by these mysterious membrane extensions but the details were poorly understood. To determine the exact mechanism behind neutrophils’ rolling, Dr. Sundd working with physicist Alex Groisman, PhD, of the University of California, San Diego, to shoot a high-speed video, using total internal reflection fluorescence microscopy
to track labeled neutrophils from mouse bone marrow rolling along an artificial venule, all driven by a microfluidic device at a shear stress of 6 to 10 dyn/cm².

In the 15-second video, the red-dyed neutrophil used its long membrane tether like a sling to anchor itself without being swept away by the high shear force of blood. Instead of a single anchor point, the sling tether is coated by patches of cell adhesion molecules that latched onto the passage walls but peeled loose, patch by patch, as the neutrophil gently rolled forward. At the tether's end, the neutrophil swung it ahead like a lasso to gain new leverage.

The researchers say their dramatic video underscores the complexity of the body's immune system. The slings are not only unique structures, says Dr. Sundd, but may help explain how rolling neutrophils are able to present their antigen-sensing ligands at the blood vessel wall before entering the site of infection.


**Mayo Clinic-led Study Unravels Biological Pathway That Controls the Leakiness of Blood Vessels**

Monday, December 17, 2012

JACKSONVILLE, Fla. — A research team led by scientists at Mayo Clinic in Florida have decoded the entire pathway that regulates leakiness of blood vessels — a condition that promotes a wide number of disorders, such as heart disease, cancer growth and spread, inflammation and respiratory distress.

They say their findings, published online Dec. 17 in the *Journal of Cell Biology*, suggest that several agents already being tested for other conditions might reverse vessel leakiness.

"Now that we understand a lot more about the pathway that leads to leaky blood vessels, we can begin to try to target it in an efficient way, and that is very exciting," says the study's lead investigator, Panos Z. Anastasiadis, Ph.D., chair of the Department of Cancer Biology at Mayo Clinic in Florida.

Physicians have attempted to regulate that pathway in cancer through use of VEGF inhibitors, such as Bevacizumab, but these drugs are not as effective as they might be if other parts of the pathway were also inhibited, Dr. Anastasiadis says.

The research team, led by Dr. Anastasiadis and Arie Horowitz, Ph.D., at Cleveland Clinic Foundation, found that VEGF is one of two different molecules that affect a key downstream protein, Syx, to regulate the permeability of blood vessels.

Blood vessels are made up of endothelial cells that have to fit tightly together to form a solid tubular structure that blood can flow through. The researchers discovered that VEGF turns off Syx, which normally ensures the junctions between endothelial cells are strong. Without Syx, adhesion between the cells is loose, and the blood vessels are leaky. When new blood vessels are needed — such as to feed a growing tumor — VEGF loosens up endothelial cells so new vessels can sprout.

Then, after new vessels are formed, a second molecule, angiopoietin-1 (Ang1) works to glue the cells back together, Dr. Anastasiadis says. "These molecules have opposing, yin and yang effects. VEGF kicks Syx out of the junctions between cells, promoting leakiness, and Ang1 brings it back in to stabilize the vessel," he says.

The issue in cancer, however, is that VEGF overwhelms the system. "There isn't enough Ang1 to glue the vessels back together, and this leakiness allows cancer cells to escape the tumor and travel to other parts of the body," Dr. Anastasiadis says. "In late stages of the cancer, it also promotes the leaking of liquids into organs, such as the lungs. This results in profound effects that are often lethal."

Other disorders, such as inflammation and sepsis, a deadly bacterial infection that can result from excess liquid in lungs, are also induced by a leaky vascular system, he says.

Based on a detailed analysis of molecules involved in the VEGF/Ang1/Syx pathway, Dr. Anastasiadis believes that several experimental agents might help reverse vascular leakiness. One of them inhibits protein kinase D1 (PKD1), which might prevent endothelial cells from coming apart from loss of adhesion, and the other is a Rho-kinase inhibitor that prevents endothelial cells from contracting — which they must do to loosen up and become leaky.

"We now have new directions for both further basic research into leaky blood vessels and for potential clinical treatment," Dr. Anastasiadis says.

**Chances seen rising for chikungunya outbreaks in NYC, Atlanta, Miami**

ITHACA, N.Y. – Global travel and climate warming could be creating the right conditions for outbreaks of a new virus in this country, according to a new Cornell University computer model.
The model predicts that outbreaks of chikungunya, a painful virus transported by travelers and spread by the invasive Asian tiger mosquito, could occur in 2013 in New York City during August and September, in Atlanta from June through September, and year-round in Miami. The probability of a disease outbreak is correlated with temperature, as warmer weather allows the Asian tiger mosquito to breed faster and grow in numbers, according to the study published in the November issue of *PLOS Neglected Tropical Diseases*.

According to the simulation, there is a high probability of a chikungunya outbreak if a single infected person arrives in New York in July or August and is bitten by an Asian tiger mosquito. The risks are the same, but with wider time frames, for transmission in Atlanta and Miami, according to the paper.

Asian tiger mosquitoes were introduced to the United States in Texas in the 1980s; they are established up the East Coast into New Jersey and are rising in numbers in New York City. The aggressive mosquito outcompetes local varieties and transmits more than 20 pathogens, including chikungunya and dengue, said Laura Harrington, associate professor of entomology and the study’s senior author.

"The virus is moving in people, and resident mosquito populations are picking it up," Harrington said.

The model estimates that with typical regional temperatures, a chikungunya outbreak in New York would infect about one in 5,000 people, said Diego Ruiz-Moreno, a postdoctoral associate and the paper's lead author.

"However, this number would increase drastically as temperatures rise due to climate change," Ruiz-Moreno said.

Chikungunya symptoms include a fever, severe joint pain, achiness, headache, nausea and fatigue, as well as "debilitating and prolonged" pain in the small joints of the hands and feet, according to the paper. The virus originated in Central Africa and is endemic in Southeast Asia.

Since no chikungunya vaccine exists, U.S. residents can help prevent an outbreak by removing standing water, wearing long sleeves and repellent during the day when the mosquitoes feed, and knowing the risk and symptoms when traveling, Harrington said.
Dec. 17, 2012 — A surprising number of microorganisms—99 percent more kinds than had been reported in findings published just four months ago—are leaping the biggest gap on the planet. Hitching rides in the upper troposphere, they’re making their way from Asia across the Pacific Ocean and landing in North America.

For the first time researchers have been able to gather enough biomass in the form of DNA to apply molecular methods to samples from two large dust plumes originating in Asia in the spring of 2011. The scientists detected more than 2,100 unique species compared to only 18 found in the very same plumes using traditional methods of culturing, results they published in July.

“The long-range transport and surprising level of species richness in the upper atmosphere overturns traditional paradigms in aerobiology,” says David J. Smith, who recently earned his doctorate at the University of Washington in biology and astrobiology. He’s lead author of a paper in the current issue of the journal Applied and Environmental Microbiology.
"It's a small world. Global wind circulation can move Earth's smallest types of life to just about anywhere," Smith said.

It's been estimated that about 7.1 million tons (64 teragrams) of aerosols—dust, pollutants and other atmospheric particles, including microorganisms—cross the Pacific each year. The aerosols are carried by wind storms into the upper reaches of the troposphere. The troposphere, the layer of air closest to earth up to about 11 miles (18 kilometers), is where almost all our weather occurs.

Co-author Daniel Jaffe, professor at UW Bothell, has previously documented especially large plumes of aerosols in the troposphere making the trans-Pacific trip in seven to 10 days. The recent findings are based on two such plumes, one in April and the other in May of 2011, detected at Mount Bachelor in the Cascade Mountains of central Oregon.

Most of the microorganisms—about half were bacterial and the other half fungal—originated from soils and were either dead on arrival or harmless to humans. A few fungal species have been associated previously with crop wilt but scientists had no way of determining if any crops were affected during either plume event.

Most of the species in the plumes can be found in low, background levels on the West Coast. The plumes, however, brought elevated levels of such organisms leading the scientists to say that it may be useful to think about microorganisms as air pollution: microorganisms that are unnoticed in background levels might be more relevant in concentrated doses.

"I was very surprised at the concentrations. One might expect the concentrations of cells to decrease with altitude based on fallout and dilution," Smith said. "But during these plume events, the atmosphere was pooling these cells just as it does with other kinds of air pollution."

Interestingly, Smith says, two of the three most common families of bacteria in the plumes are known for their ability to form spores in ways that they can hibernate safely during harsh conditions, making them especially well adapted to high altitude transport.

"I think we're getting close to calling the atmosphere an ecosystem," Smith said. "Until recently, most people would refer to it as a conveyor belt, or a transient place where life moves through. But the discovery of so many cells potentially able to adapt to traveling long distances at high altitudes challenges the old classification."

Cells also can interact with their high-altitude environment, for example, becoming the nucleus for rain drops and snow flakes and influencing the amount of precipitation that falls. Other scientists estimate that 30 percent of global precipitation stems from microbes.

On the other hand, scientists have yet to see evidence of metabolism or growth of microorganisms while aloft and there's a limited amount of time that any organism might reside there.

Sampling the upper troposphere for microorganisms in the past has been a spotty effort using aircraft and balloons, Smith said

"Because it is so difficult to get samples, I argue it's probably the last biological environment on the planet to be explored," he said.

Mount Bachelor, like many other mountains in the Cascades, has a peak tall enough to pierce the upper troposphere. Unlike other mountains in the Cascades, however, the top of Mount Bachelor is a far more accessible place for an observatory because a ski area exists there. There's power and bringing equipment and personnel to the observatory is not a major undertaking, you just take the ski lift.

Journal Reference:

People With HIV Hospitalized Less Often Since Combination Antiretroviral Drug TherapyIntroduced
Dec. 17, 2012 — People with HIV are being hospitalized in Ontario significantly less often than they were 15 years ago when combination antiretroviral drug therapy (cART) was introduced, new research has found.

However, women with HIV are still hospitalized more than men with HIV as are low-income people with HIV compared with high-income people with HIV, according to a study by Tony Antoniou, a pharmacist and researcher in the Department of Family Medicine at St. Michael's Hospital.

Immigrants with HIV who had been in Ontario three years or less had lower rates of hospital admissions than Canadian-born people with HIV or immigrants who had been in Ontario longer than three years.
His study was conducted using data at the Institute for Clinical Evaluative Sciences (ICES) and appears in the online journal Open Medicine.

Combination antiretroviral drug therapy, introduced in 1996-97, involves the use of three or more drugs to lower the amount of HIV in the body and prevent the progression of AIDS and death.

"Although our study is overall a 'good news' story for persons with HIV in Ontario, the differences in rates of hospitalization over the past decade suggest that women and low-income individuals living with HIV may face challenges accessing medication and community-based care," said Dr. Antoniou.

While rates of all hospital admissions among all persons with HIV in Ontario declined by about 2 per cent per year between 2002 and 2008, rates in women and low-income persons with HIV were 15 per cent and 21 per cent higher than those of men and high-income patients, respectively, during this period. In addition, rates of hospital admission attributable to HIV itself were 30 per cent higher in low-income persons with HIV relative to high-income persons.

Dr. Antoniou said he believes that universal access to life-saving anti-HIV treatments would be one way to address these disparities, but that, "We need to do more research to understand and address the root causes of these differences, to ensure that all persons with HIV are able to benefit equally from the advances that have been made in managing this illness."

Journal Reference:

Autoimmune Disease: Retraining White Blood Cells

Dec. 17, 2012 — How can the immune system be reprogrammed once it goes on the attack against its own body? EPFL scientists retrained T-cells involved in type I diabetes, a common autoimmune disease. Using a modified protein, they precisely targeted the white blood cells (T-lymphocytes, or T-cells) that were attacking pancreatic cells and causing the disease. When tested on laboratory mice, the therapy eliminated all signs of the pathology. This same method could be a very promising avenue for treating multiple sclerosis as well. The scientists have just launched a start-up company, Anokion SA, on the Lausanne campus, and are planning to conduct clinical trials within the next two years.

Their discovery has been published in the journal PNAS (Proceedings of the National Academy of Science).

To retrain the rebellious white blood cells, the researchers began with a relatively simple observation: every day, thousands of our cells die. Each time a cell bites the dust, it sends out a message to the immune system. If the death is caused by trauma, such as an inflammation, the message tends to stimulate white blood cells to become aggressive. But if the cell dies a programmed death at the end of its natural life cycle, it sends out a soothing signal.

In the human body there is a type of cell that dies off en masse, on the order of 200 billion per day—red blood cells. Each of these programmed deaths sends a soothing message to the immune system. The scientists took advantage of this situation, and attached the pancreatic protein targeted by T-cells in type I diabetes to red blood cells.

"Our idea was that by associating the protein under attack to a soothing event, like the programmed death of red blood cells, we would reduce the intensity of the immune response," explains Jeffrey Hubbell, co-author of the study. To do this, the researchers had to do some clever bioengineering and equip the protein with a tiny, molecular scale hook, that is able to attach itself to a red blood cell. Billions of these were manufactured and then simply injected into the body.

Complete eradication of diabetes symptoms

As these billions of red blood cells died their programmed death, they released two signals: the artificially attached pancreatic protein, and the soothing signal. The association of these two elements, like Pavlov's dog, who associates the ringing of a bell with a good or bad outcome, essentially retrained the T-lymphocytes to stop attacking the pancreatic cells. "It was a total success. We were able to eliminate the immune response in type I diabetes in mice," explains Hubbell.

Minimizing risks and side effects

Co-author Stephan Kontos adds that the great advantage of this approach is its extreme precision. "Our method carries very little risk and shouldn't introduce significant side effects, in the sense that we are not targeting the entire immune system, but just the specific kind of T-cells involved in the disease."

The scientists are planning to conduct clinical trials in 2014, at the earliest. To demonstrate the potential of their method, they plan to first test applications that would counteract the immune response
to a drug known for its effectiveness against gout. "We chose to begin with this application before we tackled diabetes or multiple sclerosis, since we knew and were in control of all the parameters," explains Hubbell.

Currently, the researchers are also testing the potential of this method in treating multiple sclerosis. In this disease, T-cells destroy myelin cells, which form a protective sheath around nerve fibers. They are also studying the potential of their method with another kind of white blood cell, B-lymphocytes, that are involved in many other autoimmune diseases.

**Journal Reference:**

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**Drug Used to Treat HIV Might Defuse Deadly Staph Infections**
Dec. 14, 2012 — A new study by NYU School of Medicine researchers suggests that an existing HIV drug called maraviroc could be a potential therapy for *Staphylococcus aureus*, a notorious and deadly pathogen linked to hundreds of thousands of hospitalizations each year. Their study is published online this week in *Nature*.

"What are the chances that a drug for HIV could possibly treat a virulent Staph infection?" asks Victor J. Torres, PhD, assistant professor of microbiology, and senior author of the study. "These findings are the result of a fantastic collaboration that we hope will result in significant clinical benefit." Staph causes toxic shock syndrome, pneumonia, and food poisoning, among other illnesses, and is becoming increasingly resistant to antibiotics.

The discovery arose from a serendipitous finding that was a part of a collaborative study between Dr. Torres, a bacteriologist, and immunologist Derya Unutmaz, MD, associate professor of microbiology and pathology and medicine, whose laboratories are adjacent to each other.

They focused on a receptor called CCR5 that dots the surface of immune T cells, macrophages, and dendritic cells. Sixteen years ago, researchers at NYU School of Medicine discovered that CCR5 is the receptor HIV uses to gain entry into T cells in order to replicate, spread, and cause an infection that can progress into AIDS.

That same receptor has now been found to be critical to the ability of certain strains of Staph to specifically target and kill cells with CCR5, which orchestrate an immune response against the bacteria. The scientists discovered that one of the toxins the bacterium releases, called LukED, latches on to CCR5 and subsequently punches holes through the membrane of immune cells, causing them to rapidly die. The LukED toxin belongs to a family of proteins called leukotoxins, encoded and produced by Staph to fight off the immune system's defenses.

This discovery was made after Dr. Torres asked Dr. Unutmaz and fellow HIV researcher Nathaniel Landau, PhD, professor of microbiology, if he might use some of the human immune cells they had collected over the course of their HIV studies. The laboratories of all three scientists are adjacent to each other. Dr. Torres was trying to find out which immune cells were affected by different leukotoxins. Dr. Unutmaz gave him a T cell line, which they were using for their HIV infection studies and had previously engineered to express CCR5, to test the effects of these toxins.

"Within one hour flat, T cells with CCR5 all died when exposed to LukED" says Dr. Torres, whereas a similar T cell line that lacked the receptor was completely resistant to the toxin's effects. This observation quickly led to another set of experiments to determine that the LukED toxin was indeed interacting with the receptor and that its presence on the cell surface was necessary for the toxin to kill the cells. The investigators then treated cells with CCR5 with maraviroc, a drug on the market that binds to CCR5 and blocks HIV infection, and then exposed the cells to the Staph toxin. The result, the scientists say, was astonishing. "It was remarkable. Maraviroc completely blocked the toxic effects of this leukotoxin at doses similar to those used to inhibit HIV infection" Dr. Unutmaz says.

"The goal in blocking the toxin with maraviroc or similar agents is to give the upper hand to the immune system to better control the infection," Dr. Torres adds. The researchers further corroborated the critical role of CCR5 in Staph infections using a mouse model. When they infected mice susceptible to Staph infection with strains that contain the LukED toxin, almost all the mice died. However, mice that were genetically engineered to lack CCR5 on their cells survived this lethal Staph infection.

Based on these findings, the investigators hope that future human clinical trials will determine whether drugs that block CCR5, such as maraviroc, could help the immune system to control the infection and potentially save lives.
Journal Reference:
Francis Alonzo III, Lina Kozhaya, Stephen A. Rawlings, Tamara Reyes-Robles, Ashley L. DuMont, David G. Myszka, Nathaniel R. Landau, Derya Unutmaz, Victor J. Torres. CCR5 is a receptor for Staphylococcus aureus leukotoxin ED. Nature, 2012; DOI: 10.1038/nature11724

Treatment with a protease inhibitor during the first trimester of pregnancy increases the risk of pre-term birth
Michael Carter
Published: 18 December 2012
Further evidence has emerged from research in the United States that antiretroviral therapy based on a protease inhibitor (PI) during the first three months of pregnancy is associated with an increased risk of pre-term delivery. The study is published in the advance, online edition of the Journal of Infectious Diseases.

“We found that PI-based combination regimen use in the first trimester was associated with both total and spontaneous preterm birth risk,” write the investigators. “HIV disease progression or effects of combination ARV [antiretroviral therapy] on the immune system among women with indications for initiation of therapy before pregnancy may contribute to increasing preterm birth risk.”

Appropriate use of antiretroviral treatment during pregnancy can reduce the risk of mother-to-child transmission of HIV to below 1% and combination antiretroviral therapy is recommended for all HIV-positive pregnant women who are ill because of HIV or who have a CD4 cell count below 350 cells/mm3.

Treatment has undoubted benefits, reducing the risk of transmission and protecting the health of the mother. However, its risks are less certain. Research conducted in Europe – but not the US – showed that combination HIV therapy during pregnancy increases the risk of pre-term delivery, especially if it is based on a protease inhibitor. The overall findings of a meta-analysis of 14 studies showed treatment during pregnancy did not increase the risk of premature delivery. Nevertheless, it also found that treatment with a protease inhibitor during the first trimester was a risk factor for premature delivery.

Given this uncertainty, investigators from the US Pediatric HIV/AIDS Cohort Study (PHACS) wanted to establish a clearer understanding of the risks associated with protease inhibitor therapy during pregnancy. They therefore looked at maternal use of antiretroviral therapy among women enrolled in the Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) study and its association with pre-term delivery and birth weight.

“The large size of the study, which includes detailed information on the specific type and timing of ARV drug regimens and other potential risk factors in pregnancy allowed us to control for many potential confounding factors and to assess combinations of factors that may influence the risk of preterm delivery,” comment the authors.

The analysis was limited to singleton births with maternal enrolment before 31 October 2010. Pre-term birth was defined as delivery before the completion of 37 weeks of pregnancy; very pre-term birth was defined as delivery before the end of week 32. Infants were small for gestational age if their birth weight was < 10th percentile for gestational age.

A total of 1869 live, HIV-negative infants born to 1506 mothers were included in the study. There were 346 (19%) pre-term births, and 55% of these were spontaneous. There were 37 (2%) very pre-term births and 135 infants (7%) were small for gestational age.

Most of the mothers (89%) used antiretroviral therapy during pregnancy, with 40% treated with anti-HIV drugs during the first trimester.

Preliminary analysis showed that a number of factors were associated with an increased risk of pre-term delivery. These included black race, income below $20,000 per year and a CD4 cell count below 200 cells/mm3 late in pregnancy.

Taking these factors into account, the investigators looked at the relationship between the pre-term delivery and the type and timing of antiretroviral treatment.

Their first analysis showed a marginal association between use of protease inhibitor-based treatment and premature birth (OR = 1.60; 95% CI, 0.96-2.67, p = 0.07) as compared to other types of therapy.

Evaluation of timing of treatment showed that use of a protease inhibitor during the first trimester increased the risk of pre-term delivery significantly (AOR = 1.55; 95% CI, 1.16-2.07, p = 0.003). Treatment with a protease inhibitor during the first three months of pregnancy also increased the risk of a spontaneous premature delivery (AOR = 1.59; 95% CI, 1.10-2.30, p = 0.014).

“The association between first trimester PI combination drug exposure and increased preterm birth risk...raises concerns which warrant further study,” comment the researchers.
Individual protease inhibitors associated with a pre-term birth were saquinavir (*Invirase*), ritonavir (*Norvir*) and lopinavir/ritonavir (*Kaletra*).

There was no relationship between infant size and use of combination HIV therapy at any time during pregnancy.

“We have observed that although combination ARV use later in pregnancy is not associated with an increased risk of preterm delivery, use in the first trimester of PI-containing combination ARV regimens may contribute to an increased risk,” the investigators conclude. “The mechanism of first trimester effect is unclear but could be related to changes in immune and inflammatory mediators. Further studies are needed to elucidate the specific drug effects and the interaction of the many factors that determine pregnancy outcome.”

Reference


December 17, 2012 09:30 AM Eastern Time

**Major Breakthrough in HIV Research: Study Published Today Online in The Journal of Experimental Medicine Identifies Population of Cells Serving as the Major Reservoir for HIV ****

LAUSANNE, Switzerland—(BUSINESS WIRE)—A study published today online in *The Journal of Experimental Medicine* has identified the population of CD4 T cells serving as the major reservoir for HIV infected cells and as the primary cell site for HIV replication and production in infected patients. The study was led by Prof. Giuseppe Pantaleo and Dr. Matthieu Perreau at the Division of Immunology and Allergy and at the Swiss Vaccine Research Institute, Lausanne University Hospital, Lausanne, Switzerland.

“The elimination of HIV infected Tfh cells will represent a critical therapeutic strategy to achieve HIV functional cure, i.e. control of HIV replication in the absence of antiretroviral therapy, and potentially HIV eradication.”

CD4 T cells are known to be the primary target of HIV. The CD4 T cells serving as reservoir for HIV infection and as primary site for HIV replication and production are not present in the blood and are exclusively found in the lymphoid tissues in a region called germinal centers. These CD4 T cells are called ‘T follicular helper’ (Tfh) cells: they represent about 2% of the total CD4 T cells residing in the lymphoid tissues and are in close contact with B cells and help B cells to mature and produce antibodies.

“This is a major discovery for the HIV field; we have finally identified the cell population predominantly responsible for supporting active HIV replication and production,” says Prof. Pantaleo. “We have also provided evidence that the Tfh cells are likely to be responsible for residual virus replication in patients effectively treated with antiretroviral therapy.”

“HIV-infected Tfh cells hide themselves within the germinal centers where they are difficult to be reached by HIV-specific cytotoxic CD8 T cells, which generally are poorly present in germinal centers,” says Dr. Perreau. “Therefore, germinal centers represent a sanctuary for HIV replication in Tfh cells.”

“The identification of the major HIV CD4 T cell reservoir will be instrumental in developing therapeutic strategies to selectively target HIV infected Tfh cells,” says Prof. Pantaleo. “The elimination of HIV infected Tfh cells will represent a critical therapeutic strategy to achieve HIV functional cure, i.e. control of HIV replication in the absence of antiretroviral therapy, and potentially HIV eradication.”

**EDITOR’S NOTES**

**T cells:** Small lymphocytes that play a major role in cellular immunity. T cells mature in the thymus and have the ability to recognize specific antigens through the receptors expressed at their cell surface. They identify and eliminate incoming microbes such as bacteria and viruses.

**CD4 T cells:** are a sub-group of small lymphocytes. CD4 T cells in the blood represent 50-60% of human T cells. The CD4 molecule serves as the primary receptor for HIV. HIV causes depletion of CD4 T cells. The depletion of CD4 T cells is associated with increased susceptibility to infection with other infectious agents in the advanced stages of HIV disease.

**CD8 T cells:** CD8 T cells recognize viral antigens on the surface of HIV-infected cells and are capable of killing virus infected cells.

**Reservoir:** cell type or anatomical site, where a replication-competent form of HIV can accumulate and persist stably.
Viiv Healthcare announces regulatory submissions for dolutegravir in the EU, US and Canada

17 December 2012

London, UK—17 December, 2012 – Viiv Healthcare today announced the submission of regulatory applications in the European Union (EU), United States (US) and Canada for the investigational integrase inhibitor dolutegravir (S/GSK1349572) for the treatment of HIV infection in adults and adolescents, specifically:

- A Marketing Authorisation Application to the European Medicines Agency for dolutegravir for the treatment of HIV infection in adults and children aged 12 years and older.
- A New Drug Application to the US Food and Drug Administration for dolutegravir for the treatment of HIV infection in adults and children aged 12 years and older.
- A New Drug Submission to Health Canada for dolutegravir for the treatment of HIV infection in adults and children aged 12 years and older.

“These regulatory submissions are an important step for Viiv Healthcare, representing our commitment as a company to bring new treatments to people living with HIV.” said John Pottage, MD, Chief Scientific and Medical Officer, Viiv Healthcare. “We are encouraged by the comprehensive data package supporting dolutegravir, and believe that it has the potential to offer an important new option for the treatment of both naïve and treatment-experienced patients with HIV.”

Single Administration of GenVec's Vaccine Provides Protective Immunity Against HSV in Pre-clinical Animal Models

GAITHERSBURG, Md., Dec. 17, 2012 /PRNewswire/ — GenVec, Inc. (NASDAQ: GNVC) announced today that data were presented on its HSV vaccine program at the Keystone Symposia meeting on Immunological Mechanisms of Vaccination, which is taking place in Ottawa, Ontario from December 13 to December 18, 2012.

The company disclosed that a single administration of its genetic vaccine was effective against HSV2 in two industry-accepted HSV disease models. Specifically, immunization was shown to reduce viral shedding, and the recurrence and severity of lesions.

GenVec's HSV vaccine candidate generated effective immune responses in animal models; and is composed of two novel antigens, as well as a proprietary, non-human adenoviral vector.

"We have substantial evidence that HSV infection can be controlled by inducing an appropriate T-cell response,” said Dr. Lisa Wei, Senior Director of Research and head of GenVec's HSV program. "The data presented at this symposium demonstrate the progress we are making towards the goal of creating a vaccine for treatment and potentially prophylaxis of HSV infection.”

About Herpes Simplex Virus (HSV)

In the United States, approximately 40 million people are currently infected with HSV2, which is responsible for most cases of genital herpes, and 1.6 million new infections occur each year. About 25% of those infected with the virus suffer clinical symptoms. Even higher infection rates are evident in developing countries. HSV2 infection is associated with increased HIV infection and transmission; and further complications of HSV are also often seen in those co-infected with HIV. HSV infections are permanent, and result in periodic virus shedding. Although antiviral regimens have become a standard of care, their inconvenience, cumulative cost and potential for drug resistance further underscore the need for safe, new approaches to reduce HSV lesions, virus shedding, and transmission. Estimated costs of treating HSV in the United States alone are close to $1 billion, primarily for drugs and outpatient medical care. There is no FDA-approved vaccine for HSV.

Louisiana Leads the Nation in Rates of Gonorrhea and Syphilis Cases, CDC Reports


CDC reported that Louisiana had the highest rates of syphilis and gonorrhea in the United States in 2011. Louisiana ranked third for cases of chlamydia. CDC figures out disease rates based on the number of actual cases reported in 2011.

The 2011 gonorrhea rate in Louisiana was almost twice as high as the national average, and the rates of primary and secondary syphilis were more than double the national average. Men who have sex with men account for about 70 percent of all syphilis infections. Men and women age 15 to 24 have the highest

Effective treatments are available for chlamydia, gonorrhea, and primary and secondary syphilis. People with syphilis are more likely to be infected with HIV, and untreated syphilis can lead to paralysis, dementia, and death. Untreated chlamydia and gonorrhea increase the risk of infertility in women.

T.J. Rogers, spokesperson for the NO/AIDS Task Force, said the Task Force provides free screening for HIV and other STDs every Wednesday, from noon to 7:30 p.m., at 507 Frenchmen St. People who would like to be tested may make an appointment at URL: www.noaidstaskforce.org/nogmwp. The NO/AIDS Task Force also provides referrals for treatment.

**Potent Antibodies Neutralize HIV and Could Offer New Therapy, Study Finds**

*Science Daily*, (12.10.2012)

Researchers at Rockefeller University, New York, appear to have found another approach to treating HIV infection. They have shown that it is possible to harness proteins from the human immune system to suppress the virus in mice without the need for daily application as is done with current antiretroviral drugs. Using a combination of five different antibodies, Florian Klein and colleagues at Michel Nussenzweig’s Laboratory of Molecular Immunology were able to effectively suppress HIV-1 replication and prevent the virus for 60 days after termination of therapy. They used “humanized mice” as normal mice do not have the receptors to be infected with HIV-1.

HIV-1 evades the human immune system’s attacks by mutating; but with the combination of the new antibodies, mutation did not work. The antibodies target HIV-1’s surface protein, gp160, a molecule that forms a spike that attaches to host cells. Five antibodies in unison were required to stop gp160. The five antibodies were too complicated for gp160 to mutate in time to avoid them. The antibodies, called broadly neutralizing antibodies, were recently discovered. They were identified and cloned from HIV-infected patients whose immune systems had an unusually high ability to neutralize HIV. These antibodies have been able to prevent HIV from infecting non-human primates, which leads to a possibility of a vaccine for humans. However, it was felt that they would have little or no effect on established infections.

Klein stated that the results are encouraging enough to prompt an investigation of these antibodies in clinical trials. He surmised that a combination of antibodies and antiretroviral therapy may lead to a treatment for humans that will not require daily medication.

The study, “HIV Therapy by a Combination of Broadly Neutralizing Antibodies in Humanized Mice,” was published in the journal *Nature* (2012; 492 (7427):118 DOI: 10.1038/nature11604).

**RH Wins!**


On December 17, Philippine lawmakers approved a Reproductive Health Bill, paving the way for a landmark law that will provide government funding for contraceptives and sex education in schools despite strong opposition from the Roman Catholic Church. In the House, the bill passed 133 to 79, and a similar bill was approved in the Senate 13 to 8. The bill is ready to be taken up December 18 by a bicameral conference committee that will work to reconcile the House and Senate versions. The final version will then need to be ratified by Congress on December 19 and signed by President Benigno Aquino III to become law. According to House Majority Leader Neptali Gonzales II, the president was responsible for the final push to pass the bill and believes it will be the legacy that he leaves behind.

**Five Polio Vaccination Workers Killed In Pakistan**

"Gunmen killed five Pakistani women working on a [three-day] U.N.-backed polio vaccination campaign in two different cities on Tuesday, officials said," the *Associated Press* reports, adding, "The attacks were likely an attempt by the Taliban to counter an initiative the militant group has opposed.” According to the news agency, "The attacks came a day after an unknown gunman killed a male volunteer for the World Health Organization’s anti-polio campaign in Pakistan’s largest city, Karachi” (Jawad, 12/18). "In Karachi, provincial Health Minister Saghir Ahmed said the government had told 24,000 polio workers it was suspending the anti-polio drive in the province," *Reuters* reports. "Some Islamists and Muslim preachers say the polio vaccine is a Western plot to sterilize Muslims," while "[o]ther religious leaders have taken part in campaigns aimed at debunking that myth," the news agency notes, adding, "There have been at least three other shootings involving polio eradication workers this year" (Shah et al., 12/18).
Scientists discover how HIV virus gains access to carrier immune cells to spread infection

Scientists from the AIDS Research Institute IrsiCaixa have identified how HIV, the virus that causes AIDS, enters the cells of the immune system enabling it to be dispersed throughout an organism. The new study is published December 18 in the open access journal PLOS Biology.

One of the reasons why we do not yet have a cure for HIV infection is that the virus infects cells of the immune system that would normally fight such an infection. The main targets of HIV are white blood cells named CD4 T lymphocytes (so called because they have the protein CD4 in their membrane), and while more than 20 different drugs are available today to help control HIV, all of them act by blocking the cycle that HIV follows to infect these CD4 T lymphocytes. However, these treatments do not fully act on another cell of the immune system, the dendritic cell, which takes up HIV and spreads it to target CD4 T lymphocytes.

Mature dendritic cells are responsible for activating an immune response by CD4 T lymphocytes, but when they carry viruses, their contact with T lymphocytes causes the virus to be passed on, thus increasing viral spread.

The results continue the research led by ICREA researchers at IrsiCaixa, Javier Martínez-Picado, and Nuria Izquierdo-Useros, in collaboration with research groups from Heidelberg University, Germany, and the University of Lausanne, Switzerland. This team published a previous PLOS Biology paper in April 2012, in which they identified molecules, called gangliosides, located on the surface of HIV that are recognized by dendritic cells and are necessary for viral uptake. The new results now identify a molecule on the surface of dendritic cells that recognizes and binds the gangliosides and allows HIV to be taken up by dendritic cells and transmitted to its ultimate target: T lymphocytes.

"We have observed that the protein that acts as a lock for the entrance of HIV could also facilitate the entrance of other viruses," explains Nuria Izquierdo-Useros. "Therefore, our results could also help us understand how other infections might exploit this mechanism of dispersion."

In order to identify the precise molecule located on the membrane of the dendritic cells capable of capturing HIV, the researchers studied one family of proteins that are present on the surface of these cells, called Siglecs. It is known that these proteins bind to the gangliosides on the HIV surface. In the laboratory, they mixed the virus with dendritic cells that displayed different quantities of Siglec-1, and found that a higher quantity of Siglec-1 led to those dendritic cells capturing more HIV, which in turn allowed for enhanced transmission of HIV to CD4 T lymphocytes, a process called trans-infection.

The team then tried inhibiting the Siglec-1 protein. Doing so in the laboratory, they found that the dendritic cells lost their capacity to capture HIV and, importantly, they also lost their ability to transfer HIV to CD4 T lymphocytes. With all these data, the scientists concluded that Siglec-1 is the molecule responsible for HIV entrance into the dendritic cells, and could therefore become a new therapeutic target.

"We had the key and now we have found a lock," explains Javier Martínez-Picado. "Now we are already working on the development of a drug that could block this process to improve the efficacy of the current existing treatments against AIDS."


Antibiotics based on a new principle may defeat MRSA ****

[PRESS RELEASE 2012-12-18] Scientists at Karolinska Institutet have presented a new principle for fighting bacterial infections, in other words, a new type of antibiotic, in the FASEB Journal. The new antibiotic mechanism is based on selectively blocking the thioredoxin system in the cells, which is crucial to the growth of certain bacteria. Scientists hope to be able to treat such conditions as stomach ulcers, TB and MRSA.

"Much work remains to be done, but we believe that it will be possible to use this mechanism when, for example, broad-spectrum antibiotics have proved to be inadequate", says Professor Arne Holmgren, leader of the study now being published.

The thioredoxin system is present in all cells and is central to the ability to make new DNA (genetic material). It is also important in protecting the cell from a process known as oxidative stress, which arises when excess oxygen radicals and other oxidizing agents are formed. This may occur, for example, during the attack by white blood cells on bacteria, and it can damage or kill the cell. The most important components of the thioredoxin system are the enzymes thioredoxin and thioredoxin reductase, of which
the first (very simplified) is required in the process of creating the building bricks of what is to be new DNA, and the second ensures that the thioredoxin remains active.

In addition to the thioredoxin system, mammals and humans, and some bacteria, have a second, similar biochemical process in the cell that is based on the enzyme glutaredoxin. The thioredoxin system and the glutaredoxin system act as each other's backup. Many bacteria that cause disease, however, such as Helicobacter pylori (which cause stomach ulcers), the TB bacterium Mycobacterium tuberculosis, and the multiresistant staphylococcus bacterium MRSA, have only the thioredoxin system. These bacteria lack the glutaredoxin system. This makes these bacteria very vulnerable to substances that inhibit thioredoxin and thioredoxin reductase.

"Furthermore, the **thioredoxin reductases in bacteria are very different in chemical composition and structure from the human enzyme**. And it is just these differences, and the fact that certain bacteria lack the glutaredoxin system, that mean that drugs that affect thioredoxin reductase can be used as antibiotics. This is what we have discovered", says Arne Holmgren.

The study now being published describes how the scientists have used a drug candidate known as ebselen, which has previously been tested in the treatment of stroke and inflammation. The scientists discovered that ebselen and similar synthetic substances inhibit, among other things, thioredoxin reductase in bacteria. The scientists saw in laboratory experiments how the ebselen killed certain types of bacteria and not others. They were able to modify the genetic properties of Escherichia coli (E. coli), which is normally not susceptible to ebselen, and in this way investigate the mechanisms behind the antibiotic effect. They showed that the bacteria in which the genes in the DNA molecule that code for the glutaredoxin enzyme or the formation of the tripeptide glutathione, which is another important component of the glutaredoxin system, had been switched off were more susceptible to ebselen than normal.

Bacteria that are resistant to several different types of antibiotic are a serious and extensive problem all over the world. The method of attacking bacteria by preventing the construction of their cell wall, which was discovered when penicillin was discovered at the beginning of the 20th century, is still used, in several variations. It has for this reason long been obvious that science must find new ways of combating diseases caused by bacterial infections. The scientists who have written the article believe that the new antibiotic principle they are presenting may be a part of the solution.

"It is particularly interesting that MRSA and the antibiotic-resistant TB are also susceptible to ebselen and new synthetic substances. And it's worth noting that ebselen is an antioxidant, just as vitamin C is. This means that it protects the host against oxidative stress, and in this way we can kill two birds with one stone", says Arne Holmgren.

**Publication:**

**Way to make one-way flu vaccine discovered by Georgia State researcher**
A new process to make a one-time, universal influenza vaccine has been discovered by a researcher at Georgia State University's Center for Inflammation, Immunity and Infection and his partners.

Associate Professor Sang-Moo Kang and his collaborators have found a way to make the one-time vaccine by using recombinant genetic engineering technology that does not use a seasonal virus. Instead, the new vaccine uses a virus' small fragment that does not vary among the different strains of flu viruses.

By using the fragment and generating particles mimicking a virus in structure, the immune system can learn to recognize any type of flu virus and attack the pathogen, preventing illness. The research appears in a recent edition of the journal *Molecular Therapy*, published by the Nature Publishing Group.

"We can now design a vaccine that makes it easier to induce a good immune system response to recognize a pathogen, regardless of how the surface proteins of the virus change," Kang said.

Health officials and scientists must alter flu vaccines every year to match expected strains, and often shortages can result, such as what happened during the 2009 Swine Flu outbreak. A one-time vaccine would prevent such a scenario, Kang said.

"Outbreaks of pandemic can be a dangerous situation, and our current vaccination procedures are not perfect," he said.
Using the new one-time vaccine, using only a fragment rather than the live viral vaccine, such as FluMist, or a killed virus itself, would be safer for people with weakened immune systems, young children and the elderly, Kang said.

The team included researchers from Georgia State, the Emory Vaccine Center at the Emory University School of Medicine, Sungshin Women's University in South Korea and the Animal, Plant and Fisheries Quarantine and Inspection Agency in South Korea.

The research was mainly supported by a grant from the National Institutes of Health and partially supported by the government of South Korea. The article is “Virus-like particles containing multiple M2 extracellular domains confer improved cross protection against various subtypes of influenza virus,” Nature Molecular Therapy, http://dx.doi.org/10.1038/MT.2012.246.

**Host cholesterol secretion likely to influence gut microbiota**

For more than half a century, researchers have known that the bacteria that colonize the gastrointestinal tract of mammals influence their host’s cholesterol metabolism. Now, Jens Walter and colleagues of the University of Nebraska show that changes in cholesterol metabolism induced by diet can alter the gut flora. The research was published online ahead of print in the journal *Applied and Environmental Microbiology*.

In the study, the researchers added plant sterol esters to the diets of hamsters. The overall effect of this was to inhibit several bacterial taxa, from the families Coriobacteriacea and Erysipelotrichaceae, says Walter. But the immediate effect of the plant sterols was to physically block cholesterol absorption by the intestine. That decreased cholesterol levels in the liver and the plasma, prompting the hamster’s body to respond by synthesizing more cholesterol. That, in turn, boosted cholesterol excretion into the gut, and that extra cholesterol was the direct inhibitor of those bacterial families.

"The abundance of these bacterial taxa and the levels of cholesterol in the fecal samples followed a mathematical model of bacterial inhibition," says Walter.

Practically speaking, the microbial inhabitants of the gut are part of the metabolic system. Researchers have shown that certain health problems are related to changes in the gut flora, such as can be induced by overuse of antibiotics. Since changes in diet can influence composition of the gut flora, health problems such as obesity might be targeted by dietary interventions designed to suppress bacteria that contribute to weight gain. "However, for these to be successful, we need to know which bacterial patterns not only are associated with disease, but actually contribute to it," says Walter, noting that his research showed that some alterations associated with metabolic disease might be the consequence, rather than the cause of the disorder.

Walter says that the work was a real student project. Among the coauthors, three were graduate students, and two were undergraduates. "As a supervisor, it is extremely nice to see young scientists work as a team, and staying dedicated through the five years that this project took to complete," he says.

A copy of the manuscript can be found online at [http://bit.ly/asmtip1212b](http://bit.ly/asmtip1212b). Formal publication is scheduled for the January 2013 issue of *Applied and Environmental Microbiology*.


**Tracking the origins of HIV ****

URBANA – Human immunodeficiency virus (HIV) may have affected humans for much longer than is currently believed. Alfred Roca, an assistant professor in the College of Agricultural, Consumer and Environmental Sciences at the University of Illinois, thinks that the genomes of an isolated West African human population provide important clues about how the disease has evolved.

HIV is thought to have originated from chimpanzees in central Africa that were infected with simian immunodeficiency virus (SIV), a retrovirus. "If you look at the diversity present across SIV in chimpanzees, it suggests that they have had it for tens of thousands of years," Roca said.

HIV-1 Type M, which accounts for 90 percent of human infections, is believed to have crossed the species barrier into human populations between 1884 and 1924. Roca said that it may have crossed much earlier and many times, selecting for genetic resistance in isolated rural populations while remaining undetected.

"Some of the scientific literature suggests that the persistence of HIV in humans required population densities typical of the larger cities that appeared in West Central Africa during the colonial era," he said.
Perhaps an even more important factor is that, before modern medicine and vaccinations, infectious diseases such as smallpox killed large numbers of people. People with compromised immune systems may have succumbed first, preventing the immunodeficiency virus from spreading.

If HIV crossed the species barrier many times, it is possible that selection favored protective genetic variants in the affected populations. Roca and his co-investigators looked for evidence of this selection in the Biaka genomes.

The Biaka are a human community that inhabits forests in the range of the chimpanzee subspecies believed to be the source of the current HIV pandemic. The researchers compared Biaka genomes with the genomes of four other African populations who live outside the chimpanzee's range.

Biaka genotypes were available through the Human Genome Diversity Project, which collected biological samples from 52 different population groups across the world. The project genotyped these diverse human communities for single nucleotide polymorphisms (SNPs, pronounced "snips"), or genomic variation, at around 650,000 locations across the genome.

Previous research that used cell lines made in the 1980s from individuals who had AIDS or were believed to be at risk for it had identified 26 genomic locations as being involved in resistance to HIV. Kai Zhao, a graduate student working in Roca's laboratory, examined these locations.

Zhao ran all 10 possible pairwise comparisons for the five human populations and looked for selection signatures. Specifically, selection for a genetic trait tends to reduce diversity in the surrounding genomic region within the affected population, increasing the differences between populations.

The researchers looked at the genomic regions that contain genes known to have a protective effect against HIV to see if there was any overlap with the selection signatures. Eight of the comparisons found overlap. Seven involved the Biaka.

They identified four genes in these overlaps that code for proteins affecting either the ability of HIV to infect the host cell or the disease progression. The researchers also found that for several genes, SNPs associated with protection against HIV-1 were common among the Biaka.

Roca cautions that these results should not be considered definitive. It is not possible to rule out false positives.

"You may detect a signature of selection, but it doesn't necessarily mean that selection has caused it. It's just a good sign that selection may have occurred," he said. Also, the signature of selection may span several genes, of which only one is actually protective against HIV-1.

However, he said that the results are intriguing and indicate that this line of research is worth pursuing.

"If additional studies confirm that these genes have undergone selection and that human populations in the region have some genetic resistance to HIV-1, one could try to find additional genes in the population that may also be protective against HIV but have not yet been identified," he said.

"The mechanism by which these genes work could be determined," he continued. "It could open up a new line of research for fighting retroviruses."

"Evidence for selection at HIV host susceptibility genes in a West Central African human populations" by Kai Zhao, Yasuko Ishida, Taras K. Olekeyk, and Alfred A. Roca has been recently published in *BMC Evolutionary Biology*. It is available online at [http://www.biomedcentral.com/1471-2148/12/237/abstract](http://www.biomedcentral.com/1471-2148/12/237/abstract).
Dark Ages Scourge Enlightens Modern Struggle Between Humans and Microbes

Dec. 13, 2012 — The plague-causing bacteria *Yersinia pestis* evades detection and establishes a stronghold without setting off the body's early alarms. New discoveries reported December 13 help explain how the stealthy agent of Black Death avoids tripping a self-destruct mechanism inside germ-destroying cells.

The authors of the study, appearing in the Dec. 13 issue of *Cell Host & Microbe*, are Dr. Christopher N. LaRock of the University of Washington Department of Microbiology and Dr. Brad Cookson, UW professor of microbiology and laboratory medicine.

Normally, certain defender cells are programmed to burst if they are either invaded by or detect the presence of pathogens, Cookson explained. This host defense mechanism called pyroptosis ("going up in flames") eliminates places for the germs to reproduce. As it splits open, the cell spills a cauldron of antimicrobial chemicals and emits signals to alert of an attack and its precise location. Tissues become inflamed as more cells arrive to fight the infection.

The bacteria are widely believed to be behind the great pestilences of the Middle Ages in the 1300s. The pathogen had evolved a tactic to delay provoking people's protective inflammatory response until it was too late. Plague claimed an estimated 30 percent to 50 percent of Europe's 14th century population.

"People and pathogens have been in an eternal struggle since the dawn of humanity," Cookson said. With a hand over hand gesture he explained, "Humans continuously ratchet up their defenses, and germs repeatedly find a way around them."

During several medieval epidemics, the plague started in rats. High-jumping fleas transmitted it to and between humans. It commonly caused lymph nodes to rupture. Respiratory forms were more deadly. They damaged the lungs and were spread by sneezing. Plague bacteria in the blood stream ended lives through sepsis, in which the burden of infection overwhelms the body.

Today, the plague-causing bacteria are still circulating in the world. It is held at bay by sanitation measures and drug treatment.

**Plague is now rare, with fewer than 15 infections annually in the United States.** The number of cases outside the U.S. is significantly larger, but not precisely known. Plague therefore remains of scientific interest for several reasons.

The *Yersinia* survival strategy against the programmed death that could kill it and its host cell may offer ideas for vaccine development, Cookson said. At present, no vaccine exists against the plague. *Yersinia* is of concern as a potential biological warfare pathogen because it can be aerosolized and unsuspectingly breathed into the lungs. Vaccines are being sought to offer widespread public safety, as are methods for enhancing people's overall infection-fighting capacity.

*Yersinia*’s techniques for modulating an inflammatory response also offer scientists an overarching perspective on a fundamental aspect of a variety of important diseases.

"Many medical problems stem from too much or too little inflammatory reaction," Cookson said. **People who launch an insufficient inflammatory response, or whose inflammatory response is suppressed by medications, are prone to viral, bacterial and fungal infections.**

"On the other hand, excessive or improperly regulated inflammatory responses are responsible for a large number of chronic conditions," Cookson said. These include vascular flare-ups leading to stroke or heart attack, and autoimmune diseases, among them lupus,
juvenile diabetes, ulcerative colitis and myasthenia gravis. Severe injury also can promote life-threatening lung inflammation.

Additionally, plague isn’t the only pathogen to enhance its virulence by sidestepping the inflammatory cell death program. Several other dangerous germs do the same, but in different ways.

Usually immune system clean-up cells that have been breached by an infection assemble a molecular platform called an inflammasome. This assembly, the researchers explained, activates a powerful, protein-cleaving enzyme called caspase-1. The enzyme is made ready to go in the presence of noxious stimuli, including germs, inorganic irritants, and pore-forming toxins.

To survive, Yersinia pestis must disarm caspase-1. Until the present study, bacterial molecules that directly modulate the inflammasome had not yet been reported. LaRock and Cookson were able to identify a leucine-rich protein secreted by Yersinia pestis that binds and disables its arch-enemy, the caspase-1 enzyme. The potent substance, called Yop M, preempts the activity of caspase-1 and sequesters the enzyme to arrest the development of the inflammasome. As a consequence, the cell fails to sacrifice itself to get rid of the Yersinia and to warn other disease-fighting cells of the infection.

According to the researchers, the Yop M-mediated inhibition of caspase-1 is required for Yersinia to subvert immune signaling, delay inflammation and provoke severe illness. Its dual mechanism for blocking inflammatory cell death, by blocking enzymatic activity and inflammasome maturation, is distinctive.

While caspase-1 is helpful in combatting a number of other microbial infections, several researchers have reported it to be harmful when its activation is aberrant or poorly controlled. Faulty caspase-1 regulation is implicated in several inflammatory disorders. Learning how pathogens manage caspase-1 to their advantage may suggest treatments to limiting its excess activity.

Read the paper, “The Yersinia Virulence Effector YopM Binds Caspase-1 to Arrest Inflammasome Assembly and Processing” in Cell Host & Microbe: http://www.cell.com/cell-host-microbe/abstract/S1931-3128%2812%2900392-7

Journal Reference:

Arizona Outbreak Fears Rise with Exemptions from Childhood Immunizations

Arizona Outbreak Fears Rise with Exemptions from Childhood Immunizations arizona.newszap.com (12.18.2012) Danielle Verbrigghe, Cronkite News Service

Unlike most states that allow parents to opt out of vaccinations for medical or religious reasons, Arizona allows parents with children in schools, preschools, and childcare centers to opt out for personal or philosophical reasons as well. The state requires parents to sign a personal beliefs exemption form acknowledging that they understand the risks of not vaccinating and that unvaccinated children could be excluded from school if an outbreak occurs.

In 2011–2012 school years, 3.4 percent of kindergartners were not vaccinated for at least one vaccine due to personal belief exemptions. In 2000–2001, there was only 1.4 percent in that category. In certain counties the number is much higher. In Yavapai County, 9.2 percent of kindergartners, 9.4 percent of sixth graders, and 11.5 percent of 10th graders had personal beliefs exemptions for the 2011–2012 school year. In Coconino County, 6.2 percent of kindergartners, 11.6 percent of sixth graders, and 4.1 percent of 10th graders had personal belief exemptions. Karen Lewis, medical director for the Immunization Program Office at the Arizona Department of Health Services, stated that clusters of higher exemption rates and lower immunity levels that result put schools and communities at risk.

University of Arizona researchers, including Kacey Ernst, an assistant professor at the College of Public Health, recently released the first part of a study commissioned by the Arizona Department of Health Services on personal beliefs exemptions. They analyzed state data, surveyed parents and doctors, and held town halls. Results showed that schools with higher rates of exemptions tended to have higher presence of white students and lower rates of free and reduced lunch. Charter schools and schools in northern Arizona tended to have higher rates of exemptions. According to Ernst, this meant that the access to vaccines was not the problem, but that parents did not want vaccines for their children. Some parents were concerned about the side effects of vaccines, others worried that children were getting too many vaccines at one time, and some parents favored a natural lifestyle with natural exposure to disease for immunization. Also, many parents who opted out did not believe the risks of disease were severe.

The Arizona chapter of the American Academy of Pediatrics plans to advocate during the 2013 legislative session for a law requiring parents seeking vaccination exemptions to be counseled by a health professional on the risks. Will Humble, director of the Arizona Department of Health Services, worries
about the risk of a severe outbreak in areas with high percentages of parents who choose the personal
beliefs exemption. He opted to evaluate the results of the university’s study on exemptions before
considering next steps, but he noted that the decision to vaccinate affects more than just the child. He is
concerned that by not vaccinating, the parent is putting not just their kids at risk, but also the whole
community.

Health Crisis of Bronx Re-Entry Populations

Health People
The study, “Health Gaps Survey of Bronx Re-entry Populations,” indicates that more than 40 percent of
parolees and released prisoners sent to the Bronx from the state prisons have two or more major chronic
conditions. The study also found that levels of hepatitis C testing and treatment in those released
individuals are very low, even though hepatitis C is a major problem in prison populations. Only 36
percent of the released persons who were interviewed reported having been tested for hepatitis C.

The study interviewed 181 Bronx releasees. Among these, 68 percent reported substance abuse
problems, 22 percent reported mental health problems, and 40 percent reported being in treatment for
HIV/AIDS. Chris Norwood, executive director of Health People and lead author of the study, stated that
the numbers underscore a crisis in health for parolees, which has to be addressed. He explained that it
was not a random survey, but was focused on the poorest parolees with many staying in homeless
shelters.

The study will be released at a public briefing at Health People Community Preventive Health
Institute in the Bronx. Also, at the briefing the challenges the Bronx faces and the progress being made
with its re-entry population will be discussed, including a discussion by the Bronx Borough Presidents’
Office on the work of the new Bronx Re-Entry task force, community efforts by the Bronx Re-Entry
working group to increase support services for returning prisoners, and early results of outcomes from a
study of Health Seeking behavior among Bronx Re-Entry populations. Norwood stated that the Bronx is
making great efforts to ensure health services and social support for parolees; but with the increase in
numbers and the serious health issues of parolees, help is needed. The study was sponsored by the Elton
John AIDS Foundation. The full study results are available by emailing ChrisNorwood@HealthPeople.org.

Three More Polio Workers Shot In Pakistan

"Three workers in a polio eradication campaign were shot in Pakistan on Wednesday, and two of them
were killed, the latest in an unprecedented string of attacks over the past three days that has partially
halted the U.N.-backed campaign," Reuters reports (Ahmad, 12/19). "Earlier on Tuesday, five health
workers involved in the vaccination drive were killed in the cities of Karachi and Peshawar," News
Pakistan notes (12/19). Another health care worker was killed on Monday, according to a statement issued
Tuesday by the WHO, UNICEF and the Pakistani and provincial governments, which condemned the
multiple attacks. "We call on the leaders of the affected communities and everyone concerned to do their
utmost to protect health workers and create a secure environment so that we can meet the health needs of
the children of Pakistan," the statement said (12/18). The Associated Press reports the WHO suspended
the vaccination campaign in two of the country’s provinces (Khan, 12/19). However, CNN reports the
"attacks prompted authorities to suspend the campaign throughout the country" (Khan, 12/19). "Under
the canceled program, Pakistani health officials planned to administer millions of ‘polio drops’ to
immunize people," according to International Business Times, which adds, "The program involved 25,000
workers targeting more than 30 million children" (Ghosh, 12/18).

"Pakistan is one of the world’s three remaining polio hotspots," Science Insider notes (Roberts,
12/18). "Militants however accuse health workers of acting as spies for the U.S. and claim the vaccine
makes children sterile," the Associated Press/Huffington Post writes (Jawad/Abbot, 12/18). "No group
claimed responsibility for the attacks, but most suspicion focused on the Pakistani Taliban," according to
the New York Times (Walsh/McNeil, 12/18). "In June, a Taliban commander in northwest
Pakistan announced a ban on polio vaccines for children in the region as long as the United States
continues its campaign of drone strikes in the region, the Taliban said," CNN notes (12/19). "Prime
Minister Raja Pervez Ashraf ... said in a statement that the country had to neutralize the message of those
resisting the government's efforts to immunize the population against polio," VOA News reports (Behn,
12/18).
Recreational Use Of HIV Drugs Leading To Pre-Treatment Resistance In South Africa

NPR’s "Shots" blog examines how "[o]pportunists who market street drugs may be undermining the global struggle against AIDS," writing, "In South Africa, two mainstay HIV drugs have found their way into recreational use." According to the blog, "[p]eople with HIV who smoke so-called whoonga—an illicit concoction of an AIDS medication and a street drug, like marijuana or heroin—can develop mutant strains of the virus resistant to the medication," or "people can become infected with a strain of HIV that came from someone who used whoonga."

"One large study showed 3 to 5 percent of people with HIV were coming in with pre-treatment resistance' to antiretroviral drugs used to treat HIV, [said] Dr. David Grelotti ...", a Harvard School of Public Health researcher who co-authored a commentary on the phenomenon in the Lancet Infectious Diseases published Tuesday," the blog notes. "Recreational use of HIV drugs isn't altogether new, though it hasn't had much attention," “Shots” writes, noting, "Some media reports documented illicit use of HIV drugs in South Africa as long ago as 2009. The blog adds, "Aside from the resistance problem, illicit use of HIV drugs poses other dangers," as "recreational use can make legitimate users of these drugs, and the clinics that dispense them, targets of thieves and violent crime" (Knox, 12/18).

'Repackaging' Of U.N. Cholera Initiative Detracts Attention From Epidemic's Origin

"Those following the two-year-old saga of the United Nations and cholera in Haiti were startled by the U.N.'s announcement last week of a $2.2 billion initiative to help eliminate cholera in Haiti and the Dominican Republic," freelance journalist Jonathan Katz and Tom Murphy, editor of the development blog "A View From the Cave," write in a Foreign Policy opinion piece. "Since [the crisis began in October 2010], scores of epidemiologists—including those appointed by the U.N. itself—have unearthed overwhelming evidence supporting the hypothesis that [U.N. peacekeepers] carried the disease and introduced it to Haiti through negligent sanitation," they continue, adding, "In response, U.N. officials have ignored, dismissed, or mischaracterized it all."

"Far from launching an ambitious new initiative, the U.N. was merely repackaging a still-unfunded, year-old effort," they write, noting, "Buried in the U.N. press release, in a line only the Miami Herald seemed to notice, was an admission that the Initiative for the Elimination of Cholera in the Island of Hispaniola had already been kicked off in January 2012 by the Haitian and Dominican governments with the support of a few U.N. agencies." Katz and Murphy continue, "Shifting around aid money—making the same promises over and over without fulfilling them—is an old game in the development world. But in this case it's especially bold." They add, "By relaunching an existing Haitian-Dominican effort under the guise of a U.N. initiative, the world body can once again claim to be too busy saving Haitian lives to comment on how those lives were put in danger in the first place“ (12/18).

HIV patients in care lose more years of life to smoking than to HIV infection

Findings emphasize importance of patient counseling to stop smoking in integrated HIV care

Among HIV patients receiving well-organized care with free access to antiretroviral therapy, those who smoke lose more years of life to smoking than to HIV, according to a Danish study published in Clinical Infectious Diseases and available online. The findings highlight the importance of smoking cessation efforts in the long-term, integrated care of patients infected with HIV.

Marie Helleberg, MD, of Copenhagen University Hospital and colleagues estimated the effect of smoking on mortality, risk of death, and life expectancy, and the number of life years lost to smoking compared to years lost to HIV among nearly 3,000 HIV-infected patients treated in Denmark from 1995 to 2010. They also compared mortality associated with smoking between HIV patients and the country's background population. Where HIV care is integrated and antiretroviral therapy is available at no cost, "more than 60 percent of deaths among HIV patients are associated with smoking," rather than HIV, Dr. Helleberg said.

Estimated life expectancy differed significantly based on smoking status. A 35-year-old HIV patient who currently smokes had a life expectancy of 62.6 years, compared to 78.4 years for a nonsmoker infected with HIV. The loss of years of life associated with smoking was twice as high as that associated with HIV among HIV-infected patients. In addition, researchers found the excess mortality of HIV-infected smokers to be three times higher than that of individuals not infected with HIV.

"Our findings emphasize the importance of counseling HIV patients on smoking cessation as smoking may impact their life expectancy considerably more than the HIV infection itself," the study authors
wrote. The results also underscore the importance of prioritizing interventions for stopping smoking in
HIV patient care and for the general population. Smokers who stop see their risk of cardiovascular disease
drop rather quickly, but they remain at increased risk of cancer until several years after quitting.

The emphasis on well-organized HIV care is crucial, according to Dr. Helleberg and her team. Continuing to smoke—or starting the habit—poses extra risks for patients with HIV. Patients who receive integrated care from a variety of health care professionals, including those who can help patients address lifestyle issues, can find support for decisions to stop smoking.

Johns Hopkins malpractice study: Surgical 'never events' occur at least 4,000 times per year

Researchers advocate public reporting of mistakes

After a cautious and rigorous analysis of national malpractice claims, Johns Hopkins patient safety
researchers estimate that a surgeon in the United States leaves a foreign object such as a sponge or a towel
inside a patient’s body after an operation 39 times a week, performs the wrong procedure on a patient 20
times a week and operates on the wrong body site 20 times a week.

The researchers, reporting online in the journal Surgery, say they estimate that 80,000 of these so-called "never events" occurred in American hospitals between 1990 and 2010 — and believe their estimates are likely on the low side.

The findings — the first of their kind, it is believed — quantify the national rate of "never events," occurrences for which there is universal professional agreement that they should never happen during surgery. Documenting the magnitude of the problem, the researchers say, is an important step in developing better systems to ensure never events live up to their name.

"There are mistakes in health care that are not preventable. Infection rates will likely never get down
to zero even if everyone does everything right, for example," says study leader Marty Makary, M.D.,
M.P.H., an associate professor of surgery at the Johns Hopkins University School of Medicine. "But the events we’ve estimated are totally preventable. This study highlights that we are nowhere near where we should be and there’s a lot of work to be done."

For the study, Makary and his colleagues used the National Practitioner Data Bank (NPDB), a federal
repository of medical malpractice claims, to identify malpractice judgments and out-of-court settlements
related to retained-foreign-body (leaving a sponge or other object inside a patient), wrong-site, wrong-
procedure and wrong-patient surgeries. They identified 9,744 paid malpractice judgments and claims
over those 20 years, with payments totaling $1.3 billion. Death occurred in 6.6 percent of patients,
permanent injury in 32.9 percent and temporary injury in 59.2 percent.

Using published rates of surgical adverse events resulting in a malpractice claim, the researchers estimate that 4,044 surgical never events occur in the United States each year. The more serious the outcome, the more the patient (or his family) was paid.

Makary says the NPDB is the best source of information about malpractice claims for never events
because these are not the sort of claims for which frivolous lawsuits are filed or settlements made to avoid jury trials. "There’s good reason to believe these were all legitimate claims," he says. "A claim of a sponge left behind, for example, can be proven by taking an X-ray."

By law, hospitals are required to report never events that result in a settlement or judgment to the
NPDB. If anything, he says, his team’s estimates of never events are low because not all items left behind
after surgery are discovered. Typically, they are found only when a patient experiences a complication
after surgery and efforts are made to find out why, Makary says.

In their study, never events occurred most often among patients between the ages of 40 and 49, and
surgeons in this same age group were responsible for more than one-third of the events, compared to 14.4
percent for surgeons over the age of 60. Sixty-two percent of the surgeons were cited in more than one
separate malpractice report, and 12.4 percent were named in separate surgical never events.

Makary notes that at many medical centers, patient safety procedures have long been in place to
prevent never events, including mandatory "timeouts" in the operating room before operations begin to
make sure medical records and surgical plans match the patient on the table. Other steps include using
indelible ink to mark the site of the surgery before the patient goes under anesthesia. Procedures have
long been in place to count sponges, towels and other surgical items before and after surgery, but these
efforts are not foolproof, Makary notes. Many hospitals are moving toward electronic bar codes on
instruments and materials to enable precise counts and prevent human error. Surgical checklists,
pioneered at The Johns Hopkins Hospital, are also often in place.
Along with better procedures to prevent never events, better reporting systems are needed to speed up safety efforts, says Makary.

He advocates public reporting of never events, an action that would give consumers the information to make more informed choices about where to undergo surgery, as well as "put hospitals under the gun to make things safer."

Currently, he notes, hospitals are supposed to voluntarily share never event information with the Joint Commission that assesses hospital safety and practice standards, but that doesn’t always happen.

**Auto-immune disease: the viral route is confirmed**

Europe Health technologies

Why would our immune system turn against our own cells? This is the question that the combined Inserm/CNRS/ Pierre and Marie Curie University/Association Institut de Myologie have strived to answer in their “Therapies for diseases of striated muscle”, concentrating in particular on the auto-immune disease known as myasthenia gravis.

Through the project known as FIGHT-MG (Fight Myasthenia Gravis), financed by the European Commission and coordinated by Inserm, Sonia Berrih-Aknin and Rozen Le Panse have contributed proof of the concept that a molecule imitating a virus may trigger an inappropriate immune response, causing muscular function to deteriorate. These results have been published in *Annals of Neurology*, accessible on line.

**Myasthenia, a rare auto-immune disease**

*Myasthenia gravis* is a rare auto-immune disease (5,000 to 6,000 patients in France) that produces muscular weakness and exhaustion. It generally affects the facial muscles first, and may then become generalised through the muscles of the limbs or the respiratory muscles, causing respiratory distress. This is due to the production of circulating **auto-antibodies** that block the **acetylcholine receptors** (RACh), these neurotransmitters being necessary for transmitting the motor nerve signal to the neuro-muscular junction.

**Could a viral infection be the origin of myasthenia?**

Myasthenia is a multi-factorial disease in which environmental factors seem to play a key triggering role. **Viral infections are suspected** but it is hard to prove the role of a virus in triggering the condition. In fact, diagnosis of myasthenia is often made months, or even years, after the actual start of the illness when the virus is no longer detectable, even though the signature left by the virus is visible long after the infection.

**Proof of the concept of a viral origin contributed by researchers**

Under the European FIGHT-MG project, the team of researchers managed to decode the trigger for the illness by using **a molecule that mimics the RNA double viral strand (Poly(I:C))**.

To do this, they concentrated on the organ that plays a central role in the disease – the **thymus**. It is in this gland located in the thorax that the T-lymphocytes mature, these being the key players in immune response that are normally programmed to avoid the development of any auto-immunity.

The researchers were thus able to show *in vitro* that the Poly(I:C) was capable of specifically inducing an over-expression of RACh through thymal epithelial cells, while activating three proteins (the “toll-like” receptor 3 (TLR3), the protein kinase R (PKR) and interferon-beta (IFN-β)); it is this last that produces inflammation in the thymus.

At the same time, they analysed pathological thymus glands of myasthenia sufferers in whom they observed over-expression of these same three proteins in the immune system, characteristic of a viral infection.

Finally, the researchers also managed to identify the same molecular changes in the thymus glands of mice, after they had been injected with Poly(I:C). After a prolonged injection period, they also observed a proliferation in the mice of B anti-RACh cells, the presence of auto-antibodies blocking the RACh receptors and clinical signs synonymous with the muscular weakness found in myasthenia.

These original results show that molecules that mimic a viral infection are capable of inducing myasthenia in the mouse, something that had never been demonstrated before.

This set of papers published in the *Annals of Neurology* provides proof of the concept that a **viral infection can cause inflammation of the thymus and lead to the development of auto-immune myasthenia**.
The next stages of the research will consist in determining which exogenous virus this may be or whether it is a case of the abnormal activation of an anti-viral response by endogenous molecules.

© Inserm / R. Le Panse

The introduction of a double strand of RNA (Poly(I:C) into the thymal epithelial cell induces the over-expression of the acetylcholine receptors (RACH), via the activation of the “toll-like” receptor 3 (TLR3) and the protein kinase R (PKR), as well as the production of interferon-beta (IFN-β)). These changes in the thymus gland cause the formation of B anti-RACH cells and the production of circulating auto-antibodies that block the acetylcholine receptors present in the neuromuscular junction.

FIGHT-MG (Fighting Myasthenia Gravis) – a European collaboration making giant leaps forward

The FIGHT-MG project seeks to determine the genetic and environmental risk factors associated with the occurrence of the illness and its development. The project aims also to identify the key immunological molecules associated with its appearance, and to study the pathogenic mechanisms at the neuromuscular junction, establish new diagnostic tests, as well as new treatments (cellular treatments, immuno-regulatory treatments, immuno-absorption of pathogenic auto-antibodies and other pharmacological treatments).

“When one is working on a rare disease, it is essential to work through networking, so as to be able to share our facilities and resources to promote fundamental and clinical research. It is also crucial to communicate permanently with patient associations. It is this combination that enables us to take giant steps in the treatment of rare conditions,” explains Sonia Berrih-Aknin.

Pigs in Southern China Infected With Avian Flu

Dec. 19, 2012 — Researchers report for the first time the seroprevalence of three strains of avian influenza viruses in pigs in southern China, but not the H5N1 avian influenza virus. Their research, published
online ahead of print in the *Journal of Clinical Microbiology*, has implications for efforts to protect the public health from pandemics.

Influenza A virus is responsible both for pandemics that have killed millions worldwide, and for the much less severe annual outbreaks of influenza. Because pigs can be infected with both human and avian influenza viruses, they are thought to serve as "mixing vessels" for genetic reassortment that could lead to pandemics, and pigs have been infected experimentally by all avian H1–H3 subtypes. But natural transmission of avian influenza to pigs has been documented only rarely.

In the study, from 2010-2012, Guihong Zhang and colleagues of the College of Veterinary Medicine, South China Agricultural University, Guangzhou, People's Republic of China, tested 1080 21-25 week old pigs for H3, H4, H5, and H6 subtypes of avian influenza virus, and H1 and H3 subtypes of swine influenza virus. Thirty-five percent of the serum samples were positive for H1N1, and 19.7 percent were positive for H3N2 swine flu virus, and 0.93 percent, 1.6 percent, and 1.8 percent were positive, respectively, for the H3, H4, and H6 subtypes of avian influenza A virus. However, no serum samples collected in 2001 were positive for any of these viruses, indicating that transmission into swine was recent.

Given the recent transmission of avian influenza into swine, "We recommend strongly that the pork industry worldwide should monitor the prevalence of influenza in pigs, considering their important role in transmitting this virus to humans," says Zhang.

Previously, novel reassortant H2N3 influenza viruses were isolated from US pigs, which "were infectious and highly transmissible in swine and ferrets without prior adaptation," according to a 2009 paper in the *Journal of Molecular and Genetic Medicine* by Wenjun Ma et al. Those viruses resembled, but were not identical to the H2N2 human pandemic virus of 1957.

**Journal Reference:**

**Pocket Test Measures Fifty Things in a Drop of Blood**

Dec. 19, 2012 — A new device about the size of a business card could allow health care providers to test for insulin and other blood proteins, cholesterol, and even signs of viral or bacterial infection all at the same time—with one drop of blood. Preliminary tests of the V-chip, created by scientists at The Methodist Hospital Research Institute and MD Anderson Cancer Center, were just published by *Nature Communications*.

"The V-Chip could make it possible to bring tests to the bedside, remote areas, and other types of point-of-care needs," said Nanomedicine faculty member Lidong Qin, Ph.D., the project's principal investigator. "V-Chip is accurate, cheap, and portable. It requires only a drop of a sample, not a vial of blood, and can do 50 different tests in one go."

Similar assays are typically done using heavy, large, complex equipment such as mass spectrometers, or require fluoroscopy analysis, which must also be done in a lab.

The V-chip, short for "volumetric bar-chart chip," on the other hand, can be carried around in a pocket. It is composed of two thin pieces of glass, about 3 in. by 2 in. In between are wells for four things: (1) hydrogen peroxide, (2) up to 50 different antibodies to specific proteins, DNA or RNA fragments, or lipids of interest, and the enzyme catalase, (3) serum or other sample, and (4) a dye—any dye will do. Initially, the wells are kept separate from each other. A shift in the glass plates brings the wells into contact, creating a contiguous, zig-zagged space from one end of the V-chip to the other.

As the substance of interest—say, insulin—binds to antibodies bound to the glass slide, catalase is made active and splits nearby hydrogen peroxide into water and oxygen gas. This approach is called ELISA, or enzyme-linked immunosorbent assay. The oxygen pushes the dye up the column. The more present insulin is, the more oxygen is created, and the farther dye is pushed up the slide. Tests show that distance is more or less proportional to the amount of substrate present, in this example, insulin. The end result is a visual bar chart. Easy to read and accurate, Qin says, though development continues.

"The sensitivity of the V-chip can be improved if narrower and longer bar channels are used," Qin said. "Our next steps are to make the device more user friendly and be so simple to use, it barely needs instructions."

**Journal Reference:**
Certain Meds Mixed With Grapefruit Juice Can Be a Fatal Cocktail

The Canadian scientist who first discovered that grapefruit can alter certain prescription drug levels in the body has released an updated list of 85 medications that may cause such reactions, 43 of which can cause fatal interactions, The New York Times reports. A clinical pharmacologist at the Lawson Health Research Institute in London, Ontario, David Bailey, PhD, updated his list to reflect releases of new medications over the past four years. The list includes drugs to treat HIV, high cholesterol and cancer, as well as immunosuppressants, psychotropic medications, synthetic opioids, birth control and estrogen.

How often such reactions occur is up for debate, but Bailey stresses that however rare they may be, anyone taking prescription medication and consuming grapefruit juice or grapefruit, as well as pomelo, lime and marmalade, should consult the list of drugs and monitor for symptoms that may indicate a side effect of the combination. Timing of grapefruit consumption is not relevant; it must be avoided entirely to avoid the potential interaction.

Appendix 1: Grapefruit Interacting Drugs and Associated Oral Bioavailability, Adverse Event(s), Risk Ranking and Potential Alternative Medications

<table>
<thead>
<tr>
<th>Interacting Drugs</th>
<th>Innate Oral Bioavailability*</th>
<th>Dose-Related Drug</th>
<th>Adverse Event(s)</th>
<th>Predicted Interaction</th>
<th>Risk Rank **</th>
<th>Potential Alternative Medication(s)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Cancer Agents</td>
<td></td>
<td></td>
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<tr>
<td>crizotinib</td>
<td>intermediate</td>
<td>torsade de pointes</td>
<td>myelotoxicity high</td>
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HIV/AIDS Talks Highlight Annual NAACP Religious Summit

At its 14th annual National Religious Leaders Summit held December 10–12 in Atlanta, the National Association for the Advancement of Colored People focused on moving the faith community back to a leadership role in matters of social justice. Faith leaders committed to working with the NAACP on HIV/AIDS and other issues. At the three-day meeting, faith and lay leaders created a post-election agenda for communities of faith, and Roslyn M. Brock, NAACP board of directors chairperson, led a dialogue session with mainline protestant denominations to discuss the NAACP's five strategic “Game Changer” areas.

In response to the dialogue, faith leaders made a national commitment to address HIV/AIDS in the black community after hearing NAACP's report, "The Black Church and HIV: The Social Justice
Imperative.” Church leaders agreed to work with the NAACP to expand HIV testing opportunities and to offer faith-based training and prevention education in churches, seminaries, historically black colleges and universities, and organizational national conventions.

The Summit presented a national training session on HIV/AIDS awareness and prevention that was attended by 100 pastors, faith leaders, and members of local NAACP units and state conferences, including representatives from cities with some of the highest rates of HIV prevalence. Brock commented that the commitment by the highest offices of these denominations to engage in this work, has solidified the Black Church’s concern and commitment to reverse the HIV/AIDS epidemic.

The churches represented at the NAACP meeting included AME Zion, Christian Methodist Episcopal, Black Methodist for Church Renewal, National Baptist Convention–USA, National Baptist Convention of America, Progressive National Baptist, and Primitive National Baptist.

Pakistan Reports 9th Death In Polio Worker Attacks, Resumes Vaccination Campaign Under Police Escort
"Another victim from attacks on U.N.-backed anti-polio teams in Pakistan died on Thursday, bringing the three-day death toll in the wave of assaults on volunteers vaccinating children across the country to nine, officials said," the Associated Press reports (Khan, 12/20). "Four female health workers were killed in Karachi, shot dead by masked men on motorbikes. The other five victims, including a 17-year-old volunteer, were slain in Peshawar andCharsadda," Inter Press Service notes (Yusufzai/Ebrahim, 12/20). The attacks "indicate a threat not only to workers but also to the effort to eradicate the disease—locally and globally," Scientific American's "Observations" blog adds (Harmon, 12/20).

"The U.N. has halted its participation in a Pakistani-run polio vaccination program following attacks on health care workers ..., but the government said it would not end the campaign," NPR's "The Two-Way" writes, adding, "Officials say the country is committed to seeing polio eradicated and has suspended vaccinations only in Sindh province, where Karachi is located" (Coleman, 12/20). "Under police guard, thousands of health workers pressed on with a polio immunization program Thursday," the AP writes in a separate article, noting, "The violence risks reversing recent progress fighting polio in Pakistan, one of three countries in the world where the disease is endemic" (Abbot, 12/21).

U.N. General Assembly Adopts Resolution Urging Countries To Ban FGM
"The United Nations General Assembly adopted a resolution on Thursday urging countries to ban female genital mutilation, calling it an 'irreparable, irreversible abuse' that threatens about three million girls annually," Reuters reports. "The resolution, which is not legally binding, asks the 193 U.N. members to 'take all necessary measures, including enacting and enforcing legislation to prohibit female genital mutilations and to protect women and girls from this form of violence,'" the news agency notes (Nichols, 12/20).

"The U.N. said in 2010 that about 70 million girls and women had undergone the procedure, and the World Health Organization said about 6,000 girls were circumcised every day," the Associated Press writes (Lederer, 12/20). According to NBC News, "Amnesty International ... says the practice is commonplace in 28 countries in Africa, as well as in Yemen, Iraq, Malaysia, Indonesia and in certain ethnic groups in South America. It also occurs in among immigrant communities, including those in Europe and the United States, though it is unclear how frequently" (Ben-Chorin/Huus, 12/20).

Cholera Strain From Guinea Identified As More Toxic, Contagious
"Scientists say the cholera outbreak that struck more than 7,000 people in Guinea this year was caused by a more toxic and more contagious generation of the bacteria," and they "suspect the same strain killed nearly 300 people and struck more than 22,000 others in neighboring Sierra Leone," VOA News reports. "Through genetic sequencing of the cholera bacteria found in Guinea, epidemiologists working with the United Nations Children's Fund [UNICEF] have identified them as atypical variants of the O1 El Tor strain," the news service writes. Francois Bellet, a member of UNICEF’s regional office for West and Central Africa, "said this discovery raises the alert level, requiring stronger epidemiological surveillance, preparedness and response to cholera outbreaks in Guinea and throughout the region," according to VOA (Palus, 12/20). "This type of strain was present in Zimbabwe in 2009, in the Lake Chad Basin in 2009, and is found in Haiti currently," IRIN notes (12/18).
First Ever 'Atlas' of T Cells in Human Body
Dec. 20, 2012 — By analyzing tissues harvested from organ donors, Columbia University Medical Center (CUMC) researchers have created the first ever "atlas" of immune cells in the human body. Their results provide a unique view of the distribution and function of T lymphocytes in healthy individuals. In addition, the findings represent a major step toward development of new strategies for creating vaccines and immunotherapies. The study was published December 20 in the online edition of the journal *Immunity*.

T cells, a type of white blood cell, play a major role in cell-mediated immunity, in which the immune system produces various types of cells to defend the body against pathogens, cancer cells, and foreign substances.

"We found that T cells are highly compartmentalized—that is, each tissue we examined had its own complement of T cells," said study leader Donna L. Farber, PhD, professor of surgical sciences at CUMC and a principal investigator with the new Columbia Center for Translational Immunology (CCTI), directed by Megan Sykes, MD. "The results were remarkably similar in all donors, even though these people were very different in terms of age, background, and lifestyle."

The researchers also discovered a receptor that is expressed on the surface of "tissue-resident" T cells but not on circulating T cells. Using this marker, Dr. Farber and her colleagues established that the blood is its own compartment. "In other words, T cells found in circulation are not the same as T cells in the tissues," said Dr. Farber.

According to the researchers, the findings establish a baseline for T-cell immunity in healthy individuals. This knowledge can be used to better understand how various tissues respond to site-specific and systemic autoimmune and inflammatory diseases. The findings can therefore powerfully inform the development of new vaccine strategies. "To make better vaccines, it may be necessary to activate a T-cell response at the site of an infection, not just in the general circulation," said Dr. Farber. "But first we have to know what types of immune cells are in those tissues and how they function. This is a first step in that direction."

To study T cells, researchers need multiple tissue samples, which cannot be taken from healthy individuals. Working with the New York Organ Donor Network, the organ procurement organization for the greater New York metropolitan area, CUMC researchers obtained tissue samples from 24 individual organ donors. Samples were taken from tissues that have direct contact with pathogens, including lymph, lung, spleen, and small and large intestines. The donors, all of whom had died suddenly of traumatic causes, ranged in age from 15 to 60. All were HIV-negative and free of cancer and other chronic or immunological diseases.

"Most of what we have known about human T cells is based on studies of the blood, because it is so accessible," said Dr. Farber. "But that is only a small sampling of the body's T cells. We already had good evidence, from mouse studies, that other tissues have their own types of T cells and that they play an important role in mediating immune protection. We wanted to find out if this was the case in humans."

**Journal Reference:**
**Deleted Forever**
By tapping local knowledge among African pastoralists and veterinarians, researchers successfully eradicated a deadly livestock virus—and are looking to replicate their success to halt other epidemics.

By Kerry Grens | December 1, 2012

In 2011, the World Organization for Animal Health (OIE) announced something that had been declared but once before: all trace of a particular virus had been completely wiped off the face of the earth, thanks to human intervention. For more than a century, rinderpest, a morbillivirus related to measles and canine distemper capable of killing an adult bull in days, had plagued livestock owners in Africa. Thanks to widespread vaccination and surveillance efforts, the virus claimed its last victim in 2001. Until then, only smallpox carried the distinction of having been eradicated. Researchers now are looking to the success of the rinderpest campaign as a model for battling other viruses that kill domesticated animals and decimate the livelihoods of the people who depend on them.

An effective vaccine against rinderpest had been available for decades, but vials of it remained viable for only 2 hours outside of a refrigerator. By the 1990s, “the eradication effort was drifting toward indefinite disease containment [in] remote endemic areas . . . such as southern Sudan, the Afar region of Ethiopia, the Karamojong region of Uganda, and the Somali rangelands, where insecurity, chronic conflict, and weak governance created challenging environments for vaccine delivery,” says Dickens Chibeu, who led the African Union’s Somali Ecosystem Rinderpest Eradication Coordination Unit.

Stopping short of totally eradicating the virus would not do. In the 1960s and ’70s, rinderpest was nearly wiped out, with just two small pockets remaining, in Mali and eastern Africa. The campaign eased back, and from these regions rinderpest exploded into sub-Saharan Africa in 1980. “Livestock owners who were wealthy men, a week later were poor and committed suicide,” says Jeffrey Mariner, a researcher at the International Livestock Research Institute in Nairobi. “That was a big lesson.” What the effort needed was a thermostable vaccine that could reach these rural strongholds.

Mariner was a veterinary student at Boston’s Tufts University in the late 1980s when he went to the US Department of Agriculture’s Plum Island lab in Long Island Sound to develop a rinderpest vaccine suitable for distribution in rural Africa. “The approach we took was very straightforward,” he says. Mariner focused on the basics of vaccine production—the chemical stabilizers used and the process needed to freeze-dry the vaccine. By swapping out the stabilizers, a protein and a sugar, for two that were thermostable and by optimizing the drying technique so that all moisture was removed, Mariner produced a vaccine that could remain viable at 37 °C for 8 months. “We were applying old technologies, and the
research was solution-oriented,” he says. “We weren’t looking to be novel or to get published in Science, but to solve people’s problems.”

Solving the technological problem was one thing, but distribution barriers still existed. Mariner and others learned that livestock owners needed to be partners in the effort. Pastoralists had firsthand knowledge of where rinderpest was hiding out—information disregarded by veterinarians in the past. “You need a systematic approach, internationally coordinated, and a good understanding of the epidemiology of the disease,” says Peter Roeder, the former secretary of the Global Rinderpest Eradication Programme at the United Nations Food and Agriculture Organization (FAO). Officials in the eradication effort enrolled local veterinarians and tribal livestock owners in remote areas to cooperate in surveillance and immunization, enabling organizers to nail down the final reservoirs of disease and target them with vaccine. “In 1999 we launched the global rinderpest eradication, which focused on these last foci. By 2001, the disease was eradicated from the world,” Roeder says (Science, 337:1309-12, 2012).

Since then, Mariner and others have turned their attention to other livestock diseases, including pest des petits ruminants (PPR), another morbillivirus that infects goats and sheep. “It’s been in epidemic proportions in Ethiopia, Kenya, Uganda, and Tanzania, and it’s now wreaking havoc in the south of Sudan—all areas where there are very many poor people dependent on small ruminants,” says Roeder. Mariner has successfully developed a thermostable PPR vaccine in the lab, and he’s planning to start pilot programs on animals in Uganda and Sudan beginning next year.

The generation of a thermostable vaccine is very much needed, says Ashley Banyard, a senior research scientist at the Animal Health and Veterinary Laboratories Agency in the U.K. But one thing the thermostable vaccine can’t yet do is enable differentiation between naturally immunized animals who have survived infection and those who have been given vaccine. “It would have made [eradication] a lot quicker and saved a lot of costs” if scientists could have distinguished between the two, Banyard says. He and his colleagues are developing a vaccine that would result in the development of antibodies slightly different than those produced by natural infection, giving vaccinated animals an immunological signature. Mariner says that, just as with rinderpest, it will be important to make “sure we’re targeting the right populations.”

**Maggot Medicine**
**The healing powers of maggots may lie in their secreted proteins, which restrain the human immune response.**

By Beth Marie Mole | December 10, 2012

Doctors have recruited squirming maggots to clean gapping gashes for centuries, and in 2004, the US Food and Drug Administration approved the fly larvae as a treatment. But, until recently, no one knew how the maggots helped heal wounds. In a study published earlier this year (October 30) in Wound Repairs and Regeneration, researchers found that maggots secrete proteins to suppress the human immune system, thereby stifling damaging inflammation.

“This research advances our understanding of how and why maggot therapy helps wounds heal faster,” pathologist Ronald Sherman, board chair of the BioTherapeutics, Education and Research Foundation in Irvine, California, who was not involved in the study, told ScienceNOW.

The researchers, led by Gwendolyn Cazander of Leiden University Medical Center in the Netherlands, mixed donated blood samples from preoperative and post-operative patients with secretions from maggots, and found that the maggot secretions reduced proteins involved in the inflammation response by more than 99 percent. Moreover, they found that the maggot discharge actually degraded immune system proteins.

Cazander told ScienceNOW that the results didn’t surprise her, explaining that the maggots likely do this to protect themselves from being attacked by the immune system. Her team is now working to identify immune-suppressing compounds from the maggots, which could point to new drugs for healing wounds.
**Ebola from Pigs to Monkeys**

A deadly Ebola virus can spread from pigs to monkeys without direct contact, pointing to pig farms as a possible contributor to outbreaks.

By Ed Yong | November 15, 2012

Although Ebola viruses can cause fatal disease in humans and other primates, pigs can carry the infections with few ill effects. Now, Canadian scientists have shown that apparently healthy pigs can pass the deadliest species of Ebola to monkeys, even without ever coming into contact with them.

The study, published today (November 15) in *Scientific Reports*, marks the first time that the virus has spread between different species in a lab experiment, and suggests that pig farms could be facilitate such species-hopping in more natural conditions.

However, Gary Kobinger from the University of Manitoba, who led the study, cautioned that “we still don’t know if pigs are playing any role in the natural transmission or ecology of Ebola virus in Africa.”

“An epidemiological survey of wild and domestic pigs in sub-Saharan Africa is now necessary,” agreed Shigeru Morikawa from the National Institute of Infectious Diseases, Japan, who was not involved in the research.

Ebola has been found in gorillas, chimps, duikers (a small antelope), humans, and recently, pigs. The identity of its reservoir species is unclear, although bats are the most likely candidate. Until recently, no one even knew that pigs could carry Ebola. But in 2009, Roger Barrette found the Reston Ebola virus—the only one of five Ebola species of that does not seem to cause disease in humans—among Philippine pigs and antibodies against it among six pig farmers. More worryingly, Kobinger’s team also showed that Zaire-Ebola virus—the deadliest of the five, with a fatality rate of up to 90 percent in humans—can also infect pigs and spread between them through direct contact.

“Pigs are remarkably versatile animals when it comes to acquiring and transmitting infections,” said Tara Smith from the University of Iowa, who studies emerging infectious diseases and was not involved in this study. “They have been implicated in the spread of a variety of nasty zoonotic viruses: influenzas, Nipah virus, possibly Hendra virus, and now at least two types of Ebola.”

In pigs, Ebola mainly infects the lungs and airways, which makes them well-suited to spreading the virus through the air. To see if this was possible, Kobinger teamed up with Hana Weingartl from the University of Manitoba. They used nose swabs to infect piglets with Zaire Ebola, then placed them in a room with four cynomolgus macaques. The monkeys lived inside a wire cage within the pig pen, so the two species never made direct contact despite sharing living quarters.

The piglets developed heavier breathing and mild fevers, but were otherwise unharmed by the infection. But the monkeys were not as lucky. After 2 weeks, the pigs had passed the virus to all their neighboring macaques, who developed bloody spots on their chest and limbs and signs of damage in their lungs.

The study shows that the virus can spread without direct contact, but “keep in mind that Ebola is not suddenly an airborne virus, like influenza,” said Kobinger. Instead, the virus could have jumped from pigs to monkeys via small droplets in the air, or larger ones that splashed into the monkeys’ cages when the handlers cleaned the floor of the pigs’ area.

Indeed, the local nature of all known outbreaks suggests that it does not disperse effectively like an airborne virus would. Furthermore, it’s still unclear how common indirect transmission between species is in the real world. It could explain why some Philippine pig farmers were infected with Reston Ebola even though they were not involved in slaughtering the swine, and had not come into contact with contaminated tissues, Kobinger noted. But, he added, “this work was done in controlled conditions, and may not be representative of pigs running outside in the field,” said Kobinger. His team is now headed to Africa, to collect samples from pigs in areas that have had Ebola outbreaks in the past. “We just started this and are looking forward to see the results.”

**Personality Predicts Placebo Effect**
People with certain personality traits are more likely to get pain relief from a placebo, a finding that could help improve clinical trials.

By Dan Cossins | November 16, 2012

Individuals who are altruistic, resilient, and straightforward show greater activity in brain regions associated with reward and are more likely to enjoy pain relief when a placebo is administered during a painful experience, according to a study reported this week (November 15) in *Neuropsychopharmacology*. The findings suggest that simple personality tests could be used to improve the accuracy of clinical trials by identifying people likely to skew results with high placebo responses.

"studies to look at how personality traits are associated with placebo analgesia not only in terms of subjective reports of pain relief, but also with quite solid objective measures in key parts of the brain," said Tor Wager, a neuroscientist at the University of Boulder, Colorado, who was not involved in the study.

Placebos are known to have strong analgesic effects. In 2007, neuroscientist Jon-Kar Zubieta of the University of Michigan showed that such effects were associated with activity in the nucleus accumbens, a brain region involved in reward and pleasure. That suggested that placebo analgesia might occur in part because positive expectations of reward (pain relief) spike dopamine levels in the brain and stimulate the release of endogenous painkillers called mu-opioids.

But individuals vary considerably in their responses, and some studies have suggested that personality traits such as optimism and anxiety may predict response levels. Others have found that a composite of personality traits—including novelty seeking, harm avoidance, fun seeking, and reward responsiveness, which are thought to be related to dopamine reward circuits—can predict a substantial portion of placebo analgesic effects. Still, “there was nothing terribly conclusive,” said Zubieta.

To better understand how personality is associated with placebo analgesia, Zubieta and his colleagues assessed the personality traits of 47 healthy volunteers. Then they asked each volunteer to lie in a positron emission tomography (PET) scanner for the duration of a standard pain challenge. First, painless isotonic saline was injected into the jaw muscle and, 20 minutes later, a pain-inducing hypotonic injection. Volunteers were told about these two conditions but not the order in which they would occur, allowing for expectation of pain in both conditions. The conditions were then repeated for another scan session but this time the volunteers were given a placebo consisting of intravenous infusions of isotonic saline every 4 minutes, which they were told would reduce pain.

The PET scan recorded the activation of endogenous opioid receptors in the brain, and blood samples were taken every 10 minutes to measure placebo-induced changes in the stress hormone cortisol. Meanwhile, the volunteers were also asked to rate the intensity of the pain they felt every 15 seconds.

The researchers observed significant reductions in pain intensity ratings in response to placebo, but found that expectation of analgesia—measured by asking the volunteers during the pain challenge—was not significantly correlated with response, suggesting that positive expectations alone are not enough for a placebo-induced pain response.

But they also found that people with certain personality traits—specifically, those who scored high on resiliency, altruism, and straightforwardness, and low on measures of “angry hostility”—were more likely to experience a placebo-induced painkilling response. Importantly, such individuals also had decreased cortisol levels and greater activation of endogenous opioid receptors in brain regions associated with reward.

“We were able to link some personality traits with analgesia response at the level of brain chemistry,” said Zubieta, as well as subjective feelings. In fact, statistical analyses showed that a composite of these four traits accounted for 25 percent of the variance in subjectively reported placebo analgesic responses, and for 27 percent of the variance observed in objective measures like the activation of endogenous opioid receptors.
“Studies like this are giving us a new set of candidate personality measures that can predict for placebo analgesia, and they’re mostly positive traits,” said Wager. “So placebo responders are being cast in a much more positive light, personality-wise, than they were a few decades ago, when they were thought to be hysterical and neurotic.”

If replicated with larger sample sizes, the results suggest that these new measures could also help to improve the accuracy of clinical trials, Zubieta added. “One big difficulty is trying to control for people with very high placebo response,” he said. “Many trials fail not because the compound doesn’t work, but because placebos are also effective, which creates noise.” By using personality measures to stratify those more likely to exhibit a placebo effect and incorporate the likelihood of a placebo response into the data analyses, researchers may be able to more effectively identify a drug’s true effect, Zubieta said.


**Real-time Outbreak Sequencing**

Sequencing the whole genomes of bacterial pathogens as they spread among hospital patients and healthcare workers could transform the control of infectious disease.

By Dan Cossins | December 19, 2012

When an infectious outbreak occurs, hospital investigators combine epidemiological data with bacterial typing to trace the source and path of the pathogen in the hopes of preventing further infections. Current methods are slow and offer limited resolution, meaning they can’t always differentiate between strains originating from the same bacterial clone. But by dramatically increasing the speed and accuracy of strain discrimination, a new generation of rapid, low-cost whole-genome sequencing (WGS) technologies promises to revolutionize outbreak surveillance and investigation.

With full genome sequences, researchers can spot the mutations that accumulate every time a bacterium divides down to the single nucleotide level. This allows them to track the evolution and movement of microbes with unprecedented precision, potentially leading to life-saving interventions and improved infection control strategies.

“I expect whole-genome sequencing will be transformative, in particular in outbreak investigations, within the next few years,” said Kathryn Holt, a microbiologist at the University of Melbourne in Australia. “The key advance is the dramatic increase in resolution, which enables us to be much surer about transmission pathways.”

**Genomic detectives**

Two studies from this year demonstrate the power of this approach. In 2011, the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, experienced an outbreak of a highly resistant form of *Klebsiella pneumoniae*, which causes urinary, respiratory, and blood infections in people with weakened immune systems, and kills more than half of it infects. The doctors knew one patient was carrying the pathogen but she was carefully isolated, so they thought it had been contained. Then, 3 weeks after she was discharged, another patient was diagnosed and more cases followed. In total, 18 patients were infected and 6 died as a direct result.

The conventional method for bacterial typing is pulse-field gel electrophoresis, in which large DNA fragments are separated by an electric field to create genetic fingerprints for each bacterial sample. But the technique “was too coarse to tell us whether our first two cases were two separate introductions or [if] one was transmitted from the other,” said Tara Palmore, an infectious disease physician at the Clinical Center. Doctors and researchers were at a loss to explain the spread—and powerless to stop it.

Once the outbreak was under control, colleagues from the National Human Genome Center sequenced the genomes of the bacteria isolated from affected patients. Genetic similarities between samples revealed that all the strains had come from the first patient (patient 1), which had seemed unlikely from the epidemiological data—because there was no direct contact between that patient and those that were subsequently infected. They also found that patient 1 harbored three genetically distinct
versions of *Klebsiella*, and that each had been transmitted on separate occasions to start three different lineages of infection.

Using an evolutionary tree to reconstruct the likely route, the researchers showed that “the dynamics of transmission were far more complex than we first realized,” said Palmore. “It was mostly being spread by asymptotically colonized patients,” or “carriers.” For example, the bacteria first jumped from patient 1 to two patients that remained asymptomatic for some time—and it was those asymptomatic patients that passed the infection on to “patient 2,” the second patient to show signs of infection. Such a counterintuitive path could not have been predicted, and would not have been detected without genetic data.

Over in the United Kingdom, as a strain of methicillin-resistant *Staphylococcus aureus* (MRSA) spread through a neonatal unit at Rosie’s Hospital in Cambridge, infecting 12 infants over a 6-month period in 2011, researchers also turned to WGS for answers. A team at Cambridge University and the nearby Wellcome Trust Sanger Institute compared full-genome sequences of bacteria from infected infants, and revealed that all the strains were descended from a common source. Then, when another baby was infected 2 months after the previous case, sequencing showed it was part of the same outbreak. That led the team to screen all the staff, which identified one person who was carrying MRSA—and was likely involved spreading it to the babies.

“It’s impossible to prove that this epidemic was stopped by this intervention, but we believe it prevented further transmission,” said Julian Parkhill, a microbiologist at the Sanger Institute and co-author of the study. But either way, he added, it demonstrates the power of whole-genome sequencing for elucidating the movements of pathogens.

**Routine practice?**

With the latest bench-top machines capable of sequencing a bacterial genome in just a few hours, outbreak analyses can now be performed in real time—with obvious benefits. “It will enable rapid identification of a [real] transmission, and save a lot of time and effort in not having to chase down spurious transmissions,” said Parkhill. And more efficient tracking of transmission allows for much more targeted and effective infection-control measures, Palmore added.

In addition, WGS will help to track antibiotic resistance mutations as they evolve. “It can be quicker than phenotypic testing, which requires growing the bacteria in the presence of a range of antibiotics,” said Holt. “With sequencing, we can quickly see which resistance mechanisms the bug has encoded in its DNA,” which can guide treatments.

Real-time sequencing of hospital pathogens is unlikely to become a routine practice quite yet, however, largely because the interpretation of genetic data requires a level of expertise that lies beyond most clinicians. To overcome that obstacle, the development of analysis tools that can provide clinically relevant information in a manner that infectious-disease physicians can understand is absolutely critical, said Parkhill. “The average clinician in a hospital is not going to be able to do this [analysis], so it has to be automated.” Parkhill’s group is working to develop such a system.

Meanwhile, the UK Health Protection Agency is already exploring whether it is cost-effective to use the approach to supplement existing methods in a select few English hospitals. Indeed, although only a handful of proof-of-principle case studies exist, it’s clear that WGS is going to have a big impact on infection control and public health in the future, said Derrick Crook, a microbiologist at the University of Oxford who worked on a pilot study for tracking MRSA and *C. difficile* in three UK hospitals. “We’re looking at this being used [in a clinical setting] over the next few years.”
How HIV Sneaks aboard Mature Dendritic Cells

HIV, the virus that causes AIDS, has an extensive repertoire of tricks that it uses to evade, manipulate, and subvert the human immune system. Perhaps most insidious is the virus’s ability to turn the immune system’s defensive tactics to its own advantage. For example, HIV-1 (the virus that causes most cases of HIV infection) uses a type of immune cell, the dendritic cell (DC), to spread its infection.

DCs found in most peripheral tissues are in an immature state. However, those found in lymphoid tissues are more highly differentiated, or mature, and help trigger protective immune responses by interacting with another kind of immune cell, the T cell. Unfortunately, T cells happen to be HIV’s favorite host cell, and mature DCs can acquire HIV particles from HIV-infected T cells. These viruses are swallowed and then stashed in a sac-like compartment within DCs, where they wait to assault new T cells.

Earlier this year, a collaboration between two groups, led by Nuria Izquierdo-Useros and Javier Martinez-Picado in Spain, and Maier Lorizate and Hans-Georg Kräusslich in Germany, examined how mature DCs recognize and take up HIV virions. They showed that mature DCs recognize sialic acid–containing glycolipids (termed gangliosides) that are present in the HIV’s lipid envelope. But at that time it still wasn’t clear which receptor on the DC surface was used to recognize these glycolipids. Now, in this month’s issue of PLOS Biology, Izquierdo-Useros and colleagues return with the answer to this question.

Work by other groups had suggested that a surface protein called DC-SIGN might be the DC receptor for HIV. But DC-SIGN interacts with viral glycoproteins and not with membrane glycolipids. Moreover, HIV capture by DCs is strongly enhanced when DCs mature in the presence of pro-inflammatory compounds such as lipopolysaccharide (LPS). As LPS is often present at high levels during HIV infection, it’s a good bet that many DCs have reached their mature state under its influence. And yet, DC-SIGN expression levels do not significantly change after DCs are exposed to LPS, so DC-SIGN cannot be responsible for enhanced viral uptake after DC maturation with LPS. The authors therefore argued that a different DC surface receptor is probably involved.

To identify other DC proteins responsible for HIV uptake, the authors first examined how surface protein expression patterns change after LPS maturation of DCs. They focused their analysis on Siglecs, a family of proteins that are known to bind to sialic acid–containing molecules, including membrane gangliosides. Indeed, they found that one Siglec in particular, namely Siglec-1, is strongly upregulated in LPS-stimulated DCs.

This finding prompted the researchers to test whether Siglec-1 contributes to HIV uptake by DCs. They observed that increased Siglec-1 expression on the surface of DCs strongly correlated with enhanced HIV uptake. Furthermore, viral uptake was dependent upon Siglec-1, as was demonstrated by the fact that blocking Siglec-1 with antibodies or reducing its expression with RNA interference strongly impaired HIV uptake.

These results suggested that Siglec-1 mediates uptake of HIV by mature DCs. In agreement with this idea, uptake of virus-like particles (which contain viral envelope gangliosides but lack HIV surface...
immune system changes may drive aggressiveness of recurrent tumors

Mouse studies suggest immune-promoting drugs might control recurrent disease

PHILADELPHIA – Nearly half of the 700,000 cancer patients who undergo surgical removal of a primary tumor each year suffer a recurrence of their disease at some point, and many of those patients will eventually die from their disease. The traditional view of recurrent tumors is that they are resistant to therapy because they’ve acquired additional genetic mutations that make them more aggressive and impervious to drugs. Now, however, researchers at the Perelman School of Medicine at the University of Pennsylvania show in an animal model that the enhanced aggressiveness of recurrent tumors may be due to changes in the body’s immune response. The findings are published this week in the Proceedings of the National Academy of Sciences.

"Typically when a patient has a tumor recurrence, their oncologist treats them, much like they treated them for the primary tumor – with drugs aimed at the tumor cells themselves. But we’ve found that it might be better to attack the tumor cells and knock down the bad immune cells that are protecting the tumor," says senior study author Sunil Singhal, MD, assistant professor of Surgery and director, Thoracic Surgery Research Laboratory at the Perelman School of Medicine.

To assess the impact of anti-cancer vaccines on primary and recurrent tumors, the researchers immunized mice that had a primary or a recurrent tumor in their flank. Although both groups of animals developed an immune response to the vaccine, only the primary-tumor animals showed tumor shrinkage in response to the vaccine. The recurrent tumors appeared unaffected by the vaccine response. Moreover, this pattern held for several different vaccines.

Despite the prevailing models of tumor recurrence — which emphasize genetic changes in the tumor cells themselves — Singhal and colleagues could not find substantial genetic or behavior differences in the recurrent versus primary tumors that might account for the pattern of response.

By contrast, when the team looked at the types of immune cells in and around the tumor, Singhal’s team saw a big difference. The recurrent-tumor mice had a large increase in the number of regulatory T cells, compared with primary-tumor animals. That could be important, says Singhal, because T regulatory cells are responsible for holding other immune cells in check and blocking immune responses.

Additionally, macrophages that protect the tumor cells from immune system also increased in number and activity in the recurrent-tumor animals.

Remarkably, when the researchers treated recurrent-tumor animals with drugs that block macrophage activity, tumor growth slowed significantly. However, the same drugs had no effect on primary-tumor animals.
Singhal says it is not clear exactly what triggers the immune system changes, but whatever it is appears to happen at the time of surgery. His group has already started looking for alterations in signaling molecules.

In the meantime, though, he notes that there are newly approved drugs and experimental agents that block regulatory T cells. Given his team’s new results, he thinks testing these agents in patients with recurrent disease – in combination with drugs that attack the tumor cells themselves – could be an important advance for patients.

“We could impact the outcomes of as many as 250,000 patients a year, if this strategy works,” he said.

**Smoking has a bigger impact on the prognosis of HIV-positive patients than HIV-related factors**

Michael Carter  
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Much of the increased mortality seen in patients with HIV can be attributed to smoking, Danish investigators report in the online edition of *Clinical Infectious Diseases*. “The loss of life-years associated with smoking was larger than that associated with HIV,” write the investigators. The authors believe their findings have important implications for HIV care, showing the importance of smoking cessation counselling and support.

Thanks to antiretroviral therapy, the prognosis of many HIV-positive patients is now excellent. Rates of HIV-related illnesses and deaths have fallen dramatically since the mid 1990s, meaning that lifestyle-related factors are now a major cause of morbidity and mortality in HIV-infected individuals.

A number of studies have shown that HIV-positive individuals are more likely to smoke than their HIV-negative peers. Illnesses that are potentially related to smoking, such as cardiovascular disease and cancers, are being seen with increased frequency in HIV-positive patients. The role of smoking and other potentially modifiable risk factors is currently unclear.

Investigators from Denmark therefore designed a study to evaluate the effect of smoking on mortality among patients with HIV. They also compared the risk of death and loss of life-years associated with smoking with the risk associated with HIV-related factors.

The study population involved 2921 adults who received HIV care between 1995 and 2010. Injecting drug users were excluded from participation. The HIV-infected patients were matched with 10,642 controls.

Both the patients and the controls were followed for a median of four years.

Among HIV-positive patients, 47% were current smokers, 18% were former smokers and 35% had never smoked. The corresponding rates for the controls were 21%, 33% and 47%.

The excess mortality rate for HIV-positive current smokers (compared to HIV-positive patients who had never smoked) was 18 per 1000 patient years. The corresponding rate for the HIV-negative controls was 5 per 1000 patient years.

The risk of non-HIV-related death was five-fold higher for current smokers compared to HIV-infected patients who had never smoked. HIV-positive patients who were current smokers also had a four-fold increase in their risk of all-cause mortality.

The risk of death due to cardiovascular disease was approximately two times higher for HIV-positive current smokers compared to HIV-positive non-smokers. Current smokers were also three times more likely to die of cancer.

Smoking had a significant impact on the life expectancy of HIV-positive patients. The authors calculated that 35-year-old non-smokers had a life expectancy of 78 years. This compared to a life expectancy of 69 years for former smokers, and a life expectancy of just 63 years for current smokers.

“Our finding of lower mortality among previous compared to current smokers emphasizes the importance of counseling HIV patients on smoking cessation,” comment the researchers.

They calculated that the HIV-positive patients lost five years of life expectancy due to their HIV infection and that twelve life years were lost because of smoking.

“The loss of life-years associated with smoking was larger than that associated with HIV,” write the investigators. “HIV-infected smokers with long-term engagement in care lose more life-years to smoking than HIV.”

**Reference**

Study Turns Parasite Invasion Theory On Its Head

Dec. 23, 2012 — Current thinking on how the *Toxoplasma gondii* parasite invades its host is incorrect, according to a study published today in *Nature Methods* describing a new technique to knock out genes. The findings could have implications for other parasites from the same family, including malaria, and suggest that drugs that are currently being developed to block this invasion pathway may be unsuccessful.

*Toxoplasma gondii* is a parasite that commonly infects cats but is also carried by other warm-blooded animals, including humans. Up to a third of the UK population are chronically infected with the parasite. In most cases the acute infection causes only flu-like symptoms. However, women who become infected during pregnancy can pass the parasite to their unborn child which can result in serious health problems for the baby such as blindness and brain damage. People who have compromised immunity, such as individuals infected with HIV, are also at risk of serious complication due to reactivation of dormant cysts found in the brain.

Researchers at the Wellcome Trust Centre for Molecular Parasitology at the University of Glasgow made the discovery using a new technique to knock out specific genes in the parasite's genome. They specifically looked at three genes that are considered to be essential for the parasite to invade cells within its host to establish an infection.

"We found that we can remove each of these genes individually and the parasite can still penetrate the host cell, showing for the first time that they are not essential for host cell invasion as was previously thought," said Dr Markus Meissner, a Wellcome Trust Senior Research Fellow who led the study. "This means that the parasite must have other invasion strategies at its disposal that need to be investigated."

The genes the researchers looked at form the core of the parasite's gliding machinery that enable it to move around. In the past, researchers have only ever been able to reduce the expression level of these genes in the parasite, which did lead to a reduction in host cell invasion but invasion was never blocked completely. This was attributed to the low levels of gene expression that persisted. However, with the new technique, the team were able to completely remove the genes of interest. Unexpectedly they found that the parasites were still able to invade.

"One of the genes we looked at is the equivalent of a malaria gene that is a major candidate for vaccine development. Our findings would suggest that such a vaccine may not be successful at preventing malaria infection and we need to revisit our understanding of how this family of parasites invades host cells," added Dr Meissner.

As well as malaria, a number of other parasites that affect livestock also belong to the same family. The findings could also provide clues to new treatments for these diseases, which cause substantial economic losses worldwide.

**Journal Reference:**
Nicole Andenmatten, Saskia Egarter, Allison J Jackson, Nicolas Jullien, Jean-Paul Herman, Markus Meissner. Conditional genome engineering in *Toxoplasma gondii* uncovers alternative invasion mechanisms. *Nature Methods*, 2012; DOI: 10.1038/nmeth.2301