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Merck demand triggers expanding patent war over Gilead's sofosbuvir
August 31, 2013 | By John Carroll
Gilead is rolling out its big legal guns to defend its control of the experimental hepatitis C drug sofosbuvir, one of the most valuable therapies in the industry's late-stage pipeline.

On Friday the company fired a preemptive shot over Merck's bow, filing suit in the Northern District of California after Merck contacted the company a few weeks ago to stake a claim to 10% of the revenue generated by sofosbuvir. Merck ($MRK) wants Gilead ($GILD) to sublicense two of its hep C-related patents, according to the lawsuit. The pharma giant sells Victrelis (boceprevir), its recently approved hep C drug, which is likely to be swept away as sofosbuvir and companion therapies make it to the market, offering a treatment less likely to trigger side effects and quicker to quell the virus. And the Gilead suit says that Merck claims to have already snagged one 10% deal on an unspecified therapy.

In a letter filed with the lawsuit, Merck's Pamela Demain, the executive director of corporate licensing, explained on Aug. 5 that Merck was seeking the 10% royalty based on the two patents: '499 and '712. And she set an August 31 deadline for a response, drawing a line in the legal sand. The Biotech Primer: An insider's guide to the science driving the biotech and pharma industries
This 200-page book takes an in-depth look at the biotech industry and the science that drives it. Although the industry itself is constantly changing, these fundamental concepts upon which it is built will remain important for years to come—and decision-makers who understand these fundamentals will be better able to evaluate and predict new trends. Click here to buy today!

Merck's terms: "Gilead shall pay Merck a 10% royalty on the Net Sales of Licensed Product ... by Gilead, its distributors or sublicensees, including sales of Licensed Product that is co-packaged with one or more other pharmaceutical products, from the first sale of sofosbuvir until the expiration of the last to expire patent within the Licensed Patent Rights."

And that's just one of several legal fights brewing as an FDA marketing decision on sofosbuvir looms in early December.

In its first-half financial report, Gilead also notes that Roche is claiming control of sofosbuvir based on a 9-year-old, $168 million partnership it struck with Pharmasset, which Gilead bought for a whopping $11 billion in order to seize full ownership of sofosbuvir while it was still in midstage development. According to the SEC filing, Roche (SRHHBY) believes that its 2004 deal to develop a nucleoside polymerase treatment with Pharmasset gives it an exclusive license on sofosbuvir, which Roche claims is a "prodrug (or precursor) of PSI-6130."

Gilead says the arbitration demand filed by Roche is without merit, noting that the deal ended about two years after it began—long before it acquired the company.

The Roche move follows an effort by Idenix ($IDIX) in 2012 to establish that it was the first to invent sofosbuvir. "Our patent covers metabolites of sofosbuvir and RG7128. Idenix is attempting to claim a class of compounds, including these metabolites, in its pending patent application," notes Gilead. Analysts at Leerink Swann initially scored the dispute in Gilead's favor.

"Both MRK and IDIX nuc patents are relatively broad, claiming a large number of compounds," noted analysts. "Based on our review, the MRK and IDIX patents do not appear to specifically provide examples of nucs with 2'-methyl, 2'-fluoro-sustituted sugar, the class of nucs including sofosbuvir that Pharmasset had focused on. Although this does not by itself automatically disqualify these claims, we believe a key issue for the IP disputes will be whether there is sufficient specification in the patent to teach those skilled in the art how to make and use the full scope of the claimed invention with regard to sofosbuvir-like compounds."

The growing flank attack on the sofosbuvir patent highlights the increasingly complex relationships among pharma companies as they become more likely to partner with academics and biotechs to broaden their pipelines. Big Phase III programs often attract litigation, like Medivation's ($MDVN) claim on Aragon's cancer therapy, ARN-509, since acquired by J&J ($JNJ). And sometimes they win, as we saw when Onyx (SONXX) successfully laid claim to a 20% royalty of Stivarga from Bayer after bristling over its similarities to their partnered drug Nexavar.

Gilead will spare no expense in this fight. Analysts believe that sofosbuvir is an almost certain blockbuster, with peak sales estimates hovering around $4 billion to $5 billion. It's the leader in a pack of programs which are in the process of rewriting the standard of care for hepatitis C as AbbVie ($ABBV),
Bristol-Myers Squibb ($BMY), J&J and other rivals hustle to catch up. And the prospect of gaining even a slice of that action is worth a considerable sum in legal costs to any company that thinks it has an actionable claim.

A spokesperson for Merck told FierceBiotech Saturday that the company has "nothing to add at this time."

Related Articles:
Gilead's sofosbuvir cures some of the toughest hepatitis C cases
Shunned Gilead/Bristol-Myers hep C combo may be too good for docs to ignore
Gilead races to FDA after hep C blockbuster hopeful scores 4th win in PhIII

Say hello to beyond positive – a new lifestyle magazine for people living with HIV
Yes yes, I know it’s Monday and I know you’d all rather be in bed than in the office but such is life. Come on, get a coffee and sit down. Right.

As most of you know by now I’ve been living with HIV for two years at this point and there’s not a single part of that journey I’ve not tweeted, blogged or spoken on TV/radio about. You’ve had front row seats to it all – the ups of getting good blood results, my birthdays, meeting my boyfriend, through to the lows of depression, nasty rumours and attempted suicide.

Over those two years I’ve been privileged enough to be able to not only share my story with you guys on UKPositiveLad.com and Twitter, but also with the general public too – I’m incredibly grateful to Attitude Magazine, FS Magazine, MidlandsZone Magazine, BASELINE Magazine, The Times, Gaydio, BBC Radio 4 & Radio 5 Live, BBC World News, Sky News and ITV Daybreak (I’m sure I’ve missed a few out) for giving me the chance to share my story with a wider audience and help me on my mission to educate and let others benefit from my misfortune.

During that time, however, I’ve noticed something of a vacuum when it comes to lifestyle content aimed at HIV-Positive people in the UK. For the most part HIV content online falls into one of two camps: 1. Prevention information aimed at HIV-Negative people or 2. Medical information aimed at keeping HIV-Positive people healthy. Now I don’t know about you, but I think we deserve better...

So, say hello to beyondpositive.

My initial vision for beyondpositive was an online lifestyle magazine written for HIV-Positive people by HIV-Positive people, but after some soul searching I felt that we were unnecessarily limiting ourselves. We often use the phrase “people living with HIV” when talking about HIV-Positive people, but at beyondpositive we’ve extended that definition to not just the person with HIV, but the people in their lives too – their partners, friends, family and co-workers.

HIV touches every facet of our lives, every person we’re close to – and so will beyondpositive. We aim to bring you the latest HIV related news from across the world, columnists from every walk of life, opinion pieces that aren’t afraid to raise a few eyebrows, reviews of products/apps/sites/etc that matter to you, healthy eating recipes and exercise plans.

So please, join us for the journey. You can subscribe on our homepage at beyondpositive.org, you can follow us on twitter and like us on facebook.

Foreign prisoners threaten court action
Gothaatone Moeng, Staff Writer
Two HIV-positive foreign prisoners have threatened to take the government to court if their request for life-saving anti-retroviral drugs is not met within seven working days.

The two, through their lawyer Tshiamo Rantao, of Rantao Kewagamang Attorneys, served a letter of demand to the Permanent Secretary (PS) in the Ministry of Health on Thursday, which asks that they, and other HIV-positive prisoners, be provided with ARVs with effect from September 10th, 2013. The Zimbabwean nationals are currently serving time at the Gaborone Maximum Prison. The new letter of demand, served at the instruction of Botswana Network on Ethics, Law and AIDS (BONELA), has been prompted by the adoption of the new National Policy on HIV and AIDS by Parliament on August 9th.

In the letter to the PS, Rantao, on behalf of the prisoners, argues that the new policy, through Clauses 1, 6.1 and 7.1.4, directs the government to provide all HIV-positive prisoners, who qualify under the Treatment Guidelines, with antiretroviral drugs, without discriminating on the basis of their nationality. Clause 1 of the policy acknowledges the “vulnerability” of some sectors of society to the negative consequences of AIDS. This clause recognises that vulnerability, which may be applied to
individuals or groups, is "made worse by poverty, fragmented social and family structures, and gender inequality."

Clause 6.1 provides for the universal access to comprehensive HIV and AIDS treatment, care and support. Although Clause 7.4.1 provides that no person in Botswana should be discriminated against in terms of access to health services, it also gives government grounds to "confer preferential treatment on its citizens." Rantao writes that if the government, without lawful cause, refuses to meet the request for the drugs, he will make an application to the High Court on the basis that the refusal violates foreign inmates' rights to equality as provided for in Section 3 of the constitution, and that it violates their rights to life—as their lack of access to drugs may lead to premature death.

He argues too that, if government refuses, the refusal will be a violation of the prisoners' rights not to be subjected to inhuman and degrading punishment, a violation of their rights to treatment necessary to restore and safeguard the health of prisoners. Botswana previously denied foreign inmates ARVs because of Presidential Directive number Cab (b)/2004. Rantao argues that the new AIDS policy now surpasses this directive.

Uganda rejects HIV prevention tool on moral grounds
KAMPALA, 3 September 2013 (IRIN)—Activists in Uganda, where some 400 people are infected with HIV every day, have called on the government to rethink its dismissal of an emerging prevention protocol demonstrated to be effective in a trial conducted partly in Uganda, and which has been approved by the US Food and Drug Administration.

The protocol in question is a form of pre-exposure prophylaxis (PrEP) involving a daily dose of two antiretroviral drugs—marketed as Truvada—taken by an uninfected person who is in a sexual relationship with an HIV-positive partner.

According to PrEPWatch, a website run by AVAC (Global Advocacy for HIV Prevention), Truvada "has been proven effective at reducing the risk of HIV via sexual exposure in heterosexual men and women, gay men and other men who have sex with men, and transgender women". One study among serodiscordant couples in Kenya and Uganda, found Truvada reduced HIV transmission by 73 percent, when compared against a placebo.

The World Health Organization guidelines issued in 2012 called for a cautious and gradual rollout. Uganda has no such plans, according to Alex Ario, programme manager in the Ministry of Health's AIDS Control Programme, who said public misunderstanding of the protocol could encourage "reckless sex".

"In our discussions, the technical committee has not recommended the use of PrEP among HIV-negative people. It's morally unfit, not right and incorrect to put people who are HIV-negative on treatment, when we have not been able to enrol those who are HIV-positive on it," he told IRIN.

"With the rate of new infections in Uganda, a reasonable prevention programme must be hungry—indeed very hungry—to add to its arsenal of tools any of the scientifically proven technologies..."

"People will engage in reckless sex behaviour and rush to health facilities, saying 'I had sex but the condom burst,'" he added. "It will be naïve for the ministry to adopt such guidelines and policy."

Ario said Uganda would continue to focus on its long-standing ABC—Abstinence, Be faithful, and Correct and Consistent Condom use—as the foundation of its HIV prevention strategy.

Experts say, however, that there is no evidence from PrEP trials to date to indicate that its use increases risky sexual behaviour.

"In fact, risk behaviours went down, not up," said AVAC Executive Director Mitchell Warren. "These were clinical trials, of course, and we don't know what might happen outside of trials, so it is an important consideration in designing PrEP programmes that might translate clinical trial efficacy into public health impact."

Ugandan activists have called on the government to rethink its decision, especially in light of the fact that the country's HIV prevalence has risen from 6.4 percent to 7.3 percent over the past five years.

Missed opportunity?
"It would be a great missed opportunity if PrEP is one of the prevention tools that the country fails to adopt," Milly Katana, a long-time HIV activist and one of the inaugural board members of the Global Fund to Fight HIV, Tuberculosis and Malaria, told IRIN. "With the rate of new infections in Uganda, a reasonable prevention programme must be hungry—indeed very hungry—to add to its arsenal of tools any of the scientifically proven technologies... This is more so for settings like Uganda, where... there is a very high presence of discordance among couples."
The Uganda AIDS Commission describes HIV discordance as one of the risk factors responsible for HIV transmission, along with, among others, multiple partners, inconsistent condom use and infection with sexually transmitted infections.

According to Rolling Back the Epidemic, a report released by the Uganda AIDS Commission (UAC) in May, some 145,000 new HIV infections are recorded annually in Uganda, with about 400 people infected with the virus daily.

Serodiscordant couples can benefit from PrEP

The report estimated that if the new infections continue to rise, the HIV burden would increase by more than 780,000 new infections in Uganda over the next five years, including an estimated 25,000 babies born with the virus annually.

"This rising number of new infections exceeds the annual number of patients enrolled on anti-retroviral treatment (ART) by two-fold," it noted.

Niche product

AVAC's Warren noted that any rollout of PrEP should be done with caution.

"We have learned a great deal from these clinical trials, but there is much we still don't know. Now we need to get serious about making PrEP available to those who can benefit from it, adhere to daily use [in order to] increase protection and reduce new HIV infections. More than two and a half years after the first positive results from a PrEP trial, sadly little has been done to answer critical questions about the best ways to roll out daily oral PrEP to key populations worldwide," he said.

"Within the next year, a comprehensive package of demonstration projects should be planned, funded and launched in countries around the world, especially in the countries where PrEP clinical trials took place."

Experts say some of the critical issues that must be addressed before PrEP is rolled out include analysing the context of the epidemic, the levels of ARV adherence and the cost of the ARVs.

"PrEP using tenofovir-based drugs is a niche product that cannot and will not replace other options that are part of combination prevention [a mix of biomedical, behavioural, and structural HIV prevention interventions]," Warren added. "Yet it is an intervention with the real possibility of preventing infections, especially where other prevention options aren't enough."

HPV vaccine for boys has 'good start' in 1st year

Article by: MIKE STOBBE, Associated Press
August 29, 2013 — 3:20 PM

ATLANTA — When the HPV vaccine was first recommended for boys, health officials worried it would be an unusually hard sell. But a new report suggests that might not be the case.

About 1 in 5 boys got at least one of the recommended three doses last year, relatively good for a new vaccine aimed at adolescents.

The shots are largely intended not to protect boys from disease, but to stop them from spreading a sexually transmitted virus to girls that could cause cervical cancer.

The vaccine hasn't been very popular among girls. The government report issued Thursday is the first real sense of how many boys are getting the shots.

"It's a good start," said Shannon Stokley, a vaccination expert with the Centers for Disease Control and Prevention.

Introduced in 2006, the vaccine protects against human papillomavirus, which is spread during sex. Most infections go away on their own, without people developing symptoms. But the virus can cause cervical cancer in females, genital warts in both sexes, and some other, less common conditions like throat and anal cancer.

The vaccine was first recommended for girls ages 11 and 12 because it works best if given before a teen starts to have sex. In 2011, it was also recommended for boys that age to help prevent the virus's spread.

The CDC report covers vaccination rates for last year, the first full year since the shots were advised for boys. It's based on telephone calls to families for about 19,000 boys and girls ages 13 to 17.

About 21 percent of the boys had gotten at least one of the three doses. Less than 7 percent were fully vaccinated.

The rates look relatively good compared to the initial rates for some other vaccines aimed at adolescents. For example, the initial rate for a meningococcal vaccine was just 12 percent.
Rates tend to start low when a vaccine is first recommended and build after. So the HPV numbers for boys are reason to be optimistic, said the CDC’s Dr. Melinda Wharton, although she added a word of caution.

"Given how the coverage level has stalled for girls, though, a solid start isn't enough," she said.

For girls, the initial rate for at least one HPV shot was 25 percent. Last year, it was about 54 percent and hadn't changed much from the previous two years. Only a third was fully immunized with all three doses last year.

"We'd really like to do much better with boys and girls," Wharton said.

**HIV Prevention Program at UCLA May Reduce Unprotected Sex Among Bisexual Black Men**

*News-Medical.net*, (08.22.2013) By University of California, Los Angeles

Researchers at the University of California, Los Angeles (UCLA) and Charles R. Drew University of Medicine and Science in Los Angeles developed and tested a culturally tailored HIV prevention program called Men of African-American Legacy Empowering Self (MAALES). African Americans have a significantly higher HIV/AIDS incidence than any other ethnic or racial group. CDC data show African Americans accounted for 44 percent of new US HIV diagnoses in 2010. Also, among men who have sex with men (MSM), black men had the largest estimated number of HIV infections. According to Nina Harawa—principal investigator, adjunct assistant professor of epidemiology at UCLA, and associate professor of research at Charles R. Drew University—few interventions exist to reduce the high rates of HIV infection among these men.

MAALES was based on the authors’ and others previous research indicating that African-American bisexual men had different experiences and concerns than MSM or heterosexual men. The researchers surveyed 437 bisexual black men and assessed key characteristics and behaviors, sociodemographics, incarceration history, self-reported HIV status, condom use, gender role expectations, experiences with racism, and drug and alcohol use. Researchers conducted the surveys at baseline and three and six months postintervention.

Researchers randomized participants to either the six-session MAALES intervention or a control group that educated them on HIV risk reduction at one session. Participants in the MAALES intervention reported 49 percent fewer episodes of unprotected sex with male or female partners after six months, 50 percent fewer episodes of unprotected vaginal sex with females, and 44 percent fewer female partners compared with controls. Dr. John K. Williams, associate professor in residence of psychiatry and biobehavioral sciences at UCLA’s Semel Institute for Neuroscience and Human Behavior and the co-principal investigator, concluded that the findings showed the ability to create change by means of culturally tailored behavioral intervention.


**First estimate of total viruses in mammals**

Minimum of 320,000 viruses; identifying them could help mitigate disease outbreaks; total cost less than a single pandemic

Scientists estimate that there is a minimum of 320,000 viruses in mammals awaiting discovery. Collecting evidence of these viruses, or even a majority of them, they say, could provide information critical to early detection and mitigation of disease outbreaks in humans. This undertaking would cost approximately $6.3 billion, or $1.4 billion if limited to 85% of total viral diversity—a fraction of the economic impact of a major pandemic like SARS.

Close to 70% of emerging viral diseases such as HIV/AIDS, West Nile, Ebola, SARS, and influenza, are zoonoses—infestations of animals that cross into humans. Yet until now, there has been no good estimate of the actual number of viruses that exist in any wildlife species.

"Historically, our whole approach to discovery has been altogether too random," says lead author Simon Anthony, D.Phil, a scientist at the Center for Infection and Immunity (CII) at Columbia University’s Mailman School of Public Health. "What we currently know about viruses is very much biased towards those that have already spilled over into humans or animals and emerged as diseases. But the pool of all viruses in wildlife, including many potential threats to humans, is actually much deeper. A more systematic, multidisciplinary, and One Health framework is needed if we are to understand what
drives and controls viral diversity and following that, what causes viruses to emerge as disease-causing pathogens."

"For decades, we’ve faced the threat of future pandemics without knowing how many viruses are lurking in the environment, in wildlife, waiting to emerge. Finally we have a breakthrough — there aren’t millions of unknown virus, just a few hundred thousand, and given the technology we have it's possible that in my lifetime, we'll know the identity of every unknown virus on the planet," adds Peter Daszak, PhD, corresponding author and president of EcoHealth Alliance.

**Secrets of the Flying Fox**

To address the challenges of describing and estimating virodiversity, a team of investigators from CII and EcoHealth Alliance began in jungles of Bangladesh—home to the flying fox. These bats are the largest flying mammal with a wingspan of up to 6 feet; they are also the source of several outbreaks of Nipah virus. The team collected 1,897 biological samples from the animals, which were captured and released. Back in the lab, they used polymerase chain reaction to identify 55 viruses in nine viral families. Of these, only five were previously known, including two human bocaviruses, an avian adenovirus, a human/bovine betacoronavirus, and an avian gammacoronavirus. Another 50 were newly discovered, including 10 in the same family as Nipah. Next the researchers adapted a statistical technique from the field of ecology to estimate that there were another three rare viruses unaccounted for in the samples, upping the estimate of viruses in the flying fox to 58. Finally, this number was extrapolated to all 5,486 known mammals, yielding a total of at least 320,000 viruses.

**A Relative Bargain**

The researchers then repeated the exercise for cost, extrapolating from an estimated $1.2 million for surveillance, sampling, and discovery of all 58 flying fox viruses to come up with a total of $6.3 billion for all mammals. Given the disproportionate cost of discovering rare viruses, they showed that limiting discovery to 85% of estimated viral diversity would bring the cost down to $1.4 billion.

"By contrast, the economic impact of the SARS pandemic is calculated to be $16 billion," says Dr. Anthony. "We’re not saying that this undertaking would prevent another outbreak like SARS. Nonetheless, what we learn from exploring global viral diversity could mitigate outbreaks by facilitating better surveillance and rapid diagnostic testing."

"If we know what’s out there, we’ll be a lot better prepared when a virus jumps over into a human population," Dr. Anthony continues, adding that prevention is crucial when it comes to viral infections since antivirals are notoriously difficult to develop.

**Plumbing the Depths of the Zoonotic Pool**

A continued systematic effort to discover mammal viruses would provide a more accurate estimate on total number of viruses in what co-author Stephen Morse, PhD, co-director of the PREDICT Project and professor of Epidemiology at the Mailman School, calls the "zoonotic pool" of potential viral pathogens that threaten humans.

The researchers say the initial estimate of 320,000 is just a starting point and will likely be considerably higher after accounting for additional viral families and employing high throughput sequencing methods developed at CII. They also point to several unknowns, including whether or not the samples from flying foxes in Bangladesh are representative of all flying foxes, which range across Southern Asia; whether or not all mammal species harbor a similar number of viruses; and the extent to which viruses are shared from species to species (as seen with the human, bovine, and avian viruses in the flying fox). Furthermore, the cost of collecting samples could vary depending on habitat (the flying fox expedition in Bangladesh was relatively low compared with similar undertaking for an animal living in more remote areas).

To help fill in some of these blanks, the team is repeating the process in two follow-up studies—one in a species of primates in Bangladesh in order to see if their viral diversity is comparable to the flying fox’s, and another in Mexico, where analysis of samples from six species of bats that share the same habitat will be undertaken to determine the extent to which they share viruses. With additional resources, they hope to expand the investigation to other species and viral families.

"To quote Benjamin Franklin, an ounce of prevention is worth a pound of cure," says senior author W. Ian Lipkin, MD, director of CII. "Our goal is to provide the viral intelligence needed for the global public health community to anticipate and respond to the continuous challenge of emerging infectious diseases." In fact, this type of large-scale zoonotic virus discovery and characterization is now being done in an economically efficient way through the PREDICT Project, funded by the United States Agency for International Development (USAID). The work described in the study has been integral to the Project’s success.
"PREDICT has already discovered more than 240 novel viruses throughout the world in areas where people and animals live in close contact and depend on the same natural resources," says study co-author Jonna Mazet, PhD, director of the UC Davis One Health Institute and co-director of PREDICT. "That includes new coronaviruses, like the ones that cause SARS and the new Middle East Respiratory Syndrome."

Aging really is ‘in your head’
Scientists answer hotly debated questions about how calorie restriction delays aging process
September 3, 2013
By Lee Phillion
Among scientists, the role of proteins called sirtuins in enhancing longevity has been hotly debated, driven by contradictory results from many different scientists. But new research at Washington University School of Medicine in St. Louis may settle the dispute.

Reporting Sept. 3 in Cell Metabolism, Shin-ichiro Imai, MD, PhD, and his colleagues have identified the mechanism by which a specific sirtuin protein called Sirt1 operates in the brain to bring about a significant delay in aging and an increase in longevity. Both have been associated with a low-calorie diet.

The Japanese philosopher and scientist Ekiken Kaibara first described the concept of dietary control as a method to achieve good health and longevity in 1713. He died the following year at the ripe old age of 84—a long life for someone in the 18th century.

Since then, science has proven a link between a low-calorie diet (without malnutrition) and longevity in a variety of animal models. In the new study, Imai and his team have shown how Sirt1 prompts neural activity in specific areas of the hypothalamus of the brain, which triggers dramatic physical changes in skeletal muscle and increases in vigor and longevity.

"In our studies of mice that express Sirt1 in the brain, we found that the skeletal muscular structures of old mice resemble young muscle tissue," said Imai. "Twenty-month-old mice (the equivalent of 70-year-old humans) look as active as five-month-olds."

Imai and his team began their quest to define the critical junctures responsible for the connection between dietary restriction and longevity with the knowledge from previous studies that the Sirt1 protein played a role in delaying aging when calories are restricted. But the specific mechanisms by which it carried out its function were unknown.

Imai’s team studied mice that had been genetically modified to overproduce Sirt1 protein. Some of the mice had been engineered to overproduce Sirt1 in body tissues, while others were engineered to produce more of the Sirt1 protein only in the brain.

“We found that only the mice that overexpressed Sirt1 in the brain (called BRASTO) had significant lifespan extension and delay in aging, just like normal mice reared under dietary restriction regimens,” said Imai, an expert in aging research and a professor in the departments of Developmental Biology and Medicine.

The BRASTO mice demonstrated significant life span extension without undergoing dietary restriction. “They were free to eat regular chow whenever they wished,” he said.
In addition to positive skeletal muscle changes in the BRASTO mice, the investigators also observed significant increases in nighttime physical activity, body temperature and oxygen consumption compared with age-matched controls.

Mice are characteristically most active at night. The BRASTO mice also experienced better or deeper sleep, and both males and females had significant increases in longevity.

The median life span of BRASTO mice in the study was extended by 16 percent for females and 9 percent for males. Translated to humans, this could mean an extra 13 or 14 years for women, making their average life span almost 100 years, Shin said. For men, this would add another seven years, increasing their average life span to the mid-80s.

Delay in cancer-dependent death also was observed in the BRASTO mice relative to control mice, the researchers noted.

Imai said that the longevity and health profile associated with the BRASTO mice appears to be the result of a shift in the onset of aging rather than the pace of aging. “What we have observed in BRASTO mice is a delay in the time when age-related decline begins, so while the rate of aging does not change, aging and the risk of cancer has been postponed.”

Having narrowed control of aging to the brain, Imai’s team then traced the control center of aging regulation to two areas of the hypothalamus called the dorsomedial and lateral hypothalamic nuclei. They then were able to identify specific genes within those areas that partner with Sirt1 to kick off the neural signals that elicit the physical and behavioral responses observed.

“We found that overexpression of Sirt1 in the brain leads to an increase in the cellular response of a receptor called orexin type 2 receptor in the two areas of the hypothalamus,” said first author Akiko Satoh, PhD, a postdoctoral staff scientist in Imai’s lab.

“We have demonstrated that the increased response by the receptor initiates signaling from the hypothalamus to skeletal muscles,” said Satoh. She noted that the mechanism by which the signal is specifically directed to skeletal muscle remains to be discovered.

According to Imai, the tight association discovered between Sirt1-prompted brain activation and the regulation of aging and longevity raises the tantalizing possibility of a “control center of aging and longevity” in the brain, which could be manipulated to maintain youthful physiology and extend life span in other mammals as well.


### Stomach Bacteria Switch Off Human Immune Defenses to Cause Disease

Sep. 2, 2013 — *Helicobacter pylori* is a bacterium that establishes a life-long stomach infection in humans, which in some cases can lead to duodenal ulcers or stomach cancer. New research, presented at this week’s Society for General Microbiology Autumn Conference, gives us a clearer understanding of how these bacteria can manipulate the human immune system to survive in the mucosal lining of the stomach.

Researchers from the University of Nottingham have shown that *H. pylori* is able to suppress the body’s normal production of ‘human beta defensin 1’ (hβD1), an antimicrobial factor present in the stomach lining that helps prevent bacterial infection. By collecting stomach tissue biopsies from 54 patients at the Queens Medical Centre, Nottingham, the team showed that patients infected with *H. pylori* had ten times less hβD1 than uninfected patients. Those with the lowest amount of hβD1 had the most bacteria present in their stomach lining.

The most damaging strains of *H. pylori* make a molecular syringe called the *cag*T4SS, through which bacterial products are injected into cells of the stomach lining. *In vitro* work using human gastric epithelial cell lines showed that this activates chemical pathways to suppress hβD1 production. These activated pathways are also involved in the stimulation of an inflammatory response, meaning that these *H. pylori* strains are able to survive and colonise more abundantly, while continuing to cause tissue damage over many decades. Previous research suggests that chronic inflammation of the stomach lining is strongly linked to gastric cancer.

It is estimated that half of the world’s population have *H. pylori* in the mucosal lining of their stomach. For most people the infection is asymptomatic, although 1-2 per cent of those infected will develop gastric cancer. Survival rates for this disease remain low, as diagnosis is often very late, when the cancer is at an advanced stage.

Katie Cook, who is presenting this work says, “To identify people who are likely to suffer from stomach cancer we need to understand how *H. pylori* interacts with the cells of the stomach lining. Because our research is patient-focused we know that our findings are directly relevant.
“We hope to combine this work with that being carried out by our colleagues in order to develop a diagnostic test to predict the future risk of gastric cancer development.”

04 September 2013—01H16

**Follow-up study backs circumcision against HIV**

A follow-up probe into the use of circumcision to thwart the AIDS virus has confirmed that foreskin removal greatly reduces the risk of HIV infection for men.

AFP—A follow-up probe into the use of circumcision to thwart the AIDS virus has confirmed that foreskin removal greatly reduces the risk of HIV infection for men.

So say a team led by French researcher Bertran Auvert, whose pioneering work, unveiled in 2006, helped unleash a circumcision campaign in AIDS-hit sub-Saharan Africa.

Three major trials took place in South Africa, Kenya and Uganda to test the effectiveness of circumcision in preventing infection by the human immunodeficiency virus (HIV) which causes AIDS.

Initial data pointed to a risk reduction of half, an estimate that was later boosted to 65 to 76 percent, according to the location.

Auvert’s team went back to Orange Farm, the South African township where the first trial took place in 2002 and 2005, in order to carry out a follow-up survey.

They asked more than 3,300 men to be tested for HIV and give details about their sexual behaviour.

Multiple partners and condom use were the same, whether the men were circumcised or uncircumcised, the investigation found.

But the risk of HIV infection was 57-61 percent lower among those who had been circumcised.

Without circumcision, prevalence of HIV in the community would have been 19 percent higher.

The finding "gives hope that the epidemic can be reduced in settings [in sub-Saharan Africa] where most men are uncircumcised," says the study, published in the peer-reviewed journal PLoS Medicine.

The rollout of adult male circumcision, endorsed by UNAIDS and WHO and backed by international donors such as the Gates Foundation, "should be accelerated".

One theory behind the effectiveness of circumcision is that the inner foreskin is an easy entry point for HIV. It is rich in so-called Langerhans cells, tissue that the AIDS virus easily latches on to and penetrates.

Still unclear, though, is whether women also gain an indirect protective effect if fewer men are infected.

Sub-Saharan Africa has around 23.5 million people living with HIV, or 69 percent of the global total, according to estimates released last year by UNAIDS.

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**Police: HIV-Positive Man May Have Exposed 300 Partners**

*USA Today* (09.05.2013) By Melanie Eversley

On August 28, the Dexter, Mo., Police Department arrested an HIV-infected man who may have “recklessly” infected more than 300 sexual partners while “knowingly infected” with HIV. The individual did not inform his sexual partners, many of whom he met through the Craigslist online classified site, that he had been infected with HIV since 2003.

The arrest came after the suspect’s former sexual partner received an HIV diagnosis and filed a complaint with the Dexter Police Department. According to an affidavit filed by Detective Cory Mills, the suspect had assured his former partner before they had sex that the suspect had no STDs. The two men met on Craigslist and lived together from November 2012 to June 2013, when the complainant found out the suspect also was having sexual intercourse with other partners.

Stoddard County Prosecuting Attorney Russell Oliver recommended that anyone who had sex with the suspect or who had met an anonymous sexual partner on Craigslist should cease sexual activity and have an HIV test immediately. Based on the suspect’s statement, police reported that 50–60 of the suspect’s sexual partners could be from Stoddard County.

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**Disease-causing genes spread easily in emerging lethal fungus infection**
A rare, emerging fungal disease that is spreading throughout Canada and Northwestern USA can easily pass its deadly genes to related fungal strains within the species but less readily to more distant relatives, according to a study part-funded by the Wellcome Trust.

The findings will help to understand the origins of infectious outbreaks and predict the likelihood of the disease spreading to other populations and geographical areas. 

*Cryptococcus gattii* is a type of fungus that was previously only found in warmer climates throughout the tropics. However, since 1999 outbreaks of highly virulent strains of the fungus have been reported in the cooler climes of Canada and Northwestern USA, causing serious illness in otherwise healthy people and domestic and wild animals and proving fatal in some cases.

To try to understand how likely it is that the disease will spread further, a team of researchers in the US and UK interbred different strains of the fungus to test how easily the characteristics of these more dangerous strains can be transferred to other less harmful strains. The results show that genes conferring traits that make the fungus more dangerous are easily passed to the offspring when the two parent strains are closely related. When the strains are distantly related to each other, the genes are much less likely to spread.

Professor Robin May from the University of Birmingham, who co-led the study with Dr. Joseph Heitman, MD, PhD from Duke University, said: "That the fungus can easily pass on the genes that make it more dangerous means that we could potentially see new strains of *C. gattii* cropping up spontaneously, causing outbreaks of disease in areas that were previously unaffected."

"Although this is still a very rare disease, with only around 400 people having been affected in the last decade, the results of our study show that surveillance efforts will be vital to stop it from spreading."

Part of the reason the 'hypervirulent' strains are so dangerous is that they have the unusual ability to survive inside cells of the infected person's immune system, where they rapidly reproduce.

The findings reveal that these characteristics can be inherited from the parent fungi through the genome and also through genetic material contained within the mitochondria, tiny structures inside the fungal cells. Mitochondrial DNA is normally inherited from only one parent but the team show that this particular strain of fungus can get mitochondrial genes from both parents.

"We were surprised to see that *C. gattii* could inherit mitochondrial genes from either or even both parents. This may make it easier for the fungus to spontaneously develop disease-causing traits that make it more of a threat," added lead researcher Dr. Kerstin Voelz.

*C. gattii* is found in the soil and in association with certain trees such as eucalyptus, pine or fir trees. It is transmitted to humans and other animals by inhaling spores of the fungus that are carried in the air. After infecting the lungs, cells of the fungus can travel through the bloodstream to infect other areas of the body, including the brain. The most common symptoms are shortness of breath, coughing, fatigue, fever, and headache.

**Programmed cell death activates latent herpesviruses**

Researchers have found that apoptosis, a natural process of programmed cell death, can reactivate latent herpesviruses in the dying cell. The results of their research, which could have broad clinical significance since many cancer chemotherapies cause apoptosis, was published ahead of print in the *Journal of Virology.*

Human herpesviruses (HHV) are linked to a range of childhood and adult diseases, including chickenpox, mononucleosis, cold sores, and genital sores, and are of a particular concern for patients who are immunosuppressed due cancer or AIDS. Some HHV types are so common they are nearly universal in humans. A key feature of these viruses is their ability to remain latent for long periods of time, and then...
reactivate after the latent phase. Previously, reactivation was thought to be primarily due to waning immunity, immunosuppression, or exposure to certain inducing agents.

This study began when principal investigator Steven Zeichner of Children’s National Medical Center and George Washington University in Washington, DC, followed up earlier findings that high concentrations of the antibiotic doxycycline can induce apoptosis, and can also activate replication by the Kaposi’s Sarcoma-associated Herpesvirus (KSHV), and a study by his former mentor, Bernard Roizman of the University of Chicago, which showed that apoptosis also triggers replication of herpes simplex virus-1, which causes cold sores in the mouth.

"We decided to test... several additional human herpesviruses that cause notable diseases and which have good latent infection cell line models, including human herpesviruses (HHV)-6A, -6B, and -7, and Epstein-Bar virus (EBV)," says Zeichner. That all of these herpesviruses were activated by apoptosis suggested that this mechanism might apply to all herpesviruses.

The clinical implications could be staggering. Some important cytotoxic cancer chemotherapeutic drugs, including doxorubicin, vincristine, and prednisone act in part by inducing apoptosis, according to the study. Additionally, treatment with glucocorticoids has been known to worsen Kaposi’s Sarcoma. The investigators also note that herpesvirus activation has been associated with poor outcomes following bone marrow transplantation.

"Activation of herpesviruses in these states and disorders has previously been variably attributed to general immune suppression, suppression of specific arms of the immune system, and increased concentrations of inflammatory and activating cytokines," write the researchers in the article. "If this activation occurs in potentially damaging ways, then perhaps patients at risk for herpesvirus activation should be treated with antiviral medications in addition to antineoplastic cytotoxic chemotherapy. Almost all humans are infected with HHV-6, and many are infected with the other aforementioned herpesviruses, as well as cytomegalovirus, oral and genital herpes, and Varicella zoster, the virus that causes chicken pox and shingles.

A copy of the manuscript can be found online at http://bit.ly/asmtip0913b. Formal publication is scheduled for the October 2013 issue of Journal of Virology.

**Growing Share of HIV/AIDS Burden Shifts to Changing Group of Regions**

Aug. 21, 2013 — The HIV/AIDS epidemic is changing in unexpected ways in countries around the world, showing that greater attention and financial investment may be needed in places where the disease has not reached epidemic levels, according to a new study from the Institute for Health Metrics and Evaluation (IHME) at the University of Washington.


In 2005, 68.7% of global HIV/AIDS burden was in countries where HIV/AIDS is the leading or second leading cause of the burden of disease. In 2010, 59.4% of the burden was in countries where HIV/AIDS ranked first or second, meaning countries where the disease ranked lower represented a larger share of the burden.

In 2010, for example, 20% of health loss due to HIV/AIDS was in countries where HIV/AIDS was not in the top 10 causes of disease burden compared to only 15.5% in 2005.

The findings were published August 21st in the study "The Burden of HIV: Insights from the GBD 2010" in the peer-reviewed journal AIDS.

IHME researchers also underscore the achievements that have been made against HIV—in terms of raising public awareness and increasing access to antiretroviral treatment—as well as the unrelenting challenges that AIDS poses to health around the world.

Millions of people, including many in low- and middle-income countries, now receive antiretroviral treatments (ARTs). There has been significant progress made against HIV/AIDS since global mortality due to the disease peaked in 2006; it has been steadily declining at an average annual rate of 4.2% since then.

The epidemic has peaked at different times in different countries, showing different rates of progress. In Botswana deaths are down 74%; in Mexico deaths are down 69.2%; and in Kazakhstan deaths are down 66.6%.
Yet HIV/AIDS remains a global issue; in 2012, 186 countries reported HIV cases or deaths. The disease is among the top five causes—but not the leading cause—of burden in 26 countries ranging from the Ukraine to Myanmar to Guyana.

"We cannot afford to become complacent when HIV/AIDS remains a tremendous threat," said researcher and lead study author Katrina F. Ortblad of IHME. "Countries that bear significant burden must scale up effective interventions and treatments. In countries where the impact of HIV/AIDS is relatively small but burden is increasing, prevention can help change the course of future epidemics."

IHME’s study examines health loss from HIV/AIDS as measured in DALYs, or disability-adjusted life years. DALYs combine years of life lost to premature death with years lived with disability and allow comparisons among different populations and health conditions.

While the global health landscape is increasingly dominated by the rise of non-communicable diseases, injuries, and disabling conditions, HIV takes a particular toll on young people around the world. It is the number one cause of disease burden for men aged 30 to 44 and women aged 25 to 44.

Globally, there are 78 countries where HIV/AIDS accounts for more than 10% of deaths in people aged 30 to 34.

In South Africa, for example, the picture is even more striking. In 2010, HIV/AIDS caused 75% of deaths among people aged 30 to 34; the figure rose to 84% for women in that age group.

Even in wealthier countries, challenges in addressing HIV/AIDS remain. In the United States, where deaths due to the disease are down 75.6% since its peak, HIV/AIDS still contributes to 0.7% of American health loss, far more than in other high-income countries like the United Kingdom, Canada, and France, and even more so than in many developing countries such as Congo, Mongolia and Sri Lanka.

Success in these countries and many others has been largely due to substantial global action, policy changes and funding. Between 2002 and 2010, development assistance for health targeting HIV/AIDS increased from US$1.4 billion to US$6.8 billion—an increase of 385.7% that does not include funds spent by low- and middle-income countries themselves.

Increased access to antiretrovirals has accompanied declines in incidence, and more interventions to prevent mother-to-child transmission.

"The success we have made in combatting HIV/AIDS illustrates what can happen when funders, advocates, governments and health experts commit to a common goal, and dedicate resources to back up the commitment," said Dr. Christopher Murray, IHME director and one of the study’s authors. "By gathering the best evidence on the spread of HIV/AIDS we can ensure continued progress."

The study also notes the challenges in collecting country-level estimates from different sources and calls for improvements in vital registration data that records a population’s births and deaths.

In sub-Saharan Africa, which accounts for 70.9% of the global health loss attributable to HIV/AIDS, progress against the disease is mixed. In Rwanda, Botswana and Zimbabwe, for example, mortality due to HIV/AIDS decreased dramatically from epidemic peak to 2010; 83.1%, 74% and 47.5% respectively. In other sub-Saharan African countries like Democratic Republic of the Congo, Angola and the Central African Republic, progress has been nearly nonexistent.

"AIDS is not just a problem in Africa," explained Dr. Rafael Lozano, IHME’s Director of Latin American and Caribbean Initiatives and one of the paper’s authors. "We see significant mortality numbers from AIDS in countries as varied as Venezuela, Thailand and Jamaica."

Journal Reference:

Bisphosphonates Could Offer Effective Pain Relief in Osteoarthritis
Sep. 5, 2013 — St George’s, University of London research has found that a drug normally given to osteoporosis sufferers could provide effective pain relief to patients with knee and hip osteoarthritis.

Bisphosphonates are a group of drugs known to change the structure of bone and are most often prescribed to patients with osteoporosis, a condition characterised by fragile bones.

It is unknown, however, whether these drugs could be used to reduce pain and discomfort for patients with the joint condition osteoarthritis, which causes cartilage damage, bony growths and sore tissue.

The researchers used existing studies to assess the effectiveness of a variety of bisphosphonates in patients suffering from osteoarthritis of the hand, knee, spine and hips.

Of 3832 patients studied, in most cases these drugs showed limited pain relief. However, a few studies did show benefit; the bisphosphonate alendronate was found to be more effective for patients with hip osteoarthritis than existing pain relieving drugs. Moreover, the use of zoledronate and alendronate, specific forms of bisphosphonates, improved pain in patients with knee and hip osteoarthritis at six months – but longer term studies are needed.

Dr Nidhi Sofat, lead researcher, said:
"Osteoarthritis is the most common form of arthritis worldwide. It causes damage to bone and cartilage in the joints of affected people. Most treatment is focused around pain relief, as no robust treatments have been discovered that slow down the progression of the disease.

"Our study looked at whether there were any bisphosphonate drugs that have been shown to influence pain and/or disease progression that could be used in osteoarthritis treatment.

"We found that, generally, bisphosphonates are ineffective at managing pain associated with osteoarthritis. But zoledronate and alendronate, which are specific forms of bisphosphonates, do show the potential for effective pain management specifically in patients with knee and hip osteoarthritis.

"More research needs to be carried out to determine which patients could benefit most from this type of intervention. Osteoarthritis is a long term chronic condition, so it’s essential that we work to understand whether the use of these medicines in the long term could be tolerated."

The research is published in full in the PLOS ONE journal

Journal Reference:

Intravenous AZT does not provide extra protection against vertical transmission in mothers with undetectable viral load
Carole Leach-Lemens
Published: 09 September 2013

Intravenous (IV)-zidovudine (AZT or ZDV) during labour and delivery is effective in reducing mother-to-child transmission (MTCT) among HIV-positive women with virological failure (viral load at or above 1000 copies/ml), even if on antiretroviral therapy (ART) during pregnancy, according to an analysis from the French Perinatal Cohort (ANRS-EPF) published in the advance online edition of Clinical Infectious Diseases.

However, for the majority (77%) with well-controlled viral load (at or under 400 copies/ml) at delivery and without obstetrical risk factors (premature rupture of membranes, preterm delivery, fever or bleeding) IV-zidovudine was not significantly associated with a lower risk of transmission.
These findings, note the authors, support recent changes in French and US guidelines to no longer recommend systematic IV-zidovudine during labour and delivery when viral load is low and no obstetrical risk factors exist.

Findings from this study – comprising over 11,000 women with HIV, on ART and not breastfeeding, who delivered at 90 centres throughout France between January 1, 1997 and December 30, 2010 – show that without IV-zidovudine overall MTCT rates among women with virological failure was higher than with, 7.5% and 2.9%, respectively, p = 0.01.

Among newborns given zidovudine monotherapy the MTCT rate was 10.2%. However, giving newborns zidovudine + lamivudine or a protease inhibitor (PI)-based ART regimen eliminated any difference in transmission rates between mothers who got IV-zidovudine and those who did not, 4.1% and 4.8%, respectively, p = 0.83.

The availability of ART in resource-rich settings has dramatically reduced MTCT rates to approximately one percent. However, the precise role ART plays during pregnancy, labour and delivery is difficult to determine as transmission can happen at any time throughout.

Studies before the era of ART, showed that most cases of MTCT happened during labour and delivery. So, in 1994, US and French researchers designing the pivotal trial ACTG076-ANRS024 recommended IV-zidovudine during labour or caesarean as a link between pre- and post-natal prophylaxis. IV-zidovudine was then included in guidelines in all resource-rich countries as a component of preventing MTCT.

With the advent of ART the benefits of IV-zidovudine have been questioned.

Following previous findings of data (1997-2004) from this cohort, before ART was recommended for pregnant women living with HIV, updated guidelines suggest IV-zidovudine may not be necessary for women on ART with well-controlled viral load near delivery (not defined in the 2010 French guidelines and defined in the updated July 2012 US guidelines as under 400 copies/ml).

The authors looked at the effect of IV-zidovudine on MTCT according to maternal characteristics, viral load and obstetric conditions.

There were no specific HIV treatment and obstetric care recommendations for women included in the cohort. From 1994, antenatal prophylaxis consisted of zidovudine prophylaxis; from 1997 of dual nucleoside therapy with elective caesarean section (C-section) based on a risk/benefit evaluation.

ART initially recommended for pregnant women needing it for their own health was revised in 2004 to include all pregnant women living with HIV. From 2002, elective caesarean for preventing MTCT was restricted to women not on ART and with a viral load over 400 copies/ml near delivery. Up until July 2010 IV-zidovudine and newborn prophylaxis was systematically recommended.

The MTCT rate was compared between women getting IV-zidovudine and those not, analysed according to viral load at delivery (under 400, 400 to 999, and at or above 1000 copies/ml) and stratified according to mode of delivery, term of delivery (under or over 37 gestational weeks) and type of post-natal prophylaxis.

For the analysis, CD4 counts and percentages and plasma viral load were obtained closest to the time of delivery and not more than seven days after delivery.

Of the 11,538 women included in the analysis, 95.2% (10,984) got IV-zidovudine while 554 did not. A PI-based ART regimen was the last one prescribed during pregnancy for the majority of women (60.2%), with 7.2% a non PI-based ART regimen, 2.6% three or more nucleoside reverse transcriptase inhibitors (NRTIs), 17.5% two NRTIs, 10.2% NRTI monotherapy and 0.9% an integrase inhibitor or CCR5-based regimen.

The median CD4 count at delivery was 461 cells/mm³ (IQR: 319-636).

Close to 80% of newborns were given monotherapy prophylaxis.

This analysis shows IV-zidovudine did not have an effect on MTCT in women with well-controlled viral load and no apparent childbirth risk factors, but remained effective in reducing MTCT among women with virological failure at delivery, even among those on ART during pregnancy.

While the study’s main strength is the large number of patients, the relative small number (5%) not getting IV-zidovudine is its main limitation.

Women not getting IV-zidovudine were more likely to be over 35, to have given birth previously, to have delivered preterm and vaginally and with high viral load at delivery. The authors hypothesize this may be because they presented in advanced labour, too late to start IV-zidovudine.

Preterm delivery is a risk factor for MTCT, Vaginal delivery in the absence of ART or with zidovudine monotherapy alone is linked to higher transmission rates compared to elective C-section.
However, there was a significant five-fold increased risk of MTCT without IV-zidovudine than with (9.5% compared to 1.8%, p = 0.01) among women with virological failure delivering at term by elective C-section.

No transmission occurred among women with viral load under 400 copies/ml (0/369) or even under 1000 copies/ml (0/28) who did not get IV-zidovudine compared to 0.6% (42/7576), p = 0.17 and 0.9% (5/556), p = 0.61, respectively among those who got IV-zidovudine.

This finding led the authors to comment that given the large size of the cohort and few infected infants, the study lacked the power to evaluate the safety of withholding IV-zidovudine in cases of obstetrical risk factors. They propose, while awaiting more data, IV-zidovudine be continued in women, even with low viral load, in cases of complicated deliveries.

These results, consistent with the authors’ previous findings (1997-2004), allowed the authors to look at IV-zidovudine with an increased power and within the context of systematic ART recommended for all pregnant women since 2004. The proportion of those on PI-based regimens increased from 38% in 1997-2004 to 86% in 2005-2010.

Evaluation of HIV-uninfected infants in the first six months of life showed IV-zidovudine was not associated with increased short-term haematological toxicity or lactate levels.

Reference

Fourth porn actor diagnosed with HIV
Calls heighten in California for moratorium on new productions and mandatory use of condoms

A fourth American porn actor has reportedly tested positive for HIV, fuelling fears of a significant outbreak in California’s adult film industry.

A male performer told a Los Angeles-based advocacy group he had been diagnosed with the virus that causes AIDS, it emerged on Monday, following three other cases in recent weeks.

"I can confirm that a male performer came to us and indicated that he had become infected with HIV," said Michael Weinstein, president of the AIDS Healthcare Foundation.

The disclosure will likely pressure the industry to continue a moratorium on production and bolster calls for mandatory use of condoms. "It's Russian roulette. I don't know how many people have to be infected before things change," Weinstein said.

Citing confidentiality, he declined to identify the latest performer to come forward or to elaborate on his circumstances.

A 29-year-old female actor who uses the screen name Cameron Bay was the first to go public in August, saying she tested positive after a routine HIV test.

The Free Speech Coalition, a Los Angeles-based trade organisation for the industry, called for a week-long suspension of filming pending tests for other performers.

On 3 September, soon after the moratorium was lifted, a male performer who uses the screen name Rod Daily and has been romantically linked to Bay announced via Twitter he had the virus. "Drumroll please!! I'm 32 years old and I'm HIV positive. Acute HIV, which means I recently was infected." A test one month earlier had been negative, he said. "I'm blessed for the fact that I caught it so early that I can blast that shit with meds."

The Free Speech Coalition reinstated the moratorium on 6 September when an industry-affiliated doctor contacted it to say a third performer had tested positive. The fourth case has not been officially confirmed.

Weinstein said questions over whether the virus was transmitted on or off set, and the duration and enforcement of moratoriums, distracted from the fundamental issue. "What works is condoms."

The industry, which is based in the San Fernando Valley area of Los Angeles, has resisted efforts to impose condom use, saying it would kill the business and that regular screening protects performers. The Free Speech Coalition did not immediately respond to news of the latest case. It has said it is considering making tests for sexually transmitted diseases more frequent, from 28 to 14 days.

Last year voters approved a measure mandating condoms for productions in Los Angeles county but enforcement has been lax. A bill that would mandate condoms in porn productions across California has stalled in Sacramento.

Is This the New Condom?
9.9.2013
By Tim Murphy

Taken once daily, the pill Truvada can prevent HIV. It’s safe, effective, FDA-approved, and usually covered by health plans. So why are so few gay men taking it?

The gay 40-something well-known New York City doctor with many gay patients — let’s call him Dr. John — can barely talk freely about what he’s doing. “It’s telling, how reluctant I am to talk about this, even anonymously,” he says. “This isn’t being talked about in our community at all.”

The subject causing such anxiety for Dr. John is an oval blue pill called Truvada. He takes it once a day — not to treat HIV, but to keep him from getting it. It’s even covered by his insurance, thanks to a decision by the FDA last year to approve it as a prophylactic against HIV. That approval followed a groundbreaking study in 2010, called iPrEx, that found that HIV-negative gay men who faithfully adhered to a one-a-day regimen of Truvada reduced their risk of getting HIV by more than 99%.

Those findings, which HIV specialists had been keenly awaiting for several years, were enough to make Dr. John talk to his own doctor and start the regimen himself. “I don’t want to become HIV-positive,” he says. “But I don’t love using condoms.” Sexually active with multiple partners, Dr. John admits he avoided condoms about 20% of the time. He was tired of stressing constantly over whether he’d gotten HIV. “Even if my sex was relatively safe, I would have long periods where I’d be freaked out that something had happened.”

Since he started taking daily Truvada, or PrEP (pre-exposure prophylaxis), as the regimen is called, Dr. John has remained HIV-negative and has experienced no side effects from the drug. “My sex life has been much less anxiety-provoking,” he says. “Now if I don’t use a condom, I feel like there’s a safety net.”

So why isn’t he shouting about PrEP from the rooftops? Partly, he says, because he doesn’t want people to think that because he’s a doctor, he’s endorsing PrEP for everyone: “There’s a difference between giving medical advice and making individual choices.”

But his reluctance is deeper than that. He also doesn’t want to be judged for eschewing condoms from time to time. “Gay men talking about not using condoms is really stigmatized,” he says. “Most of us have never known sex without condoms or without threat of a ‘deadly disease.’” But he adds passionately, “I think it’s a lot to ask an entire generation of gay men to use condoms forever.”

**Slow to Catch On**

Dr. John is not alone in his reluctance to say that he doesn’t always use condoms, or that he’s on PrEP. I talked to dozens of LGBT health workers in the United States, as well as HIV-negative men on PrEP, and a clear picture emerged: Even though PrEP is the first proven new HIV prevention tool since the condom, and even though it’s FDA-approved and is widely covered by health plans, few gay men appear to be on it.

“The uptake has been extraordinarily slow,” says Dr. Bill Valenti, who works at an HIV-positive and LGBT-serving health care center in Rochester, N.Y. He says that of their 75 HIV-negative patients, three had started PrEP. At D.C.’s LGBT-serving Whitman-Walker Health, staff said that about 90 of their 3,000 HIV-negative patients had started PrEP. The clinic’s patient population is made up primarily of African-American gay or bisexual men, the group at highest risk for HIV in the United States, along with transgender women.

It is difficult to know exactly how many guys in the U.S. are taking PrEP. Cara Miller, a rep for Gilead, the company that makes Truvada, said she couldn’t pinpoint such numbers because the company doesn’t know who is being prescribed Truvada in combination with other HIV drugs — which is necessary for treating HIV — and who is getting Truvada alone for PrEP purposes.

But Jim Pickett, who heads prevention advocacy at AIDS Foundation of Chicago, says that he has heard through inside sources that only one of the country’s largest insurers has, to date, covered all 300 prescriptions for Truvada alone, presumably for PrEP. That is a tiny number considering that Truvada, approved for use against HIV infection in 2004, has become a multibillion-dollar seller for Gilead. (The two drugs that comprise Truvada are sold separately or as part of the No. 1-selling HIV med, Atripla.)

Despite its slow uptake, PrEP comes along at a moment when it could potentially help reverse a 22% rise in HIV rates in young gay men in recent years, with young gay and bi men of color most affected. The CDC recently calculated that, if HIV infections continue to rise at current rates, half of young gay men will have HIV by age 50.

At the same time, the longstanding admonition to “use a condom every time,” an approach pioneered in the ’80s and ’90s with posters and ads making condoms look sexy and fun, does not seem to be working. True, condoms are highly effective at protecting against HIV, as well as other STDs, including syphilis, herpes, and gonorrhea. They also sometimes break.
Moreover, studies since the 1980s have consistently shown that gay men forego condoms up to half the time, depending on the situation, for reasons ranging from “the heat of the moment” to alcohol and drug use to a plain old dislike of how condoms feel. Taken once daily, the pill Truvada can prevent HIV. It’s safe, effective, FDA-approved, and usually covered by health plans. So why are so few gay men taking it?

According to Pickett, this means that condom-only prevention campaigns will never succeed in bringing HIV rates close to zero. “If condoms were so wonderful and a part of human nature, we wouldn’t have a problem with rising infections,” he says.

And yet, PrEP doesn’t seem to be catching on yet. Part of that is simply PR — not enough people even know what it is. Miller says that Gilead prefers to support LGBT health centers in getting the word out over doing direct advertising. Why would they not go full throttle to boost sales of PrEP? “They know it would be a potential PR disaster,” says Pickett.

And indeed, public reaction to PrEP has been mixed, with many concerned that widespread PrEP use will lead to an explosion of unprotected sex in gay men. Says Kevin Cates, who works in HIV prevention at Chicago’s LGBT-serving Howard Brown clinic, “I hear a lot, ‘Oh my God, this PrEP thing is so awful because people are going to bareback like crazy.’ ”

One group in particular, the large Los Angeles–based AIDS Healthcare Foundation, has taken a vocal stance against the FDA approval of PrEP, creating posters and other media warnings against it. Michael Weinstein, the group’s president, says it’s wrong for the FDA to have approved Truvada for PrEP when the iPrEx study showed that a large percentage of participants failed to take it once daily as prescribed. “It’s giving people a false sense of security,” he says.

**Risks Involved**
The truth is that PrEP comes with risks. Truvada can cause stomach upset in the first weeks of taking it. The drug, though low on side effects as HIV meds go, has been linked to mild kidney and bone problems in a small percentage of HIV-positive takers. However, Dr. Robert Grant, a professor at the University of California, San Francisco, and head of the iPrEx study, says he saw only mild side effects in his HIV-negative participants. Among the dozen or so men on PrEP with whom I spoke for this story, some of whom had taken PrEP for more than a year, none reported serious side effects.

It’s true that if someone takes PrEP spottily, they lower the amount of the drug in their body, exposing themselves to HIV. There is also the possibility of developing resistance to Truvada, thus losing it as an HIV treatment option. Granted, Truvada is just one among many HIV treatment options. Moreover, Grant says that the only people in the iPrEx study who developed Truvada resistance were a few whose HIV infections were not picked up during the initial screening process.

The more you adhere to the recommended daily dosage of PrEP, the closer to 100% protection you get. According to Grant, those in the study whose blood levels indicated they used PrEP four times a week still had a 96% risk reduction. Those with blood levels showing they used PrEP twice a week had 76% risk reduction. Grant says that experts still aren’t certain exactly how little, and at what intervals, one can use PrEP to have it still be effective, which is why one pill daily is currently recommended.

There is also validity to fears about “barebacking.” Even if PrEP protects against HIV, condomless sex still invites other STDs. Some, like syphilis, gonorrhea, and herpes, are fairly easily treatable. But in recent years, there have been outbreaks among HIV-positive men of sexually transmitted hepatitis C, for which treatment is improving but still difficult, expensive, and imperfect. In certain parts of the world, such as Japan and India, a new antibiotic-resistant strain of gonorrhea has rung alarm bells of a new STD epidemic. Simply put, nobody knows what new infections lie in wait down the road.

But despite those risks, several PrEP users I spoke with said they were unfazed. “I’m not going to let fear rule my life,” says Damon Jacobs, 42, a Brooklyn family counselor who has not only taken PrEP for two years now, he’s also started a Facebook page, “PrEP Facts: Rethinking HIV Prevention and Sex,” to promote an open conversation and breaking news about it. Dr. John admitted he worried about getting hep C or drug-resistant gonorrhea, but “so far, I haven’t gotten any STDs, so it’s an abstract concern.” “I have to admit that since being on PrEP, I’ve become much riskier,” says “James,” 51, a New York City computer programmer.

Importantly, recent research has made it clear that HIV-positive people reduce their chance of passing on the virus by 96% if they take meds that make their blood levels of HIV consistently undetectable on tests.

James says he began PrEP because he has multiple sex partners and hates condoms — “Every instinct in my body says I don’t want to wear them” — but he didn’t want to potentially pass HIV to his HIV-
negative boyfriend. “I can’t tell him I’m on PrEP, but I’m trying to protect him,” he says. He’s contracted chlamydia a few times, he says, but in the near year he’s been on PrEP, he’s stayed HIV-negative. Taken once daily, the pill Truvada can prevent HIV. It’s safe, effective, FDA-approved, and usually covered by health plans. So why are so few gay men taking it?

**PrEP As a Health Booster**

Then again, there is the argument that being on PrEP actually makes people safer because it raises their consciousness about their health. The iPrEX study found that participants reported decreased anal sex and increased condom use, though that might partly be because participants were regularly meeting counselors as a requirement of the study. In addition, participants initially did not know whether they were on Truvada or a placebo.

Being on PrEP requires seeing a doctor four times a year for an HIV test and kidney and bone tests. Being that connected to one’s health, say PrEP advocates, may actually bolster safer choices.

That seems to be the case for Gustavo Varela, 25, a program coordinator for an LGBT youth group in Chicago. Varela was on PrEP in the iPrEx study, but isn’t on it currently. “I used condoms when I was on PrEP, and if I went back on PrEP, I would still use condoms,” he says. So why be on PrEP at all? “I’ve had slip-ups where I didn’t use a condom in the heat of the moment, or if I was drinking,” he admits. “It’s an extra precaution.”

That extra protection is also sought by Darius Mooring, 34, an African-American college bookstore manager in Bethlehem, Penn. He says he is researching if his health plan will cover PrEP. “There are times I use condoms and times I don’t,” he says. “I will have sex with guys who I know are HIV-positive.”

“If I go on PrEP, will I be condomless in all my sexual encounters?” Mooring asks. “I don’t think so. But I’m not going to live in fairy tale where I tell myself I use condoms all the time. PrEP will be adding another strategy to my HIV prevention.”

That is how PrEP advocates want to frame it — as another tool in the kit of HIV prevention, in the mix with condoms, monogamy, negotiated safety, and keeping HIV-positive people treated and undetectable. For example, you might be on PrEP and forego condoms with your HIV-negative boyfriend, but use them when you play outside the relationship. Or you may go on PrEP for periods of time when you’re having multiple partners, then off PrEP once you’re in a relationship.

**Daring to Talk About It**

Certainly, PrEP may be a good option for guys who put themselves at risk again and again. At D.C.’s Whitman-Walker Health, Dr. Raymond Martins speaks of a patient who came to him three times for post-exposure prophylaxis, or PEP, otherwise known as the HIV “morning-after” regimen: After possible exposure to HIV, a patient takes HIV meds for a month to block the infection.

According to Martins, that patient is a perfect candidate for PrEP. “He never uses condoms. Better that he’s on PrEP as a permanent backup for his lifestyle than come in every month for PEP.”

In some ways, it’s easy to accept PrEP if you think of it as an extreme solution for turbo-sluts who fail again and again to use a condom — if, in other words, you pathologize it. Several friends I spoke with about this story said they couldn’t understand a person having such a hard time using condoms that they would have to actually go on an HIV med to prevent getting HIV. To that, PrEP advocates say it’s far safer to be on Truvada for a period of time than to live with HIV for a lifetime. Even well-treated HIV has been shown to have myriad effects on health, such as accelerated aging, in the long-term.

But it also can be easy for us to forget that only 30 years ago, nobody thought of a condom as a routine part of sex. “If HIV infections truly were a hetero issue, there’d be an alternative to condoms by now,” says Dr. John. “I don’t think the world of straight men would settle for using a condom their whole lives.”

Several men I talked to for this story told me of their dislike of condoms defiantly, without shame. In Boston, hairstylist Scott Owen, 48, said he’d never used condoms and had somehow stayed HIV-negative all these years. “I don’t like condoms,” he says. “I can’t enjoy sex with them. They desensitive it for me. I always just figured that if I became HIV-positive, I’d deal with it.”

When he heard about the Boston branch of the iPrEx study four years ago, he immediately signed up. He’s off PrEP now that he’s finished the study, but he wants to go back on it. He also wants to do another upcoming study, to test the effectiveness of a rectal microbicide gel.

That gel may be among the many new tools in the HIV prevention arsenal years down the line. Others in development include looking at another HIV drug, Selzentry, for use as PrEP, as well as “mini-vaccines” that would require injections three or four times a year. Meanwhile, studies of Truvada as PrEP continue as a way to assess effectiveness, adherence, and safety over time.

Advocates often talk of PrEP in birth-control terms: If a condom is like a diaphragm, then PrEP is the Pill, with perhaps more options in the works. “Women change methods of contraception over time,” says
Pickett. Likewise, he says, “No one thinks of PrEP as a lifetime strategy. It’s for when you need the support.”

In the meantime, Dr. John has no apologies for being on PrEP, even if he’s not ready to go public about it. “We need to be able to talk about our desire to have sex without a barrier,” he says. “Sex is about getting as close to someone as you possibly can. I think we’re entitled to that. And as long as the answer is, ‘Well, you should just wear a condom all the time,’ you’re obviously not reaching everybody.”

Senate OKs Condom Handout in California Prisons to Cut Disease, Despite Ban on Sex Behind Bars

*Daily Journal (Frankin, Ind.),* (09.09.2013)  By Associated Press

The California Senate recently approved Assembly Member Rob Bonta’s (D-Oakland) bill to provide condoms in adult prisons, even though the law bans sex while imprisoned. The bill was meant to prevent transmission of HIV, hepatitis C, and other diseases within prisons and other locations where prisoners are kept during parole. The law, known as AB999, would require the California Department of Corrections and Rehabilitation to provide condoms in five prisons by 2015 and in all 33 adult prisons by 2020.

Democratic lawmakers viewed the bill as filling a public safety need as well as a way of saving the state funds. State Sen. Rod Wright (D-Los Angeles) explained that providing condoms was cheaper than treating the disease after inmates became infected. Other lawmakers interpreted the bill as encouraging inmates to break the law (sex in prison currently is a felony).

Former Gov. Arnold Schwarzenegger vetoed a bill in 2007 in which nonprofits and health organizations would have provided condoms to state prisoners. He requested that the corrections department test condom distribution in one prison. Inmates in California State Prison, Solano, could get free condoms from a vending machine for a year, beginning November 2008. In the 2011 report on this pilot program, health officials reported few problems and recommended expansion. At present, inmates who qualify for overnight family visits have limited permission to get condoms, as spouses and partners are allowed to bring up to 10 for such visits.

**High adherence to HIV prophylaxis may raise efficacy for couples where one partner has HIV**

High adherence to antiretroviral pre-exposure prophylaxis (PrEP) is associated with a high level of protection from HIV acquisition by HIV-uninfected partners in heterosexual couples where only one of the partners is HIV positive, according to a study published in this week’s *PLOS Medicine.*

The study, which was led by Jessica Haberer, from Harvard Medical School, Boston, United States, included 1,147 HIV-uninfected participants who were enrolled in three Ugandan sites of the Partners PrEP Study - a randomized controlled trial to determine efficacy and safety of PrEP. All participants had a partner who was HIV-positive. These participants were a convenience sample reflecting 66% of all participants in the study sites (they were not randomized as part of this substudy). They were actively monitored for adherence to antiretroviral drugs and received adherence counselling throughout the study, which was intensified if unannounced pill count adherence fell below 80%.

Several randomized controlled trials in various populations (i.e. men who have sex with men, women at high risk for HIV) have shown that PrEP has provided varying levels of protection against HIV infection. One possible explanation for this varying efficacy is differential adherence to the antiretroviral drugs. Within this substudy, where adherence to antiretroviral drugs was very high (99% by unannounced pill counts and 97% by electronic monitoring), only 14 individuals became HIV-positive during an average follow up of 11 months per participant, and all of these individuals were taking a placebo drug.

Although the study has some limitations, such as the non-randomized nature of the study and limitations inherent in any form of adherence monitoring, the findings indicate that the high level of PrEP adherence achieved in the setting of active adherence monitoring and counselling support was associated with a high level of protection from HIV acquisition by the HIV-uninfected partner in heterosexual serodiscordant couples.

The authors note, “These data provide further support that PrEP is highly efficacious at preventing HIV acquisition when it is taken.”

The authors conclude, “Proper support and assessment of adherence will be critical for determining efficacy of PrEP outside of clinical trials. This data will be important for guiding ethical decisions about resource allocation for both prevention and treatment of HIV.”
2 common drugs may help treat deadly Middle East Respiratory Syndrome
The drugs subdue inflammation, reduce viral replication and promote lung repair

Treatment with two common drugs reduced viral replication and lung damage when given to monkeys infected with the virus that causes Middle East Respiratory Syndrome. The condition is deadly pneumonia that has killed more than 100 people, primarily in the Middle East.

Middle East Respiratory Syndrome, or MERS, was first reported in Saudi Arabia last year. The infection is caused by a coronavirus, called MERS-CoV, which is closely related to several coronaviruses that infect bats. About half of patients who developed the syndrome have died. Currently, there is no proven effective treatment.

The new findings show that a combination of interferon-alpha 2b and ribavirin, drugs routinely used to treat hepatitis C, may be an effective treatment for MERS-CoV infection, said Dr. Angela L. Rasmussen, a research scientist in the Department of Microbiology at the University of Washington in Seattle and co-author of the study.

"Because these two drugs are readily available, they could be used immediately to treat patients infected with MERS-CoV," Rasmussen said.

The study was conducted by researchers from the U.S. National Institute of Allergy and Infectious Diseases; the Universite Pierre et Marie Curie in Paris, France; the University of Manitoba in Winnipeg, Canada; and the University of Washington in Seattle. The results were published online September 8 by the journal Nature Medicine. Darryl Falzarano, of the National Institute of Allergy and Infectious Disease's Rocky Mountain Laboratory in Hamilton, Mont., was the paper's lead author.

Instead of directly targeting the virus like most conventional antivirals, these drugs work primarily by moderating the body's immune response to the virus and by promoting repair of damaged lung tissue, said Rasmussen.

Working with the team of scientists in the UW Viromics Lab, led by Dr. Michael Katze, UW professor of microbiology, Rasmussen and her colleagues watched how the lung cells responded to the new treatment by tracking their gene expression profiles.

They did this by studying RNA extracted from the infected monkeys' lungs to track changes in what is called the transcriptome. When a cell needs to use a gene, it copies the gene's DNA-encoded instructions into RNA. That RNA transcript is then read to direct the assembly of a protein. By using a "lab on a chip" technology, called a microarray, it is possible to detect and measure RNA transcripts from all the genes in a population of cells. By analyzing the transcriptome, it is then possible to track how cells or a tissue respond to infection, a drug, or some other stimulus. In this case, it allows researchers to study the host response to MERS-CoV in the context of the entire complex biological system, rather than one gene at a time.

Treatment with interferon-alpha 2b and ribavirin appeared to have several interesting effects. The combination increased the transcription of genes that fight viral infections, for example, and reduced transcription of genes that promote inflammation. Of particular interest to Rasmussen and her colleagues, however, was the finding that treatment increased the transcription of genes that assist in regulating a protein called sonic hedgehog.

The sonic hedgehog protein helps moderate the immune response so that it targets the virus more precisely. This honing in reduces collateral damage from broader, less discriminate attack, and helps stimulate repair and growth of lung tissue.

During infection with many severe respiratory viruses, such as influenza, much of the damage is done, not by the virus, but by the body's uncontrolled immune response to the virus, Rasmussen said.

The findings of this new study suggest that, in the case of MERS-CoV infections, interferon-alpha 3b and ribavirin may work primarily by reducing damaging inflammation of the lung and promoting healing by altering the host response, rather than directly targeting the virus.

If that is the case, other drugs that can similarly modulate the body's reaction to viral infections may also prove to be effective against MERS-CoV and other infectious agents, she said.


Copper Destroys Highly Infectious Norovirus
Sep. 9, 2013 — Scientists from the University of Southampton have discovered that copper and copper alloys rapidly destroy norovirus—the highly-infectious sickness bug. Worldwide, norovirus is responsible for more than 267 million cases of acute gastroenteritis every year. In the UK, norovirus costs the National Health Service at least £100 million per year, in times of high incidence, and up to 3,000 people admitted to hospital per year in England.

The virus, for which there is no specific treatment or vaccine, can be contracted from contaminated food or water, person-to-person contact, and contact with contaminated surfaces, meaning surfaces made from copper could effectively shut down one avenue of infection.

The study, which was designed to simulate fingertip-touch contamination of surfaces, showed norovirus was rapidly destroyed on copper and its alloys, with those containing more than 60 per cent copper proving particularly effective. Copper alloys have previously been shown to be effective antimicrobial surfaces against a range of bacteria and fungi.

The Southampton research reported rapid inactivation of murine norovirus on alloys, containing over 60 per cent copper, at room temperature but no reduction of infectivity on stainless steel dry surfaces in simulated wet fomite and dry touch contamination. The rate of inactivation was initially very rapid and proportional to the copper content of alloy tested. Viral inactivation was not as rapid on brass as previously observed for bacteria but copper-nickel alloy was very effective.

One of the targets of copper toxicity was the viral genome and a reduced number of the gene for a viral encoded protein, VPg (viral-protein-genome-linked), which is essential for infectivity, was observed following contact with copper and brass dry surfaces.

Lead author Sarah Warnes, from the Centre for Biological Sciences at the University of Southampton, says: "The use of antimicrobial surfaces containing copper in clinical and community environments, such as cruise ships and care facilities, could help to reduce the spread of this highly infectious and costly pathogen.

"Copper alloys, although they provide a constant killing surface, should always be used in conjunction with regular and efficient cleaning and decontamination regimes using non-chelating reagents that could inhibit the copper ion activity."

Co-author Professor Bill Keevil, from the University's Institute for Life Sciences, adds: "Although the virus was identified over 40 years ago, the lack of methods to assess infectivity has hampered the study of the human pathogen.

"The virus can remain infectious on solid surfaces and is also resistant to many cleaning solutions. That means it can spread to people who touch these surfaces, causing further infections and maintaining the cycle of infection. Copper surfaces, like door handles and taps, can disrupt the cycle and lower the risk of outbreaks." The study ‘Inactivation of norovirus on dry copper alloy surfaces’ is published in the latest issue of the journal PLOS ONE. Previous laboratory studies by the University of Southampton have described the rapid death of bacterial, fungal and viral pathogens such as MRSA on copper alloy surfaces and also prevention of antibiotic resistance horizontal gene transfer between pathogens.


Strain of MERS Coronavirus Engineered for Use in a Vaccine

Sep. 10, 2013 — Scientists have developed a strain of the Middle East respiratory syndrome coronavirus (MERS-CoV) that could be used as a vaccine against the disease, according to a study to be published in mBio®, the online open-access journal of the American Society for Microbiology. The mutant MERS virus, rMERS-CoV-ΔE, has a mutation in its envelope protein that makes it capable of infecting a cell and replicating its genetic material, but depriv es it of the ability to spread to other tissues and cause disease. The authors say once additional safe guards are engineered into the virus, it could be used as the basis of a safe and effective live-attenuated vaccine against MERS.

"Our achievement was a combination of synthetic biology and genetic engineering," says co-author Luis Enjuanes of The Autonomous University of Madrid (Universidad Autónoma de Madrid). "The injected vaccine will only replicate in a reduced number of cells and produce enough antigen to immunize the host," he says, and it cannot infect other people, even those in close contact with a vaccinated person.

Since MERS was first identified in June 2012, the World Health Organization has been notified of 108 cases of infection, including 50 deaths. Although the total number of cases is still relatively small, the case fatality rate and the spread of the virus to countries beyond the Middle East is alarming to public health...
officials. If the virus evolves the ability to transmit easily from person to person, a much more widespread epidemic is possible. Diagnostic assays and antiviral therapies for MERS have been described, but reliable vaccines have not yet been developed.

Enjuanes and his team applied what they had learned from 30 years of research on the molecular biology of coronaviruses to synthesize an infectious cDNA clone of the MERS-CoV genome based on a published sequence. They inserted the viral cDNA chromosome into a bacterial artificial chromosome, and mutated several of its genes, one by one, to study the effects on the virus' ability to infect, replicate, and re-infect cultured human cells.

Mutations that disabled accessory genes 3, 4a, 4b and 5 did not seem to hinder the virus: mutant viruses had similar growth rates as the wild-type virus, indicating that the mutations do not disable the virus enough to deploy the mutants in a vaccine. Mutations in the envelope protein (E protein), on the other hand, enabled the virus to replicate its genetic material, but prevented the virus from propagating, or infecting nearby cells.

A large amount of the rMERS-CoV-ΔE virus would be needed for a live attenuated MERS vaccine. A virus that can't propagate itself would be unable to grow the volume needed without help. Enjuanes says they provided the virus with a supplemental form E protein.

"To grow the virus, we create what are called 'packaging cells' that express the E protein missing in the virus. The gene to encode this protein is integrated in the cell chromosomes and will not mix with the viral genes. Therefore, in these cells, and only within them, the virus will grow by borrowing the E protein produced by the cell," says Enjuanes. "When the virus is administered to a person for vaccination, this person will not be able to provide the E protein to the defective virus," so the virus will die off after producing antigens to train the human immune system to fight a MERS-CoV infection.

Enjuanes says rMERS-CoV-ΔE is a very promising vaccine candidate, but more work remains before they can start clinical trials. He says the mutation in the E protein that prevents the virus from propagating represents one safe guard, but the US Food and Drug Administration requires that a recombinant live attenuated vaccine strains include at least three safe guards to ensure the virus doesn't revert easily back to its virulent form. His group is currently working on introducing other disabling mutations in genes that are located in regions of the virus' genome that are far away from the E protein gene to ensure the virus cannot revert back to virulence in a single recombination event.

Journal Reference:
Fernando Almazána, Marta L. Dediegoa, Isabel Solaa, Sonia Zañigaa, Jose L. Nieto-Torresa, Silvia Marquez-Juradoa, German Andrésb, Luis Enjuanesa. Engineering a Replication-Competent, Propagation-Defective Middle East Respiratory Syndrome Coronavirus as a Vaccine Candidate. mBio, September 2013 DOI: 10.1128/mBio.00650-13

Autoimmune Disease Strategy Emerges from Immune Cell Discovery
Sep. 9, 2013 — Scientists from UC San Francisco have identified a new way to manipulate the immune system that may keep it from attacking the body's own molecules in autoimmune diseases such as type 1 diabetes, rheumatoid arthritis and multiple sclerosis.

The researchers, led by immunologist Mark Anderson, MD, PhD, a professor with the UCSF Diabetes Center, have discovered a distinctive type of immune cell called an eTAC, which puts a damper on immune responses.

Anderson’s research team found that eTACs reside in lymph nodes and spleen in both humans and mice, and determined that they could be manipulated to stop the destruction of the pancreas in a mouse model of diabetes. The study appears in the September issue of the journal *Immunity*.

Using green fluorescent protein (GFP) to highlight a key regulatory protein called AIRE, Anderson’s research team tracked down the rare eTACs and their role in a phenomenon known as peripheral tolerance, which helps prevent autoimmune disease throughout the body.

The newly described immune cells are of a type known as dendritic cells, which make up less than 3 percent of the cells in the immune system. ETAC cells account for a small fraction of all dendritic cells, Anderson said.

Dendritic cells already have been the focus of new cell therapies to treat cancer. These therapies, which include treatments evaluated in clinical trials at UCSF, have been used to prod dendritic cells to rev up a complementary class of immune cells, called T cells. Treatment causes the T cells to target cancer cells, which, despite being abnormal, would not otherwise be subjected to vigorous attack in the same way as foreign microbial invaders.

However, eTAC cells have the opposite effect. Instead of priming T cells to do battle, eTACs counteract the overactive immune response in autoimmune diseases. Anderson’s team took advantage of this property to demonstrate that eTACs could prevent autoimmune diabetes in mice.

By displaying “self” molecules to T cells that target them, and turning off these T cells for good, eTACs help the immune system tolerate the molecules naturally present within us, Anderson said.

"The mouse model we are working with involves using T cells that normally attack the islet cells of the pancreas, specifically by recognizing a molecule called chromagranin A that is present on islet cells," Anderson said. "But if the eTACs can get to the T cells first and display chromagranin A, they can prevent T cells from attacking the islets."

Anderson aims to exploit eTACs therapeutically by finding out how to grow them in large numbers outside the body. "We need to figure out how to grow a lot of these cells, to load them up with whatever molecule it is that we want to induce tolerance to, and then to load them back into a patient," he said. "Such a strategy could help selectively shut down an unwanted immune response, such as the anti-islet immune response in type 1 diabetes."

Dendritic cells work with T cells a bit like a sheriff working with a bloodhound. Dendritic cells present not an article of clothing, but rather a specific molecule. If the molecule displayed by the dendritic cell matches the one the T cell was born to target, then that T cell would be activated to expand its numbers and to attack cells or tissues where the molecule is present.

When the interaction is between eTACs and T cells, however, the targeted T cell instead is turned off forever, and never seeks its molecular prey, Anderson said.

The first signal required for activation of a T cell is the display and recognition of the targeted molecule. But a second signal also is required, and eTACs are unable to deliver it, Anderson and colleagues discovered. They lack the molecular arms—molecules called B7-1 and B7-2—needed to hand off the activating message, which are present on other dendritic cells.

The eTACs arise in the bone marrow from adult stem cells that generate the entire blood system, including immune cells, Anderson said. Compared to using pluripotent stem cells of nearly unlimited potential, it should be easier to figure out how to guide the development of eTACs from bone marrow stem cells, he said.

Anderson’s search for an immune cell that turns off T cells began with the AIRE protein. Anderson helped discover its function more than a decade ago for specialized cells in the thymus. In the thymus, AIRE plays a key role in central tolerance, the phenomenon whereby immune cells in thymus learn to tolerate the body’s naturally occurring molecules shortly after birth. Peripheral tolerance complements central tolerance, and its failure often is responsible for autoimmune diseases that arise long after birth.
Many UCSF faculty members are experts on immune tolerance and autoimmune disease. Another strategy for manipulating the immune system to fight autoimmune disease, pioneered by Jeffrey Bluestone, PhD, the A.W. and Mary Clausen Distinguished Professor of Medicine, Pathology, Microbiology & Immunology at UCSF, already has led to a new treatment being evaluated in a clinical trial for type 1 diabetes. The treatment is based on a type of T cell called the regulatory T cell, which plays a natural role in ending immune responses when infection ends.

**Journal Reference:**

**Mechanism Discovered in First Line of Immune Defense**
Sep. 10, 2013 — Scientists from A*STAR's Singapore Immunology Network (SIgN) have discovered a new defense mechanism that the immune system utilises to combat infections. The team’s discovery of how a novel protein unexpectedly activates an immune response shows how this mechanism can also be used to get rid of tumour cells. This research was done in collaboration with University Hospital Basel, Switzerland, published in July 2013 in *Nature Immunology.*

The immune system combats microbes using several strategies, of which early activation of defence is one of the most important. The mechanisms used by the immune system to counterattack microbes often rely on the immediate recognition of microbes, or of cells that have been affected by the infection of microbes.

The team at SIgN led by Prof Gennaro De Libero has identified a novel mechanism of how the immune system readily detects invading microbes and effectively initiates early immune responses, by activating a special class of cells called gamma delta lymphocytes. Gamma delta lymphocytes were discovered more than 30 years ago and had been identified as cells that are capable of early protection as they play a decisive role in the first line of immune defence. However, many studies into discovering the mechanisms of how these cells are activated when microbes attack have been unfruitful.

The team’s discovery of a protein called Butyrophilin 3A1 shows how it binds to microbial antigens and hence activates human gamma delta cells. These cells are then able to coordinate an immune response to clear the infection caused by invading microbes.

This protein has also been found to bind antigens that are produced in large amounts in tumour cells, which then activates gamma delta cells against these tumour cells. The discovery of this mechanism thus represents a novel target that will help to eradicate tumours and combat infections.

Prof De Libero said, "The identification of the molecular mechanisms of how human gamma delta cells get activated opens doors to novel opportunities for immunotherapy of infections and tumours."

Prof Philippe Kourilsky, Chairman of SIgN said, "This study is a breakthrough in immunology and also an excellent example of basic science as an important premise to medicine."

Prof Laurent Rénia, Acting Executive Director of SIgN said, "We are delighted that this excellent science has paved the way for many others in immunology and other fields. I believe that these findings present great promise in developing new treatments for cancer therapy and infectious diseases."

**Journal Reference:**

**Yin-Yang Effect of Sodium and Chloride Presents Salt Conundrum**
Sep. 8, 2013 — Eat less salt’ is a mantra of our health-conscious times and is seen as an important step in reducing heart disease and hypertension.

Too much salt in the diet—and specifically sodium—is widely acknowledged as a major risk factor for high blood pressure however, scientists have found that salt’s other oft-overlooked constituent chloride might also play an important role.

A study by researchers at the University of Glasgow has revealed that low chloride levels in the blood is an independent indicator of mortality risk in people with hypertension. The role of chloride in hypertension has received little attention from scientists hitherto.
After analysing data from almost 13,000 patients with high blood pressure, followed up over 35 years, the researchers found that low levels of chloride was associated with a higher risk of death and cardiovascular disease.

The group with the lowest level of chloride in their blood had a 20% higher mortality rate compared to the other subjects. The results are published in the journal *Hypertension*.

Dr Sandosh Padmanabhan of the Institute of Cardiovascular and Medical Sciences, said: "Sodium is cast as the villain for the central role it plays in increasing the risk of high blood pressure, with chloride little more than a silent extra in the background."

"However, our study has put the spotlight on this under-studied chemical to reveal an association between low levels of chloride serum in the blood and a higher mortality rate, and surprisingly this is in the opposite direction to the risks associated with high sodium.

"It is likely that chloride plays an important part in the physiology of the body and we need to investigate this further."

Chloride is already measured as part of routine clinical screening and so monitoring of chloride levels could easily be incorporated into clinical practice to identify individuals at high risk.

Dr Padmanabhan added: "The results we see from this study are confounding against the knowledge that excess salt is a bad thing, yet higher levels of chloride in the blood seems to be an independent factor that is associated with lower mortality and cardiovascular risk. We seem to have entered a grey area here that requires further investigation.

"It is too early to draw any conclusions about relating this finding to salt intake and diet. We need more research to establish exactly what the relationship between chloride and health risk is."

**Journal Reference**


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**Portrait of an HIV Conspirator**

The three-dimensional structure of CCR5, a protein which HIV uses to infect humans' cells, could lead to better anti-HIV drugs.

By Ed Yong | September 12, 2013

After a six-year struggle, a team of Chinese scientists has produced a three-dimensional portrait of CCR5, a human protein that allows HIV to invade host cells.

This detailed snapshot, in which CCR5 is attached to the HIV drug Maraviroc, provides important clues about how HIV infections begin and how they might be stopped. “Our hope is to lay a foundation for the next generation of anti-HIV drugs,” said Beili Wu from the Chinese Academy of Sciences in Shanghai, who led the study. Her team’s results were published today (September 12) in *Science*.

“It’s very exciting,” said James Hoxie from the University of Pennsylvania, who studies how HIV interacts with human proteins and was not involved in the study. “For the first time, we can look at structures that are the keys to how the virus homes in on particular cell types. That’s what infection is all about.”

HIV infections begin when gp120, a protein that studs the virus’s outer coat, docks at a receptor molecule called CD4 on the surface of white blood cells. This interaction changes the shape of gp120, allowing it to bind to a second co-receptor—either CCR5 or CXCR4.

Normally, CCR5 and CXCR4 respond to chemicals called chemokines, which help alert the immune system to incoming infections. HIV hijacks these molecules to start infections itself. Once bound, HIV can fuse with the cell’s membrane, infiltrate, and start copying itself.

To better understand the process of HIV infection, Wu set out to solve the structure of both co-receptors in 2007. She cracked CXCR4 in 2010, while a postdoc at The Scripps Research Institute in La Jolla, California, before returning to China to deal with CCR5 as the head of her own research group.
It has been a challenging task. Both CCR5 and CXCR4 are examples of G-protein coupled receptors (GPCRs)—a class of proteins that snake through a cell’s membrane seven times, allowing external signals to trigger biochemical events inside. GPCRs are involved in everything from vision to inflammation. They are also unstable, and only found at very low levels. It is hard to gather enough of them to form the large, pure crystals needed to fully determine their structure.

Wu’s team, led by student Qiuxiang Tan and research assistant Ya Zhu, solved this problem by fusing CCR5 to a small protein, which stabilizes the receptor molecule without changing its shape. They also added Maraviroc, an anti-HIV drug that targets CCR5, and solved the structures of the drug and the protein bound together.

They showed that Maraviroc does not bind to the same part of CCR5 that gp120 or chemokines do. Rather, the drug attaches to a different site, which warps CCR5’s shape, locking it into an inactive state where it can no longer interact with gp120. This ability, which previous studies had suggested but not confirmed, explains how the drug thwarts HIV infection.

“CCR5 is very important in the HIV field,” said Bernard Lagane, who studies HIV at the Pasteur Institute in Paris and was not involved in the study. HIV often evolves resistance against drugs that target CCR5. “Knowing its structure will allow us to rationally and more efficiently design molecules that will act against resistant viruses,” he said. It might also be possible to develop drugs that block HIV without compromising CCR5’s ability to bind to chemokines and propagate immune signals.

Wu’s team also compared the structures of CCR5 and CXCR4 and simulated their interactions with different HIV strains. They found that these receptors have small but important differences in the pockets that gp120 binds to. Subtle features such as the spread of electric charge in the pocket, and physical obstructions from surrounding amino acids, can explain why some viruses prefer one receptor to the other.

And this choice is important. The vast majority of HIV viruses use CCR5 to break into cells, but some eventually switch their allegiances to CXCR4. When this happens, the virus can attack a broader range of cells, and patients progress toward AIDS more quickly. “Now that both structures are solved, we can find ways of blocking binding to both co-receptors,” said Wu. She also hopes to use the structure of CCR5 to understand why people with a certain mutation in the protein, known as delta-32, are almost invulnerable to HIV.

“The limitation is that any crystal is a snapshot,” said Hoxie. CCR5 can take on many shapes and, by adding Maraviroc, Wu locked it into a shape that would not allow HIV to start an infection. “Obviously, I’d also love to see how the protein enables infection too,” said Hoxie, “but there’s no question that we’re already looking at the molecule in a way we’ve never been able to.”


**SIV Vaccine Success**

A cytomegalovirus-based vaccine eliminated simian immunodeficiency virus from rhesus macaques, raising hopes of a similarly effective HIV vaccine.

By Kate Yandell | September 13, 2013

A vaccine has eliminated simian immunodeficiency virus (SIV) in some rhesus macaques, which remained uninfected for as long as three years post-treatment, according to a study published in *Nature* yesterday (September 12).

Previously, researchers had shown that about half of rhesus macaques given the vaccine were protected from SIV infection. The new study showed that monkeys given the vaccine and then infected with SIV showed no signs of the virus in their systems even though it had originally taken hold.

“The virus got in, it infected some cells, moved about in various parts of the body, but it was subsequently cleared, so that by two or three years later the monkeys looked like normal monkeys,” study coauthor Louis Picker from Oregon Health and Science University told *Gizmodo.*
The vaccine contains a cytomegalovirus that expresses SIV proteins, stimulating the immune system to recognize and attempt to eliminate the virus. The researchers now hope to determine whether the vaccine can eliminate SIV if administered after an SIV infection has taken hold, *BBC News* reported. The researchers hope to launch human trials within two years.

“It’s always tough to claim eradication—there could always be a cell which we didn't analyze that has the virus in it,” Picker told *BBC*. “But for the most part, with very stringent criteria . . . there was no virus left in the body of these monkeys.”

**Precision Epigenetics**

*Visualizing specific epigenetic marks at single gene loci is now possible in individual cells.*

By Ruth Williams | September 1, 2013

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**THE TECHNIQUE:** A gene of interest is hybridized with a biotin-tagged DNA probe (red). Next, an anti-biotin antibody (pink) and an antibody (blue) recognizing an epigenetic mark—e.g., histone H3 methylation—are applied. These antibodies are then each tagged with PLA antibodies (orange and yellow). If the biotin and epigenetic mark are in close proximity, the two PLA antibodies will interact and create a signal detectable with a fluorescent DNA probe.

*GEORGE RETSECK*
Techniques exist to visualize specific gene loci within tissue sections. And separate test-tube experiments exist to determine those genes’ epigenetic modifications.

Now Gary Owens, a professor of cardiovascular research at the University of Virginia, has devised a new technique that enables gene visualization and epigenetic analysis at the same time.

“The dirty little secret of epigenetics research is that we report quantitative differences from a cell population,” says Andrew Feinberg, a professor of molecular medicine at Johns Hopkins University who was not involved in the study. “If you really want to understand mechanisms, you also need to measure individual cells.”

To achieve single-cell precision, Owens modified an existing technique called a proximity ligation assay (PLA) that is used to determine if two proteins are in close proximity within a cell. Antibodies to the two proteins are tagged with overlapping complementary single strands of DNA. If the two strands are close together, they can be ligated to form an amplifiable circular DNA molecule that is detectable with a fluorescently labeled DNA probe.

Owens simply combined the method with in situ hybridization (ISH) to reveal whether a specific gene was in close proximity to a particular epigenetic mark—for example, methylation of lysine 4 in histone H3. First he hybridized his gene of interest with a DNA probe tagged with biotin. He then used an anti-biotin antibody tagged with one of the single-stranded DNAs for PLA. The other PLA tag was attached to the antibody recognizing the particular epigenetic mark.

The concept of combining ISH with PLA “was a real technical tour de force,” says Feinberg.

At present, Owens’s PLA-ISH technique allows examination of one type of epigenetic mark at one gene locus per experiment. But he says that with the development of further PLA reagents, it should be possible to look at multiple loci, epigenetic marks, and even transcription factors at the same time. (Nat Methods, 10:171-77, 2013)

**Expeditious TB Tests**

*New rapid tests for extensively drug-resistant tuberculosis appear highly accurate.*

By Kate Yandell | September 10, 2013

Drug-resistant tuberculosis continues to evolve. Three new rapid and accurate tests for extensively drug-resistant tuberculosis (TB) may reduce the time it takes to identify the most sweeping form of drug resistance in TB to under a week, according to MedPage Today.

“Our findings suggest these three tests could provide a quicker way to identify patients who need alternative treatment regimens,” University of California, Davis, professor Antonino Catanzaro, who presented the study results at the European Respiratory Society’s Annual Congress in Barcelona earlier this week (September 8), said in a press release. “This is very important and could potentially save lives as well as help to curb the rise of drug-resistant TB.”

Researchers tested the three methods on more than 1,000 tuberculosis patients in South Africa, Moldova, and India. They compared the results to those obtained through the traditional Mycobacteria Growth Indicator Tube (MGIT) test, which takes a median of 25 days to produce results.

One new method, called the Line Probe Assay (LPA), detects common mutations behind drug resistance in only one to two days. A second, called the Microscopic Observation Drug Susceptibility (MODS) test, took five to seven. A third method, based on pyrosequencing, took as little as one day or as long as a few hundred days, and was more difficult to use, MedPage Today reported.

The new methods matched traditional MGIT results more than 95 percent of the time for most forms of antibiotic resistance. The new methods only matched MGIT results for kanamycin resistance 91 percent to 92 percent of the time.
Rapid tests for extensive drug resistance are important because patients often disappear during long waits for their test results or continue to move around their community, spreading drug-resistant TB, Francesco Blasi, the president of the European Respiratory Society, told MedPage Today.

The Many Mysteries of MERS
As researchers test a treatment for Middle East respiratory syndrome, the deadly coronavirus that causes it slowly reveals itself.

By Tracy Vence | September 8, 2013

Unsure of its origin, mode of transmission, and the best course of treatment, clinicians have been working to quell Middle East respiratory syndrome (MERS) on a case-by-case basis since it emerged in Saudi Arabia last year. Writing in Nature Medicine today (September 8), a team led by investigators at the National Institute of Allergy and Infectious Diseases (NIAID) presents a therapeutic approach validated in nonhuman primates. Because the treatment was successful in vivo, the authors recommend it be used to treat human MERS patients. NIAID’s Darryl Falzarano and his colleagues showed in a rhesus macaque model of the disease that treatment with interferon-α2b and the nucleoside inhibitor ribavirin improved clinical outcome when administered eight hours post-infection.

“Our in vitro data suggested that we needed both together for it to work,” Falzarano told The Scientist. “We went with those two drugs because they’re available on the shelf, they’re approved for use in humans [and] easily accessible.”

“We started this combination therapy not because we think it is the greatest treatment strategy, but because it is something that can be applied quickly,” added study coauthor Heinz Feldmann, chief of NIAID’s Laboratory of Virology. “This is one option that now is out there.”

Although its first symptoms—fever, cough, and shortness of breath—are typical of most lower respiratory illnesses, MERS is an infectious disease unlike any seen in humans before. The coronavirus (CoV) that causes it appears similar to the infectious agent behind the 2002-2003 severe acute respiratory syndrome (SARS) outbreak that infected more than 8,000 people across the globe, killing 775. But MERS differs from SARS in several respects. For one, it is more deadly. Since September 2012, the World Health Organization (WHO) has recorded a total of 114 lab-confirmed cases of MERS-CoV infection worldwide, including 54 deaths—giving it a much higher fatality rate than SARS.

In the time since the first reported death last June, scientists have generated complete genome sequences for the novel CoV and resolved the crystal structure of its receptor-binding domain. Using advanced epidemiological and genomic surveillance techniques, they’ve even pinpointed a suspected source of the infectious agent—bats—and are gradually piecing together how it might be transmitted from the winged mammals to humans. Still, for all that’s now known about the MERS-CoV, there’s much more left to learn.

“Allison McGeer was among the researchers at the front lines of SARS when the outbreak reached Toronto 10 years ago. This May, she traveled to Al-Ahsa at the request of her colleague Ziad Memish, the assistant deputy minister of health for preventive medicine in Saudi Arabia. McGeer, Memish, and their colleagues published a paper describing a cluster of hospital-acquired MERS-CoV infections in the New England Journal of Medicine in August.

“People are dying in the Middle East,” Feldmann said. “SARS was a wake-up call. Is this going to be SARS, or is it going to be worse?”

Allison McGeer was among the researchers at the front lines of SARS when the outbreak reached Toronto 10 years ago. This May, she traveled to Al-Ahsa at the request of her colleague Ziad Memish, the assistant deputy minister of health for preventive medicine in Saudi Arabia. McGeer, Memish, and their colleagues published a paper describing a cluster of hospital-acquired MERS-CoV infections in the New England Journal of Medicine in August.

“The big difference at the moment between MERS and SARS is we don’t know what the exposure is . . . for MERS yet,” McGeer said. “The source of the exposure to humans before the outbreak was much more rapidly identified during SARS.”

Researchers who sequenced the MERS-CoV genome last year had an idea about its origins early on. Their initial phylogenetic analyses pointed them to bats. The researchers found that MERS-CoV was more similar to two viruses isolated from bats than to human SARS. And last month, scientists from Columbia University and the nonprofit EcoHealth Alliance, based in New York, reported in Emerging Infectious
Diseases on their discovery of a stretch of viral RNA in a fecal sample from a single bat that matched similar sections of viral RNA found in humans infected with MERS-CoV. While the finding has yet to be validated, it marked the first tangible evidence of MERS’s animal origin.

“Although bats may ultimately turn out to be the origin of MERS, it is still a mystery as to exactly how the initial case patient became infected with MERS coronavirus,” said the University of California, San Francisco’s Charles Chiu, a clinical microbiologist specializing in viral diagnostics.

“To date, most patients with MERS have not reported any direct contact or exposures with bats, so there must be an intermediate source between bats and humans,” Alimuddin Zumla, a professor of infectious diseases and international health at University College London told The Scientist in an e-mail. “If we know that answer then we can interrupt that transmission and put control measures in place.”

Beyond identifying intermediate hosts, there are several other questions. In order to better detect and treat MERS, researchers must first fully resolve its epidemiology. “Are we looking at the tip of the iceberg with the 108 cases today?” NIAID’s Feldmann asked. “How many mild or asymptomatic cases do we have that could contribute big time to spread of the virus and transmission?”

The reproductive and mutation rates of the MERS-CoV also remain unclear, as do the functional consequences of its genomic characteristics. “We do not know the function of several MERS-CoV genes,” the Erasmus University Medical Center’s Ron Fouchier, who led one of the first teams to sequence the complete genome of the novel CoV, told The Scientist in an e-mail. “Understanding the function of the products encoded in the virus genome is crucial.”

Along those same lines, Chiu noted genomic surveillance is needed to help ascertain whether there are quasi-species of the MERS-CoV, and whether their existence might affect pathogenesis and/or host immune response.

While scientists continue to focus their efforts on understanding MERS in a field-specific manner, most agree that the most pressing need is to identify the origin of the CoV and how it spreads to humans. “If we know that, there’s a possibility we can stop it, like H7N9 and SARS—you close the animal markets, the risk goes away,” said McGeer. “If we knew what the risk was, then we might be able to stop it . . . and we wouldn’t have to worry about the virus evolving as it grows in humans, and we wouldn’t have to worry about ongoing hospital transmissions in the Arabian peninsula and henceforth, to other countries.”


More than Water
A comprehensive analysis of human urine identifies more than 3,000 metabolites.

By Erin Weeks | September 6, 2013

Everything you ever wanted to know about the chemical makeup of human urine is now freely accessible in an online database, thanks to a team of researchers who are cataloguing their way through the complex metabolic compositions of bodily fluids. Studying the metabolome—or the sum of all metabolites in a biological sample—can reveal a wealth of information about how environmental factors affect human health. So far, the team has inventoried the metabolites found in blood serum, saliva, cerebrospinal fluid, and now, as reported in PLOS ONE this week (September 4), urine.

Urine does far more than eliminate water-soluble waste from our bodies. “While largely viewed as a waste product, urine has considerable value as a diagnostic biofluid,” the study’s authors write. Humans have leveraged that value for millennia, using

![Flickr Sarah Oros](Hippuric acid, one of the most abundant organic metabolites in human urine)
urine to diagnose diseases from ancient Egypt to the Byzantine Empire. Today, urinalysis remains a noninvasive, cost-effective way to test for genetic disorders, renal conditions, and even some types of cancer.

To systematically characterize the metabolites found in human urine, the researchers searched existing literature and conducted their own extensive experiments using nuclear magnetic resonance spectroscopy, gas and liquid chromatography, and mass spectrometry. Previously, only a few hundred metabolites had been documented—a mere fraction of the 3,000 counted in this newest study.

To foster future research, the team established a comprehensive database of known urine metabolites. “We had no idea there could be so many different compounds going into our toilets,” lead author David Wishart from the University of Alberta told Popular Science.

Out of Sync
Why eating at the wrong times is tied to such profound and negative effects on our bodies
By Kerry Grens | September 1, 2013

Few environmental factors are as reliable as the 24-hour day, and an evolutionary argument can be made for why the diurnal rhythms of the Earth’s rotation are so coupled with human metabolism. Our behavior, our physiology, and our biochemistry reflect the daily cycles of the planet, and people who fall out of sync with these cycles are more likely to suffer from diabetes, obesity, and heart disease. Gastrointestinal disorders, depression, and other ailments are also more common among people who don’t have normal sleep habits. But according to new research, it’s not just disrupted sleep that can lead to these myriad physiological symptoms; it’s also the altered patterns of food consumption that go along with keeping such strange hours.

Shift workers who punch in in the evening have offered epidemiologists a glimpse into the importance of keeping normal sleep-wake patterns—that is, with activity coinciding with daylight. It’s been shown repeatedly that these employees are prone to developing metabolic disorders, and one review of the research concluded that night-shift workers are 40 percent more likely to develop cardiovascular disease.

The mechanisms for these associations have been less clear, but a wealth of animal studies and emerging research on humans implicate the timing of eating as an important factor in maintaining energy balance and good health. In rodents, “simply restricting feeding to incorrect times has adverse consequences,” says Joe Bass of Northwestern University. Mouse studies have shown that a high-fat diet, freely available around-the-clock, will make the animals obese and unhealthy. But if mice are fed only at night—when these nocturnal animals are normally active—the untoward metabolic effects are drastically reduced, despite consuming the same number of calories.

Even less dramatic affronts to our normal circadian cycles may affect the way we process food. Earlier this year, Frank Scheer of Harvard Medical School and Marta Garaulet of Murcia University published the results from a study of 420 dieters in Spain. The participants had signed up for a weight-loss program, and the investigators tracked their eating habits. Half of the participants ate their main meal earlier in the day, before 3 p.m., while the other half ate later. Both groups followed a similar diet, exercised about the same amount, slept the same number of hours, and even produced similar levels of hunger-related hormones. Yet the early eaters lost weight faster and by the end of the study had shed a greater percentage of their body weight than the late eaters. “These data indicated that the timing of the main meal, which [for Spaniards] is lunch, predicted the success of weight loss,” says Scheer.

Scheer’s findings add to the growing recognition that our metabolisms are primed by the circadian machinery written in our genes, and that discord between the two can wreak havoc on our systems. According to Satchidananda Panda of the Salk Institute, “we are very different animals between the day and night.”

Peripheral clocks
Until recently, our circadian rhythms were attributed entirely to the oscillations of activity in a group of about 20,000 neurons in the hypothalamus—a cluster known as the suprachiasmatic nucleus (SCN). The SCN was believed to be the master clock, entrained by the length of the day, that dictated the body’s 24-hour rhythms. Now scientists recognize that many of the body’s tissues can tell time and that these peripheral clocks can be influenced by other environmental cues, known as zeitgebers, such as the timing of food consumption. It’s still unclear how the SCN and these other body clocks interact. Below are several organs that maintain 24-hour cycles and some of their rhythmic physiological functions.

A couple of decades ago, most circadian researchers would have described the circadian clock as a system regulated by the suprachiasmatic nucleus (SCN), a group of about 20,000 neurons in the
hypotheses that serve as the conductor of our body’s 24-hour rhythms. Lesions of the SCN abolish behavioral rhythms in animals. The rest of the body, it was thought, passively follows the SCN’s lead. “That picture changed pretty rapidly in the late ’90s after the first clock genes were cloned,” says Joseph Takahashi, an investigator with the Howard Hughes Medical Institute and a professor at the University of Texas Southwestern Medical Center. Upon identifying the key genes that synchronize organisms’ behavior and bodily functions with the Earth’s rotation, Takahashi and others began finding clock genes expressed in nearly every tissue of the body. “That sort of threw everybody into kind of a quandary,” says Vincent Cassone, a biology professor at the University of Kentucky: Was the SCN really our primary pacemaker, or were clocks throughout the body keeping their own time? The search was on to discover what these genes and the proteins they encode were doing outside of the brain. (See “Time and Temperature,” The Scientist, February 2011.)

Sure enough, researchers discovered that the SCN is not the body’s only timepiece. Additional oscillators in the peripheral tissues help adjust the daily rhythmic functions of organs. (See illustration here.) In the gut, for instance, intestinal motility and absorption differ depending on the time of day. Like all of the body’s clocks, these rhythms are guided by clock genes that operate in a transcriptional feedback loop. Transcription factors such as CLOCK and BMAL1 activate the expression of a large number of genes, including Period and Cryptochrome, whose proteins, in turn, inhibit CLOCK and BMAL1, causing daily oscillations in their expression.

Circadian clocks in the periphery are guided by the SCN, and all of the clocks are vulnerable to the influence of zeitgebers (from the German for “time giver”), environmental stimuli that tell the body what time it is. The SCN’s primary zeitgeber is light. Clocks of peripheral tissues, on the other hand, can take their cues from other inputs, such as food consumption.

In the mouse liver, for instance, about 300 different transcripts oscillate when mice are prohibited from eating. Give the animals access to food throughout the day and night, and the number of oscillating transcripts jumps to about 3,000. If you then consolidate the availability of food to 8 or 9 hours during the day—when mice should be sleeping—that number surges to 5,000. “This means that eating has a big effect,” says Panda.

Similarly, Cassone has shown that some of the rhythmically expressed genes driving the circadian clock in the mammalian gastrointestinal tract are sensitive to the timing of eating. Clock proteins in the colon peak in abundance at dramatically different times during a 24-hour cycle, depending on whether the animals eat throughout the day or during a restricted time period. Furthermore, animals with a dysfunctional master clock—those with a lesioned SCN, for example—can use food consumption as a way to get back on schedule. “If we give animals a timed feeding, the gastrointestinal system learns the time of day,” Cassone says.

Despite the seemingly strong influence of food intake on the body’s peripheral clocks, the SCN appears much less affected. Thus, researchers speculate that at the heart of the health problems seen in shift workers and in mice fed during their normal sleeping periods is an uncoupling of the SCN and the peripheral clocks. “We suspect that eating at the inappropriate time of the day ends up with peripheral clocks—in the liver, in fat, in the pancreas, in the muscle—being in a phase which is now different from the SCN,” says Georgios Paschos, a researcher at the University of Pennsylvania. “This, we think, can be the initiation of issues in energy homeostasis.”

**Metabolism and the clock**

Taking a closer look at the genes whose expression can be impacted by mistimed eating, Panda has found impacts on glucose metabolism, fatty acid synthesis and breakdown, cholesterol production, and liver function. He argues that some proteins require a period of fasting to operate properly. PhosphoCREB (pCREB), for example, regulates the process of glucose release when animals are sleeping. “This [gene] should only be on during the day when the mice are fasting,” says Panda. Instead, in animals fed throughout the day and night, pCREB levels remain high, and the consequence is a high blood-sugar level. (See “Feeding Time,” The Scientist, January 2013.)

Indeed, studies that directly disturb peripheral tissue clocks by ablating clockwork genes yield dramatic metabolic problems. Paschos has found that knocking out Bmal1 in the fat cells of mice, for instance, leads to obesity and changes in the concentration of circulating polyunsaturated fatty acids. Additionally, Bass found that mice whose pancreatic clocks are knocked out by a mutant Bmal1 or Clock specific to the pancreas can’t produce insulin properly and develop diabetes. The animals maintained normal feeding rhythms and body weight, but they ended up with impaired glucose tolerance and decreased insulin secretion. “The clock is a very dominant regulator of gene expression in the pancreas, and that has a very big effect on function,” Bass says.
“We are very different animals between the day and night.”—Satchidananda Panda, Salk Institute

From these studies it’s clear that the clocks in peripheral tissues—vulnerable as they are to the timing of eating—are vital to metabolism in the body’s organs. “I would say the clock is playing a very fundamental role regulating all metabolic pathways,” says Takahashi, “not just in organ systems, but at a cellular level.”

One striking example of metabolism’s marriage to the body’s clocks came to light about 25 years ago, when the University of Pennsylvania’s Mitch Lazar discovered Rev-erba, a nuclear receptor that regulates gene expression through an epigenomic modulator, histone deacetylase 3 (HDAC3). In Lazar’s long quest to understand the role of Rev-erba, he became fascinated by the remarkable circadian oscillation in its expression. In the case of the liver, “it’s almost like in a mouse every day the molecule gets knocked out by 5 a.m., and by 5 p.m. it’s one of the more highly expressed genes in the cell,” says Lazar.

In 2011, Lazar’s team found that when they knocked out HDAC3 in the liver, they got “a really dramatic” result, Lazar says: the liver filled up with fat. The study provided a molecular explanation for what had been known for decades—that there is a circadian rhythm for lipid storage and synthesis. During sleeping periods, the body burns lipids, and during waking, the liver stores them up. HDAC3, which is highly expressed during the day when the rodents are sleeping, apparently helps mediate the use of lipids while the animals fast. When Rev-erba and HDAC3 are shut down at night, when the animals are awake and presumably eating, glucose precursors are shunted towards lipid synthesis and storage. Later, when the animals are sleeping, they can reverse the process so that their livers make glucose for use by the rest of the body, Lazar says. He and his colleagues suspect that the circadian cycling of Rev-erba and HDAC3 “is one of these protective mechanisms for allowing the liver to produce glucose at times when the mammal is not eating,” says Lazar.

Subsequent work in Panda’s lab, published last year, found that mice fed a high-fat diet throughout the day had blunted oscillations of Rev-erba expression, as well as increased fat deposits in liver cells and markers of liver disease.

Again, researchers suspect that the root of the problem is the asynchrony of the master clock of the SCN and the peripheral clocks in the liver, gut, pancreas, and other organs involved in metabolism. The brain may be getting the signal from one zeitgeber, light, that it’s time to sleep (and, say, burn lipids), says Lazar, while another zeitgeber, food, is telling the cell that it’s time to be active (and store lipids). “Now you’re going to be giving conflicting signals to that animal, and the net result could be dysregulating metabolism,” he says. “I think a lot of the pathology here, when we finally understand it, will be about dissonance between signals.”

Circadian metabolites
Circadian function is married to metabolism through a variety of pathways, most notably by its relationship to the histone deacetylase SIRT1 and the metabolite it depends upon, NAD+. The well-known clock components CLOCK and BMAL1 initiate the expression of NAMPT (1), a key enzyme in the production of NAD+ (2). This contributes to the circadian-dependent availability of NAD+, and, in turn, the daily rhythm in activity of SIRT1 (3). SIRT1 is not only involved in myriad cellular processes, including insulin secretion, gluconeogenesis, decreased adipogenesis, and mitochondrial biogenesis, but it can inhibit the activity of CLOCK as well (4).

THE SCIENTIST STAFF
Taken together, Panda's and Lazar's experiments show how the clock can influence metabolism and how eating can influence the clock. "It's like a thermostat, almost, in that it's maintaining timing, but it can be adjusted according to the energy environment," says Bass.

In 2006, Sassone-Corsi's group discovered that CLOCK itself is a histone acetyltransferase, which adds acetyl groups to histones. The corresponding deacetylase, SIRT1, can remove acetyl groups from histones and other proteins, including BMAL1. As part of these discoveries, Sassone-Corsi found that SIRT1's function requires NAD+ (nicotinamide adenine dinucleotide), an energy metabolite. (See illustration here.) "That was the moment where I realized it's a molecular link between the clock system and epigenetics and metabolism," he says.

NAD+ itself cycles in a circadian rhythm. Sassone-Corsi's group, concurrently with Takahashi, Bass, and their colleagues, showed in a pair of 2009 papers that the clock system controls an enzyme, NAMPT, which is a rate-limiting step in the production of NAD+. "It's a perfect example" of how inseparably metabolism and the clock function, says Sassone-Corsi.

Humans, particularly those in developed countries with abundant artificial light, late-night TV, and 24-hour diners, have been putting themselves through an inadvertent experiment over the last few decades.

Acetyl-CoA—an enzyme vital to the energy balance within cells—is another metabolite that appears to be intimately intertwined with the circadian clock. Preliminary results from Sassone-Corsi’s lab suggests that acetyl-CoA synthase?1, the enzyme that regulates acetyl-CoA's production, is itself activated by circadian acetylation. That's because SIRT1 is the deacetylase of acetyl-CoA synthase?1. And SIRT1's activity, again, is itself dependent upon a metabolite, NAD+.

The intertwining of metabolites and circadian clockwork is likely extensive. Sassone-Corsi and his colleagues have since found that of about 600 metabolites in the liver, more than half oscillate in a clock-controlled manner. He and his colleagues have developed an online resource, called Circadiomics, to catalog metabolites that have a circadian rhythm in the liver, and they plan to expand their database to the muscle. His group is also now exposing animals to various diets to see how networks of cellular pathways affiliated with a particular metabolite are affected.

Overall, his research and others have revealed the ubiquitous and complex interplay of regulation and feedback between metabolism and the clock. "The clock controls metabolites, and then metabolites feed
back on the clock system,” says Sassone-Corsi. How this interplay is affected by different diet regimes remains to be seen.

**A modern experiment**

Takahashi has shown that the targets of clockwork genes in the liver are broad and include components of myriad metabolic pathways. They are managed by the clock via chromatin regulation and the recruitment of RNA polymerase to activate transcription. “Because of the clock’s global regulation of transcription and chromatin state, you can imagine the genome is really in a different state at different times of the day,” Takahashi says.

It’s possible, then, that presenting food at times when the genome is hunkered down for fasting and energy storage might lead to weight gain and metabolic disorders. Lazar says the experiment has yet to be done to connect the dots between inappropriate food timing, epigenetic activity dysregulated by the clock, and metabolic diseases. But humans, particularly those in developed countries with abundant artificial light, late-night TV, and 24-hour diners, have been putting themselves through an inadvertent experiment over the last few decades. No longer does daylight dictate the times when we eat. “That is the cycle that has gone wrong in the last 50 years,” says Panda.

With caution and caveats, one could speculate that this is, in part, why obesity and metabolic disorders have escalated to epidemic levels, particularly when mistimed eating is coupled with a high-fat, high-carbohydrate diet. It stands to reason that our metabolic functions, as controlled by the circadian clock, evolved to cycle in harmony with the Earth’s daily rhythms, to optimize processes such as energy use and storage. In doing so, we became adapted to eat during the daytime, and maladapted for eating at night. Opposing these rhythms, as many of us now do, may challenge our bodies’ normal cycles and set us up for disease. “Like many evolutionary arguments, it’s hard to prove,” says Lazar. “But otherwise it’s hard to imagine why else we would need things so tightly linked to the Earth’s rotation.”

**References**


September 16, 2013

**DNA Double Take**

**By Carl Zimmer**

From biology class to “C.S.I.,” we are told again and again that our genome is at the heart of our identity. Read the sequences in the chromosomes of a single cell, and learn everything about a person’s genetic information — or, as 23andme, a prominent genetic testing company, says on its Web site, “The more you know about your DNA, the more you know about yourself.”

But scientists are discovering that — to a surprising degree — we contain genetic multitudes. Not long ago, researchers had thought it was rare for the cells in a single healthy person to differ genetically in a significant way. But scientists are finding that it’s quite common for an individual to have multiple genomes. Some people, for example, have groups of cells with mutations that are not found in the rest of the body. Some have genomes that came from other people.

“There have been whispers in the matrix about this for years, even decades, but only in a very hypothetical sense,” said Alexander Urban, a geneticist at Stanford University. Even three years ago, suggesting that there was widespread genetic variation in a single body would have been met with skepticism, he said. “You would have just run against the wall.”
But a series of recent papers by Dr. Urban and others has demonstrated that those whispers were not just hypothetical. The variation in the genomes found in a single person is too large to be ignored. “We now know it’s there,” Dr. Urban said. “Now we’re mapping this new continent.”

Dr. James R. Lupski, a leading expert on the human genome at Baylor College of Medicine, wrote in a recent review in the journal Science that the existence of multiple genomes in an individual could have a tremendous impact on the practice of medicine. “It’s changed the way I think,” he said in an interview.

Scientists are finding links from multiple genomes to certain rare diseases, and now they’re beginning to investigate genetic variations to shed light on more common disorders. Science’s changing view is also raising questions about how forensic scientists should use DNA evidence to identify people. It’s also posing challenges for genetic counselors, who can’t assume that the genetic information from one cell can tell them about the DNA throughout a person’s body.

**Human Blueprint**

When an egg and sperm combine their DNA, the genome they produce contains all the necessary information for building a new human. As the egg divides to form an embryo, it produces new copies of that original genome.

For decades, geneticists have explored how an embryo can use the instructions in a single genome to develop muscles, nerves and the many other parts of the human body. They also use sequencing to understand genetic variations that can raise the risk of certain diseases. Genetic counselors can look at the results of genetic screenings to help patients and their families cope with these diseases — altering their diet, for example, if they lack a gene for a crucial enzyme.

The cost of sequencing an entire genome has fallen so drastically in the past 20 years — now a few thousand dollars, down from an estimated $3 billion for the public-private partnership that sequenced the first human genome — that doctors are beginning to sequence the entire genomes of some patients. (Sequencing can be done in as little as 50 hours.) And they’re identifying links between mutations and diseases that have never been seen before.

Yet all these powerful tests are based on the assumption that, inside our body, a genome is a genome is a genome. Scientists believed that they could look at the genome from cells taken in a cheek swab and be able to learn about the genomes of cells in the brain or the liver or anywhere else in the body.

In the mid-1900s, scientists began to get clues that this was not always true. In 1953, for example, a British woman donated a pint of blood. It turned out that some of her blood was Type O and some was Type A. The scientists who studied her concluded that she had acquired some of her blood from her twin brother in the womb, including his genomes in his blood cells.

Chimerism, as such conditions came to be known, seemed for many years to be a rarity. But “it can be commoner than we realized,” said Dr. Linda Randolph, a pediatrician at Children’s Hospital in Los Angeles who is an author of a review of chimerism published in The American Journal of Medical Genetics in July.

Twins can end up with a mixed supply of blood when they get nutrients in the womb through the same set of blood vessels. In other cases, two fertilized eggs may fuse together. These so-called embryonic chimeras may go through life blissfully unaware of their origins.

One woman discovered she was a chimera as late as age 52. In need of a kidney transplant, she was tested so that she might find a match. The results indicated that she was not the mother of two of her three biological children. It turned out that she had originated from two genomes. One genome gave rise to her blood and some of her eggs; other eggs carried a separate genome.

Women can also gain genomes from their children. After a baby is born, it may leave some fetal cells behind in its mother’s body, where they can travel to different organs and be absorbed into those tissues. “It’s pretty likely that any woman who has been pregnant is a chimera,” Dr. Randolph said.

**Everywhere You Look**

As scientists begin to search for chimeras systematically — rather than waiting for them to turn up in puzzling medical tests — they’re finding them in a remarkably high fraction of people. In 2012, Canadian scientists performed autopsies on the brains of 59 women. They found neurons with Y chromosomes in 63 percent of them. The neurons likely developed from cells originating in their sons.

In The International Journal of Cancer in August, Eugen Dhimolea of the Dana-Farber Cancer Institute in Boston and colleagues reported that male cells can also infiltrate breast tissue. When they looked for Y chromosomes in samples of breast tissue, they found it in 56 percent of the women they investigated.

A century ago, geneticists discovered one way in which people might acquire new genomes. They were studying “mosaic animals,” rare creatures with oddly-colored patches of fur. The animals didn’t inherit
the genes for these patches from their parents. Instead, while embryos, they acquired a mutation in a skin cell that divided to produce a colored patch.

Mosaicism, as this condition came to be known, was difficult to study in humans before the age of DNA sequencing. Scientists could only discover instances in which the mutations and the effects were big.

In 1960, researchers found that a form of leukemia is a result of mosaicism. A blood cell spontaneously mutates as it divides, moving a big chunk of one chromosome to another.

Later studies added support to the idea that cancer is a result of mutations in specific cells. But scientists had little idea of how common cases of mosaicism were beyond cancer.

“We didn’t have the technology to systematically think about them,” said Dr. Christopher Walsh, a geneticist at Children’s Hospital in Boston who recently published a review on mosaicism and disease in Science. “Now we’re in the midst of a revolution.”

Benign Differences

The latest findings make it clear that mosaicism is quite common — even in healthy cells.

Dr. Urban and his colleagues, for example, investigated mutations in cells called fibroblasts, which are found in connective tissue. They searched in particular for cases in which a segment of DNA was accidentally duplicated or deleted. As they reported last year, 30 percent of the fibroblasts carried at least one such mutation.

Michael Snyder of Stanford University and his colleagues searched for mosaicism by performing autopsies on six people who had died of causes other than cancer. In five of the six people they autopsied, the scientists reported last October, they found cells in different organs with stretches of DNA that had accidentally been duplicated or deleted.

Now that scientists are beginning to appreciate how common chimerism and mosaicism are, they’re investigating the effects of these conditions on our health. “That’s still open really, because these are still early days,” Dr. Urban said.

Nevertheless, said Dr. Welsh, “it’s safe to say that a large proportion of those mutations will be benign.” Recent studies on chimeras suggest that these extra genomes can even be beneficial. Chimeric cells from fetuses appear to seek out damaged tissue and help heal it, for example.

But scientists are also starting to find cases in which mutations in specific cells help give rise to diseases other than cancer. Dr. Walsh, for example, studies a childhood disorder of the brain called hemimegalencephaly, in which one side of the brain grows larger than the other, leading to devastating seizures.

“The kids have no chance for a normal life without desperate surgery to take out half of their brain,” he said.

Dr. Walsh has studied the genomes of neurons removed during those surgeries. He and his colleagues discovered that some neurons in the overgrown hemisphere have mutations to one gene. Two other teams of scientists have identified mutations on other genes, all of which help to control the growth of neurons. “We can get our hands on the mechanism of the disease,” said Dr. Walsh.

Other researchers are now investigating whether mosaicism is a factor in more common diseases, like schizophrenia. “This will play itself out over the next 5 or 10 years,” said Dr. Urban, who with his colleagues is studying it.

Moving Cautiously

Medical researchers aren’t the only scientists interested in our multitudes of personal genomes. So are forensic scientists. When they attempt to identify criminals or murder victims by matching DNA, they want to avoid being misled by the variety of genomes inside a single person.

Last year, for example, forensic scientists at the Washington State Patrol Crime Laboratory Division described how a saliva sample and a sperm sample from the same suspect in a sexual assault case didn’t match.

Bone marrow transplants can also confound forensic scientists. Researchers at Innsbruck Medical University in Austria took cheek swabs from 77 people who had received transplants up to nine years earlier. In 74 percent of the samples, they found a mix of genomes — both their own and those from the marrow donors, the scientists reported this year. The transplanted stem cells hadn’t just replaced blood cells, but had also become cells lining the cheek.

While the risk of confusion is real, it is manageable, experts said. “This should not be much of a concern for forensics,” said Manfred Kayser, a professor of Forensic Molecular Biology at Erasmus University in Rotterdam. In the cases where mosaicism or chimerism causes confusion, forensic scientists can clear it up by other means. In the Austrian study, for example, the scientists found no marrow donor genomes in the hair of the recipients.
For genetic counselors helping clients make sense of DNA tests, our many genomes pose more serious challenges. A DNA test that uses blood cells may miss disease-causing mutations in the cells of other organs. “We can’t tell you what else is going on,” said Nancy B. Spinner, a geneticist at the University of Pennsylvania, who published a review about the implications of mosaicism for genetic counseling in the May issue of Nature Reviews Genetics.

That may change as scientists develop more powerful ways to investigate our different genomes and learn more about their links to diseases. “It’s not tomorrow that you’re going to walk into your doctor’s office and they’re going to think this way,” said Dr. Lupski. “It’s going to take time.”

**Depression linked to episodes of detectable HIV in cerebrospinal fluid**

Evaluation and treatment of depression may improve HIV control, researchers conclude

Liz Highleyman  
Published: 18 September 2013

People who experience episodes of major depressive disorder (MDD) are significantly more likely to have episodes of detectable HIV in their cerebrospinal fluid (CSF), according to an analysis of the large CHARTER study presented as a late-breaker poster at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) last week in Denver.

Although effective antiretroviral therapy (ART) has dramatically lowered rates of AIDS-related dementia, many people living with HIV still experience more subtle cognitive impairment or neuropsychiatric problems.

Edward Hammond from Johns Hopkins University in Baltimore and colleagues conducted a study to determine if major depressive disorder is associated with HIV escaping or shedding into CSF, the fluid that surrounds the central nervous system comprised of the brain and spinal cord.

Past research has linked MDD to poor virological control and faster disease progression among people with HIV, the researchers noted as background. While major depression is known to be associated with persistent detectable HIV RNA in CSF, it is not clear whether the same association holds for sporadic detectable CSF viral load among people with undetectable blood plasma viral load while on ART.

Certain antiretroviral drugs are able to cross the blood-brain barrier to fight HIV in the central nervous system. Some experts favour specifically including such drugs in antiretroviral regimens, but others think that all guideline-recommended modern combinations that fully suppress HIV in the blood are adequate to control virus in the brain.

The researchers looked at data from participants in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort, a prospective cohort of people with HIV at six US centres designed to evaluate neurocognitive and neuropsychiatric outcomes of HIV treatment.

The investigators used logistic regression and discrete-time survival models to examine associations between MDD diagnosis (according to the 1994 edition of the *Diagnostic and Statistical Manual of Mental Disorders*, or DSM-IV) and HIV “escape” into CSF, both at study entry and over time.

CSF viral escape was defined as detectable HIV RNA (>50 copies/ml) in the presence of undetectable blood viral load (<50 copies/ml), or CSF viral levels at least 1 log greater than blood levels.

The main analysis included 803 participants. Most (81%) were men, 41% were white and 46% were black. The average age was 44 years and they'd had HIV for about 11 years. The median current CD4 cell count at study entry was 445 cells/mm³, but the nadir (lowest-ever) level was 149 cells/mm³. Half had a prior history of major depression episodes.

At study entry, 18% of participants overall were found to have detectable HIV in their CSF despite undetectable blood viral load. People with major depression were nearly twice as likely to have CSF viral escape than non-depressed participants: 26 vs 16% (p = 0.016; adjusted odds ratio 2.10).

A subset of 212 participants who did not have detectable CSF viral load at the start of the study underwent at least three more spinal taps during follow-up to see if they experienced new-onset viral escape into their CSF.

Over 18 months of follow-up (2736 total person-months), cumulative incidence of CSF viral escape was again significantly higher among people with MDD compared to non-depressed participants (p<0.05).

New-onset CSF viral escape was somewhat more common earlier in the study. At six months, incidence rates were 27 cases per 1000 person-months among people with MDD compared to 16 per 1000 person-months among non-depressed participants. At 12 months, cumulative incidence rates were 19 vs
12 cases per 1000 person-months, respectively. At 18 months, incidence rates remained stable at 20 vs 12 cases per 1000 person-months.

After controlling for other factors, the adjusted hazard ratio for new-onset CSF escape among people with MDD was 3.01, or three times higher.

Plasma viral load levels did not differ significantly between people with MDD and those without at any time point. Having a lifetime history of major depression was a significant risk factor for later episodes, and current CD4 count (but not lowest-ever count) approached statistical significance.

"MDD is associated with increased risk for CSF viral escape," the researchers concluded. "Ongoing CSF viral replication may occur in more persons than previously estimated. Evaluation and treatment of depression may improve HIV control."

"Additional research is needed to continue to improve our understanding of mechanisms that may be responsible for the relationship between depression and HIV viral replication," they added.

Reference

South American survey finds rectal microbicide formulated as a douche acceptable
Hazardous current douching practices uncovered
Gus Cairns
Published: 18 September 2013
A qualitative study of 140 men who have sex with men (MSM) and transgender women (TGW) in three cities in Peru and Ecuador has found that most thought that a rectal microbicide formulated as a douche, rather than as a gel or lubricant, might offer additional safety or efficacy.

However, it also found that participants doubted the practicality of such a formulation for use in sex away from home. The researchers also comment that interviewees who regard douching as hazardous would be unlikely to change their minds and adopt a microbicide douche.

The researchers also discovered in the course of their research that some participants were already using a variety of homemade douching preparations before anal sex, some of them potentially hazardous or downright toxic. They comment that regardless of the desirability of a rectal microbicide douche, "education on rectal douching practices is needed now".

This study follows on from several other studies of rectal douching in MSM and TGW. A study in the USA (Carballo-Diéguez) found that 53% of HIV-negative MSM there douch ed rectally in preparation for anal sex. A global survey (Stahlman) by International Rectal Microbicide Advocates (IRMA), presented at the Microbicides 2012 Conference in Sydney last year, found that 63% of the people who answered the survey (mainly MSM) douch ed rectally before receiving anal sex, with only 25% using commercial enema products and most using shower hoses and homemade kits made from bottles. Douching was more common in people with HIV, and people who douch ed averaged five partners a month compared with two among those who did not douche, suggesting that a rectal douche focused on people at high risk of HIV might be effective.

A previous study from three cities in Peru (Kinsler) found that only 27% of MSM/TGW douch ed rectally before receptive anal sex but that 80% said they would use a microbicide douche if it had efficacy against HIV infection. Participants who already douch ed were more than twice as likely to say they would use a rectal microbicide douche and those from the capital, Lima, were twice as likely to say they would use a microbicide douche as those from the other two cities, which were the smaller and more remote jungle cities of Iquitos and Pucallpa.

The current survey interviewed 104 participants in focus groups and 36 in indepth interviews, with approximately equal numbers coming from Lima and Iquitos in Peru and Guayaquil in Ecuador. Participants were in the main mixed-race, aged under 30 (only 10-12% were 30 or older in Iquitos and Guayaquil, 38% in Lima), had at least high-school education and were employed.

Participants thought that a douche microbicide would be useful because it would "kill two birds with one stone, because I would take care of hygiene and protect myself at the same time".

People thought a rectal douche might be more protective than a lubricant-type gel "because this is going to have more effect; it is going to go deeper into your body".
Some people found, however, that douching increased the discomfort of sex because it removed natural mucus: "You end up really dry, you don't have anything from your body to lubricate, and in the end your partner is going to be uncomfortable".

Others doubted that a douche microbicide would be practical in many situations: "sometimes there's no time to put on a condom, much less apply an enema."..."Wouldn't you have to carry a huge tube around? You can put a condom and lube in your pocket".

While some participants doubted that a douche microbicide would be protective as they had heard that douching actually increased the risk of HIV: "You use enemas forcefully because that does the cleaning, don't you? And that is extremely harmful to our health".

The researchers conclude that a douche microbicide might well find a market among people who would see it as potentially more efficacious than a gel or lube, but that concerns had emerged about its practicality in away-from-home situations. They also comment that the use of a rectal microbicide douche would likely "be confined to those who already practise the procedure."

The researchers also discovered, serendipitously, that many participants were already using a variety of homemade douches that could increase the risk of acquiring HIV and which in some cases were hazardous to health.

The most popular single douche was simply to use water from a shower hose, but participants also used a variety of liquids including soap and water, detergent or shampoo; lemon juice or vinegar; camphor; a mixture of soap, bleach and isopropyl (rubbing) alcohol; and drinking alcohol in the form of vodka or other spirits. They used plastic soda or hair-dye bottles as applicators.

The researchers comment that this finding shows that there needs to be more research into how MSM and TGW use douches and why: are alcohol douches, for instance, aimed at cleanliness or intoxication? Which partner, insertive or receptive, instigates douching?

They also comment that "regardless of rectal microbicide development, there appears to be an immediate need for HIV prevention messages to include information on safer rectal douching practices, specifically with regard to 'homemade' douching liquids".

References

Gene discovery could lead to new types of HIV treatments
By Kate Kelland
LONDON | Wed Sep 18, 2013 1:06pm EDT
(Reuters)—Scientists have identified a gene which they say may have the ability to prevent HIV, the virus that causes AIDS, from spreading after it enters the body.

In an early-stage study in the journal Nature, researchers said the gene, called MX2, appears to play a key role in how HIV is controlled in human cells, so using it could lead to the development of new, less toxic treatments that harness the body's natural defenses and mobilize them against the virus.

Although there are many more years of research ahead, Mike Malim, who co-led the research at King's College London, described the finding as "extremely exciting" and said it advanced scientists' understanding of how the HIV virus interacts with the immune system.

"Until now we knew very little about the MX2 gene, but now we recognize both its potent anti-viral function and a key point of vulnerability in the life cycle of HIV," he said in a statement about the study, published on Wednesday.

Some 34 million people worldwide are infected with the human immunodeficiency virus (HIV) that causes AIDS—the vast majority of them in poor and developing countries.

But while, particularly in wealthy nations, there are many effective drugs available that allow HIV patients to live long, healthy lives, they often have side-effects and drug resistance can become a problem with long-term use.
In this study, Malim and a team of researchers conducted experiments on human cells in the laboratory, introducing the HIV virus to two different cell lines—one in which the MX2 gene was "switched on", and in the other it which was "silenced"—and then observing the effects.

They found that in the cells where MX2 was silenced, the AIDS virus replicated and spread, while in the cells where it was switched on, the HIV was unable to replicate and produce new viruses to spread.

Malim said the findings suggest MX2 is a key player in establishing viral control in people with HIV, and that armed with this new knowledge, there are two possible routes for potential drug development using the gene.

"It may be possible to develop either a molecule that mimics the role of MX2 or a drug which activates the gene's natural capabilities," he said.

**Can’t Hardly Wait: Federally Funded Abstinence-Only Education Finds its Way to New Mexico**

*Santa Fe Reporter* *(09.17.2013)* By Joey Peters

The New Mexico Department of Health (DOH) and New Mexico State University (NMSU) quietly began to accept federal funding for abstinence-only education programs in fall 2012, six years after DOH rejected a federal grant for abstinence-only education in public schools. According to DOH Spokesperson Kenny Vigil, the state had accepted more than $470,000 in federal abstinence-only funds, to which the state added in-kind contributions of more than $350,000. Vigil stated that the funding offered New Mexico another sex education option. New Mexico reported the highest teen pregnancy rate and highest chlamydia and gonorrhea rates in the country, and DOH stated that 30 percent of students under 15 reported they had had sex.

According to the Sexuality Information and Education Council of the United States (SIECUS), DOH used the money to fund a community-based curriculum called "Sex Can Wait" in Chavez, Cibola, Curry, Doña Ana, Eddy, Lea, and Luna counties. SIECUS advocated for comprehensive sex education for teens and tracked abstinence-only federal dollars. However, Vigil stated that DOH had piloted the "Sex Can Wait" program, developed in 1994 by Dr. Michael Young, and would offer the curriculum in Curry County middle school after-school programs.

The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics both opposed abstinence-only education, and a 2007 US Department of Health and Human Services study confirmed that students who took abstinence-only courses were likely to have their first sex at the same age and to have as many partners as students who did not receive abstinence-based sex education. Critics noted that abstinence-based education failed to teach teens about birth control and contraception.

Santa Fe Public Schools refused abstinence-only funding and partnered with Planned Parenthood to provide comprehensive sex education for public school students in grades 7–9.

**Kenya Sees Drop in HIV Prevalence**

*allAfrica* *(09.16.2013)*

Preliminary Kenya AIDS Indicator Survey (KAIS) results showed that Kenya’s overall HIV prevalence dropped from 7.2 percent in 2007 to 5.6 percent in 2012. Peter Cherutich, head of prevention for Kenya’s National AIDS and Sexually Transmitted Infections Control Program, attributed the prevalence decrease to more HIV-infected people receiving antiretroviral therapy (ART). Early ART could reduce heterosexual HIV transmission by as much as 96 percent, according to recent studies.

Officials feared that these gains would not be sustainable unless Kenya reduced its reliance on donor funding. At present, more than 70 percent of HIV-infected Kenyans with a CD4 count of 350 or lower were on ART. The HIV virus was undetectable for 80 percent of those, which meant there was low risk of transmitting the virus.

Allan Ragi, executive director of the Kenya AIDS NGO Consortium, attributed Kenya’s progress to the fact that government, donors, civil society, and HIV-infected people had worked together at all levels to put in place effective policies, messages, and interventions. Other HIV prevention efforts included mother-to-child prevention, medical male circumcision, and counseling and testing programs.

KAIS reported that approximately 1.2 million Kenyans had HIV, and HIV prevalence varied by gender and region. Overall prevalence among women was 6.9 percent, compared to 4.4 percent overall prevalence among men and 0.9 percent overall prevalence among children. The survey indicated “substantial” drops in the Coast, Nairobi, and Rift Valley regions, but recorded an overall prevalence increase in Nyanza region from 14.9 percent prevalence in 2007 to 15.1 percent in 2012.
Costs Spike for 2nd- and 3rd-Line ARVs and Late Treatment

*AIDSMEDS* (09.19.2013)

The National AIDS Treatment Advocacy Project has reported on the increase in cost to treat HIV-infected individuals on second- and third-line antiretrovirals (ARVs). Researchers calculated costs after reviewing data from 2007 to 2011 in the MarketScan Commercial Claims and Encounters Database and from the MarketScan Lab Database, which covered 2007 to 2010. The researchers followed 9,931 individuals in the first group, whose treatment moved from first- to third-line therapy, and 486 individuals on ARVs in the second group who provided data on CD4 counts.

The researchers adjusted for factors such as AIDS diagnosis, sex, age, region of the country, and type of health insurance. Results showed that the average cost for total care of HIV-infected individuals on first-line therapy was $28,861, cost for second-line therapy was $35,805, and for third-line, $40,804. Also, the average cost to treat a patient who started treatment with more than 350 CD4 cells was $2,526 per month. Treatment for individuals who started with 100–350 CD4 cells was $2,378 per month, and for individuals with fewer than 100 CD4 cells, the price increased to $4,860 per month.


Scripps Research Institute Study Explores Barriers to HIV Vaccine Response

LA JOLLA, CA—September 20, 2013—Researchers at The Scripps Research Institute (TSRI) discovered that an antibody that binds and neutralizes HIV likely also targets the body’s own “self” proteins. This finding could complicate the development of HIV vaccines designed to elicit this protective antibody, called 4E10, and others like it, as doing so might be dangerous or inefficient.

“We developed two new mouse models that allow us to visualize the fate of the rare B cells that can see HIV and we thought could be stimulated by vaccines to produce neutralizing antibodies—the type of antibodies we seek to produce in response to a vaccine,” said David Nemazee, PhD, professor in the Department of Immunology and Microbial Science at TSRI and senior author of the study. “We were able to study vaccine responses of b12, an antibody that sees the CD4 binding site of HIV, but, surprisingly to us, not 4E10, an antibody that sees the stem of the HIV envelope protein.”

Nemazee and his team went on to discover that cells with the potential to produce 4E10 antibodies trigger several natural safeguards that shut down the production of any antibody that might recognize and destroy the body’s own tissues. They concluded that 4E10 cross-reacts with host tissues in this way, prompting its removal before it can do any harm—or good. The study was recently published by *The Journal of Immunology*.

HIV Vaccine Development

4E10 antibodies were originally isolated from a human HIV patient. The antibodies specifically recognize and bind an HIV surface protein called gp41. The virus uses gp41 like a long spike to poke holes in its host’s immune cells. But when 4E10 antibodies clog up gp41, the virus is neutralized and host cells are protected.

4E10 especially interests HIV researchers because the antibody recognizes and binds to gp41 on the surface of many different strains of the virus, not just the one strain with which the patient was most recently infected. If a vaccine could be made to specifically and safely stimulate 4E10-like production, recipients would likely be protected against multiple HIV strains.

In humans, HIV slowly destroys the immune system, leading to Acquired Immune Deficiency Syndrome (AIDS). According to the Centers for Disease Control and Prevention, more than 1.1 million people in the U.S. are living with HIV infection. While treatments developed in the past decade can keep the virus in check for many years, there is no vaccine and there is no cure.

Proceeding with Caution

In several ongoing studies, the TSRI team and others are working out how to make a vaccine that stimulates the production of 4E10, b12 and other broadly neutralizing anti-HIV antibodies. However, this latest study indicates that this approach might be complicated by unwanted self-reactivity. Antibodies that cross-react with host tissue—like 4E10 has now been shown to do—are associated with autoimmune diseases such as multiple sclerosis and lupus.

The TSRI study also raises the question of how 4E10 was generated in the first place. According to Nemazee, 4E10 may be a fluke, cropping up in an HIV patient who was also prone to autoimmune
diseases. Alternatively, the autoreactive antibody could have arisen in the patient as a consequence of the disease—perhaps the body’s normal mechanism for weeding out such antibodies failed, allowing the serendipitous production of an anti-HIV antibody.

Despite this new concern, there is still hope for 4E10’s role in HIV vaccine development. A companion paper published in the same issue of *The Journal of Immunology* (http://www.jimmunol.org/content/191/6/3179.long) found that another potent, broadly neutralizing anti-HIV antibody, b12, was not self-reactive and could respond to a candidate vaccine preparation provided by Richard Wyatt, TSRI Professor of Immunology and Director of Viral Immunology at the International AIDS Vaccine Initiative Neutralizing Antibody Center.

“It’s still possible that we could safely elicit the 4E10-like antibody in order to protect against HIV,” Nemazee said. “We just have to think about how to generate the best antibodies without causing other problems. We have a lot of questions. And now we have a good model to help us answer them.”

For more information on the paper, see http://www.jimmunol.org/content/191/6/3186.abstract

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**Coma: Researchers Observe Never-Before-Detected Brain Activity**

Sep. 18, 2013 — Researchers from the University of Montreal and their colleagues have found brain activity beyond a flat line EEG, which they have called Nu-complexes (from the Greek letter n). According to existing scientific data, researchers and doctors had established that beyond the so-called "flat line" (flat electroencephalogram or EEG), there is nothing at all, no brain activity, no possibility of life. This major discovery suggests that there is a whole new frontier in animal and human brain functioning.

The researchers observed a human patient in an extreme deep hypoxic coma under powerful anti-epileptic medication that he had been required to take due to his health issues. "Dr. Bogdan Florea from Romania contacted our research team because he had observed unexplainable phenomena on the EEG of
a coma patient. We realized that there was cerebral activity, unknown until now, in the patient's brain," says Dr. Florin Amzica, director of the study and professor at the University of Montreal's School of Dentistry.

Dr. Amzica's team then decided to recreate the patient's state in cats, the standard animal model for neurological studies. Using the anesthetic isoflurane, they placed the cats in an extremely deep—but completely reversible—coma. The cats passed the flat (isoelectric) EEG line, which is associated with silence in the cortex (the governing part of the brain). The team observed cerebral activity in 100% of the cats in deep coma, in the form of oscillations generated in the hippocampus, the part of the brain responsible for memory and learning processes. These oscillations, unknown until now, were transmitted to the master part of the brain, the cortex. The researchers concluded that the observed EEG waves, or Nu-complexes, were the same as those observed in the human patient.

Dr. Amzica stresses the importance of understanding the implications of these findings. "Those who have decided to or have to 'unplug' a near-brain-dead relative needn't worry or doubt their doctor. The current criteria for diagnosing brain death are extremely stringent. Our finding may perhaps in the long term lead to a redefinition of the criteria, but we are far from that. Moreover, this is not the most important or useful aspect of our study," Dr. Amzica said.

From Nu-complexes to therapeutic comas
The most useful aspect of this finding is the therapeutic potential, the neuroprotection, of the extreme deep coma. After a major injury, some patients are in such serious condition that doctors deliberately place them in an artificial coma to protect their body and brain so they can recover. But Dr. Amzica believes that the extreme deep coma experimented on the cats may be more protective.

"Indeed, an organ or muscle that remains inactive for a long time eventually atrophies. It is plausible that the same applies to a brain kept for an extended period in a state corresponding to a flat EEG," says Professor Amzica. "An inactive brain coming out of a prolonged coma may be in worse shape than a brain that has had minimal activity. Research on the effects of extreme deep coma during which the hippocampus is active, through Nu-complexes, is absolutely vital for the benefit of patients."

"Another implication of this finding is that we now have evidence that the brain is able to survive a an extremely deep coma if the integrity of the nervous structures is preserved," said lead author of the study, Daniel Kroeger. "We also found that the hippocampus can send 'orders' to the brain’s commander in chief, the cortex. Finally, the possibility of studying the learning and memory processes of the hippocampus during a state of coma will help further understanding of them. In short, all sorts of avenues for basic research are now open to us."

Journal Reference:

Getting Rid of Unwanted Visitors
Sep. 20, 2013 — Gut-dwelling bacteria are attracting increasing attention, particularly those associated with human diseases. Helicobacter pylori is found in the stomach of humans, where it may cause chronic gastritis and gastric ulcers, although the majority of infections are asymptomatic. The bacterium has been associated with man since over 100,000 years ago, when it first infected San hunter-gatherers. An international consortium coordinated by Yoshan Moodley at the University of Veterinary Medicine, Vienna (Vetmeduni) has discovered that the Baka pygmies of Cameroon, another community of hunter-gatherers, have a surprisingly low rate of Helicobacter infection. The findings are reported in the online journal PLOS Genetics and cause us to question how the bacteria are maintained in human populations.

The digestive systems of all animals contain a large number of different bacteria. Humans are no exception and our intestines provide warmth, shelter and food to a vast range of unicellular organisms, many of which are either beneficial to their hosts or at least cause no ill effects other than consuming some of the food we ingest. However, several species have been associated with disease. Among them is Helicobacter pylori, which may play a part in causing chronic gastritis and gastric ulcers.

An ancient colonizer recently discovered
Helicobacter pylori was only discovered about thirty years ago. Subsequent investigations have shown that it originated in Africa and has been associated with humans for at least 100,000 years. The first humans to be infected with the bacterium were San hunter-gatherers in southern Africa and the infection spread to Europe and Asia when humans left Africa and migrated north and east. Eventually, colonization of Australia and the Americas brought Helicobacter pylori into these continents. The bacterium is now
found in about 50% of humans worldwide, making it the most widespread and prevalent infection in our species.

In view of the ancient nature of the association between Helicobacter pylori and man, it seems likely that the stomachs of other hunter-gatherer communities might also contain longstanding and distinct populations of the bacterium. This assumption has now been tested—and shown to be incorrect—by an international consortium coordinated by Yoshan Moodley of the Vetmeduni’s Department of Integrative Biology.

**Baka pygmies show a low incidence of Helicobacter infection**

Gastric biopsies were taken from Baka pygmies and neighbouring agricultural communities in south-eastern Cameroon and sent to the Hannover Medical School in Germany for sequencing. The researchers found the expected high prevalence (over 80%) of Helicobacter pylori in the guts of non-Baka individuals, although only about 20% of the hunter-gatherer Baka pygmies were infected with the bacterium. Furthermore, the scientists were unable to detect any strains of Helicobacter pylori specific to the pygmies: the bacteria instead appeared to come from groups associated with Nilo-Saharan populations or with a new subpopulation that seemed to relate to the expansion of Bantu-speaking tribes.

**Bacteria are lost from small populations**

Valeria Montano in Moodley’s lab in Vienna used a population demographic model to estimate the age of association between Baka and non-Baka Helicobacter populations, which she found to be as recent as two to four thousand years. Further simulations suggested that the pygmies could easily "lose" the bacterium from their guts because of the small population size of the Baka tribe, possibly combined with the relatively low life expectancy of individual tribe members. The Helicobacter now infecting Baka pygmies are thus not the descendants of an ancient bacterial population but instead come from repeated re-infections from the pygmies’ non-Baka neighbours over the last few thousand years.

Moodley is naturally excited by the findings. "We had expected to find an ancient lineage of bacteria in the pygmies but instead showed that certain demographic factors such as small population size and unusually low life expectancy could lead to the natural eradication of the bacteria from human populations."

**Journal Reference:**


**Switching from Atripla to Eviplera reduces central nervous system side-effects**

Liz Highleyman

Published: 23 September 2013

People who switched single-tablet regimens from Atripla (efavirenz/tenofovir/emtricitabine) to Eviplera (rilpivirine/tenofovir/emtricitabine) maintained viral suppression and saw improvement in central nervous system (CNS) side-effects such as abnormal dreams and depression, according to a late-breaking poster presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) this month in Denver. Two other studies looked at the safety and efficacy of Eviplera amongst women and black patients.

Atripla, a recommended first-line regimen in European and US antiretroviral treatment guidelines, is widely used, highly effective, convenient and generally considered safe and well tolerated. But many people taking efavirenz – an ingredient in the all-in-one pill – experience neuropsychiatric symptoms that may include insomnia, vivid dreams or nightmares, and depression or anxiety.

Mark Nelson from the Chelsea and Westminster Hospital in London and colleagues evaluated outcomes amongst people with HIV who switched from Atripla to Eviplera, a similar once-daily single-tablet coformulation that substitutes a newer NNRTI, rilpivirine (sold separately as Edurant), for efavirenz. Eviplera is a recommended regimen in European guidelines and an 'alternative' in US guidelines.

This phase 4 multicentre pilot study enrolled 40 people taking Atripla who had fully suppressed viral load but continued to be bothered by efavirenz-associated CNS side-effects after at least 12 weeks on treatment. All but four were men, the average age was 47 years and the median baseline CD4 T-cell count was high at 640 cells/mm³. They had been on efavirenz-based ART for a median of 40 months (range 4 to 165 months).
The researchers assessed CNS toxicity at four and twelve weeks after the switch using ACTG adverse event scores and a 19-item sleep questionnaire, with scores converted to percentages. The CNS adverse events questionnaire asked about 10 symptoms – dizziness, depression, insomnia, anxiety or nervousness, confusion, impaired concentration, headache, somnolence or drowsiness, aggressive mood and abnormal dreams – each rated as absent, mild, moderate or severe.

The total CNS side-effects score declined significantly by four weeks after switching from Atripla to Eviplera, falling from a median of 40 to 12, with lower scores indicating fewer symptoms. By week 12 the median score rose somewhat, to 20, but was still a significant improvement over baseline.

Scores for each individual symptom, except for headache, also showed significant improvement. The largest declines in the proportion of people experiencing moderate to severe (grade 2 to 4) symptoms were seen for abnormal dreams (about 75% at baseline to 10% at week 4), insomnia (60 to 20%), depression (just over 50% to just over 10%), somnolence (50% to about 12%) and impaired concentration (about 48% to under 10%). A few symptoms rebounded by more than 10% from week 4 to 12, but dizziness, aggressive mood and headache continued to decrease, whilst insomnia, confusion, somnolence and abnormal dreams remained fairly stable.

Total sleep scores also decreased significantly, from a median of 30 at baseline to 19 at week 4, and continued to fall to 16 at week 12, with lower scores again indicating improvement.

All participants maintained viral suppression after switching to Eviplera. The median CD4 count fell to 584 cells/mm\(^3\) at week 12, but this was not a statistically significant change. Blood lipids improved by week 12 after the switch, including significant declines in total cholesterol (-0.6mmol/l), LDL ('bad') cholesterol (-0.49mmol/l) and triglycerides (-0.28mmol/l).

"Switching Atripla to Eviplera led to significant improvement" in CNS adverse events and sleep questionnaire scores with maintenance of virological suppression, the researchers concluded. "Identification of individuals with efavirenz toxicity is essential as alternative agents lead to improvements in toxicity profile and quality of life."

**Eviplera in women**

The open-label STaR trial compared the Eviplera and Atripla coformulations in people starting ART for the first time. Unlike the earlier ECHO and THRIVE trials, which compared the same drug combinations taken as separate pills plus placebos, both STaR arms took one pill once daily.

Researchers performed a sub-analysis of 56 women in the study, largely from the US south, who made up 7% of the total patient population (n=786). About two-thirds were white, one-quarter were black, the median age was 36 years and the mean baseline CD4 count was approximately 390 cells/mm\(^3\).

Overall, both single-tablet regimens produced good viral suppression at 48 weeks, with 86% in the Eviplera arm and 82% in the Atripla arm achieving undetectable viral load (<50 copies/ml) in a 'snapshot' analysis, showing that Eviplera was non-inferior to Atripla.

Response rates were a bit lower for women in both arms and the difference between the regimens was greater, 79 vs 61% respectively. The difference was attributable to a lower rate of virological failure (7% vs 14%), less missing data and fewer early discontinuations due to adverse events (7 vs 11%) amongst women taking Eviplera.

Women in the Eviplera arm reported fewer CNS side-effects (29 vs 36%), fewer psychiatric symptoms (7 vs 14%) and less skin rash (4 vs 25%) compared with Atripla recipients. Eviplera was associated with smaller increases in total and LDL cholesterol, but also HDL ('good') cholesterol.

"[Eviplera] has a better safety profile than [Atripla] in the female subpopulation," the researchers concluded, but added that the statistical power of this analysis was limited by the small number of women in each arm.

**Switch from protease inhibitor**

Finally, the open-label phase 3 SPIRIT study looked at outcomes amongst people with suppressed viral load on their first or second regimen who switched from a boosted protease inhibitor plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) to Eviplera.

At baseline about one-third each were taking atazanavir (Reyataz) and lopinavir/ritonavir (Kaletra) whilst one-fifth were on darunavir (Prezista); most also used tenofovir/emtricitabine (Truvada). Participants were randomly assigned to switch to Eviplera either immediately or after six months.

The study included a total of 476 participants in the US. Nearly 90% were men, about three-quarters were white, the median age was just over 40 years and the mean CD4 count approached 600 cells/mm\(^3\).

The researchers also did a sub-analysis of 83 black/African-American patients

Overall, Eviplera was again shown to be non-inferior, with 94% of participants who switched right away and 90% who stayed on a protease inhibitor regimen maintaining undetectable HIV RNA (<50
alleles in gene expression. 

The researchers say in Sub-Saharan Africa around two-thirds of schistosomiasis — a neglected tropical disease transmitted by flatworm in dirty water — occur because of genital and urinary tract infections caused by Schistosoma haematobium.

Women with genital schistosomiasis are three to four times more likely than those without the disease to have HIV, according to the researchers.

"We used cross-sectional and clinical data from Zimbabwe together with mathematical models to predict over a ten-year period the potential economic and health benefits of mass administration of praziquantel in school-age children for reducing HIV transmissions in women," says Martial Mbah, the study's lead author and a public health expert at Yale University in the United States.

The study, published in PLoS Neglected Tropical Diseases last month (1 August), says that the intervention could save up to US$100 million in HIV/AIDS healthcare costs in that country in ten years.

It also shows that if the drug is assumed to be 30 per cent effective, then giving it yearly can prevent 41,500 HIV cases in women over ten years but if it is assumed to be 70 per cent effective, almost 97,000 HIV cases could be prevented over the same duration.

Mbah tells SciDev.Net that because genital schistosomiasis is very common among African girls and women the results of this study can be applied to other countries where S. haematobium and HIV are prevalent.

He adds that given the economic challenges faced by many African countries, for instance, Zimbabwe, major initiatives committed to HIV/AIDS prevention in Africa such as the US President’s Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, TB and Malaria should embrace mass administration of the drug and support its expansion throughout the affected areas across Africa.

But an HIV/AIDS expert and a former executive director of Family AIDS Caring Trust in Zimbabwe, Jephias Mundondo, says that the research does not address the ethical and human rights issues surrounding the mass drug administration. He adds that there is a saving money motive and everything else is forgotten.

"While the idea is economically sound, the challenge lies in its ethicality and the acceptability of [mass application],“ he says.

Link to full paper in PLoS Neglected Tropical Diseases

This article has been produced by SciDev.Net’s Sub-Saharan Africa desk.

References
UNAIDS reports a 52% reduction in new HIV infections among children and a combined 33% reduction among adults and children since 2001

World closing in on Millennium Development Goal 6, globally the AIDS epidemic has been halted and reversed—race is on to reach universal access to HIV treatment.

GENEVA, 23 September 2013—As world leaders prepare to meet at the United Nations General Assembly to review progress towards the Millennium Development Goals—a new report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) shows dramatic acceleration towards reaching 2015 global targets on HIV.

New HIV infections among adults and children were estimated at 2.3 million in 2012, a 33% reduction since 2001. New HIV infections among children have been reduced to 260,000 in 2012, a reduction of 52% since 2001. AIDS-related deaths have also dropped by 30% since the peak in 2005 as access to antiretroviral treatment expands.

By the end of 2012, some 9.7 million people in low- and middle-income countries were accessing antiretroviral therapy, an increase of nearly 20% in just one year. In 2011, UN Member States agreed to a 2015 target of reaching 15 million people with HIV treatment. However, as countries scaled up their treatment coverage and as new evidence emerged showing the HIV prevention benefits of antiretroviral therapy, the World Health Organization set new HIV treatment guidelines, expanding the total number of people estimated to be in need of treatment by more than 10 million.

“Not only can we meet the 2015 target of 15 million people on HIV treatment—we must also go beyond and have the vision and commitment to ensure no one is left behind,” said Michel Sidibé, Executive Director of UNAIDS.

Significant results have also been achieved towards meeting the needs of tuberculosis (TB) patients living with HIV, as TB-related deaths among people living with HIV have declined by 36% since 2004.

Despite a flattening in donor funding for HIV, which has remained around the same as 2008 levels, domestic spending on HIV has increased, accounting for 53% of global HIV resources in 2012. The total global resources available for HIV in 2012 was estimated at US$ 18.9 billion, US$ 3-5 billion short of the US$ 22-24 billion estimated to be needed annually by 2015.

As well as outlining new global HIV estimates, the 2013 UNAIDS Report on the global AIDS epidemic reviews progress on ten specific targets which were set by United Nations Member States in the 2011 UN Political Declaration on HIV and AIDS.

The report finds that progress has been slow in ensuring the respect of human rights, securing access to HIV services for people most at risk of HIV infection, particularly people who use drugs, and in preventing violence against women and girls—a key factor in vulnerability to HIV. Gender inequality, punitive laws and discriminatory actions are continuing to hamper national responses to HIV and concerted efforts are needed to address these persistent obstacles to the scale up of HIV services for people most in need.

The 2013 UNAIDS Report on the global AIDS epidemic is available online at unaids.org

In 2012, an estimated:

- 35.3 million [32.2 million – 38.8 million] people globally were living with HIV
- 2.3 million [1.9 million – 2.7 million] people became newly infected with HIV
- 1.6 million [1.4 million – 1.9 million] people died from AIDS-related illnesses

Seven ways to speed up the HIV treatment pipeline

Monday, 23 September 2013

John McCullagh interviews long-time HIV activist Mark Harrington about getting the best HIV treatments to as many people as quickly as possible.

Those who saw the documentary How to Survive a Plague (reviewed by PositiveLite.com) may remember Mark Harrington, one of the young activists who founded the Treatment Action Group (TAG), whose efforts accelerated the discovery and licencing of protease inhibitors, the anti-retroviral...
drugs that, in 1996, changed the face of HIV from a virtual death sentence into a chronic, manageable disease.

This month, an older Mark Harrington, now the executive director of TAG, which is still fighting for better treatment of HIV, a vaccine and a cure, was in Toronto to give the keynote speech to the first national conference of the Canadian Treatment Action Council (CTAC). The subject of his address was the recently released report Seven Ways to Speed up the Pipeline. I spoke to him just before his presentation to delegates at the CTAC conference.

**John McCullagh:** Mark Harrington, welcome to Toronto. You’re in town today to give the keynote address at the CTAC conference on the report authored by you and others about Seven Ways to speed up the Pipeline. Before we talk about that report, perhaps you’d tell me about the Treatment Action Group.

**Mark Harrington:** TAG is a community-based organization that’s now in its 22nd year. We were founded in 1992 by alumni from ACT UP New York who worked in the treatment and data groups there. Our focus at TAG has always been on indigenous research and expediting access to the best quality treatments for HIV infection. More recently we’ve also been addressing tuberculosis (TB) and hepatitis C co-infection because they are the leading killers of people with HIV, besides being huge public health issues on their own. And in various ways they are lagging behind the HIV response even though both of them are curable.

**So what’s the pipeline?**
The HIV treatment pipeline is a way of describing adult and paediatric antiretroviral therapy development and dose-optimization research as well as alternative prevention technologies, research towards a cure, and immune-based and gene therapies. We look at what’s in development like new diagnostic tests, a drug or a vaccine. In the old days we used to look at the pipeline from Phase II to approval...

**Phase II is?**
When something is in clinical trials it usually goes through stages known as phases. Short, early studies are known as Phase II and then, later, more broader trials are conducted which prove that they either work or not. That’s Phase III, which leads to approval or rejection.

In the U.S., we’ve traditionally looked at trials from Phase II to approval and what happened recently was that, working with our colleagues in the UK at HIV i-Base, we worked on a report that addressed the time that it takes to go from discovery of a potential new drug to when it reaches the patient, no matter where they live, not just in developed countries like the U.S. and Canada but anywhere in the world. That meant broadening our perspective on the development pipeline to include regulation in developing countries, normative guidance from organizations like the World Health Organization and the work of generic drug manufacturers.

Basically, if our goal is to get the best treatments to as many people as quickly as possible, and it is, we need to think about all the institutions that need to be addressed, and not just the ones in the rich world.

**What are the barriers to getting the best treatments to as many people as quickly as possible?**
There are multiple barriers but the three biggest ones that we see right now are the regulatory capacity in developing countries, which is very mixed and often very poor, so they lack the ability to quickly evaluate new drugs and new combinations. This means that the time lag between the approval of a new drug, say in the U.S., compared to, for example, South Africa, which has the biggest epidemic in the world, is about four years. And not all the drugs that are available in the States and other rich countries are available in developing countries like South Africa.

A second major barrier is around so-called incestuous combinations of HIV drugs made by pharmaceutical companies. In other words, combinations of drugs only among those of which a particular company may own the intellectual property as opposed to drugs from two or more companies that would provide a more effective combination. And probably the worst offender these days is Gilead Sciences, which has tried to co-package some of it’s new HIV drugs and Hep C drugs from their own company, which may not be the best combination.

And the third piece is that in rich countries in the current decade we’ll see a wave of drugs coming off patent which can then be manufactured by generic drug manufacturers. Governments will need the political will to commission the best combinations of drugs that will not only meet the needs of their populations but that could also end up saving billions of dollars if it’s done correctly.

**So I’m assuming that the recommendations to address these and other barriers contained in your report Seven Ways to Speed up the Pipeline are focused at governments and other decision makers?**
Yes. What we tried to do was to break down the seven barriers into areas that needed a lot of sustained attention versus ones that were going okay. For example, one area that’s going okay is the discovery of new drugs for HIV and Hep C (although it’s not going so well for TB as there’s not enough money being invested by industry because most of the cases of TB are in the global South).

Most of the issues we’ve focused on in the report look at those issues that could be moved on quickly, for example improving regulatory capacity in developing countries and addressing the public health needs of people by getting them the best combinations of drugs regardless of who the manufacturers are. Those issues could be solved by government action.

**So how optimistic are you that your recommendations will be heard and met?**

Well, if we’re too optimistic we won’t be fighting hard enough to get the changes that we need to get through. It’s a tough set of problems. We’re dealing with over 100 countries that don’t have sufficient regulatory capacity to deal with their own epidemics. In India, for example, the whole drug development scene is paralyzed by bureaucratic infighting between different agencies and the government, allegedly over alleged ethical infractions. But it’s not clear to me that that’s really what’s happening. Rather, I think, it’s just wrestling between various groups of government bureaucrats. And indeed, there is a freeze on all new clinical trials in India right now, not just for HIV or TB but for all conditions. These kind of bureaucratic roadblocks need to be removed if progress is to be continued to be made.

**For those interested in knowing more, where can they read the report Seven Ways to Speed up the Pipeline?**

They can go to [www.pipelinereport.org](http://www.pipelinereport.org) where the full report is available to read online or can be downloaded.

Thank you so much, Mark, for taking the time to talk with PositiveLite.com and for the work TAG is doing on behalf of those of us living with HIV and other related conditions.

This interview has been edited for clarity.

**Maine Confronts Aging Population with HIV/AIDS**

*Seacoastonline*, (09.22.2013)  By Shelby Carignan

The US Senate Aging Committee heard testimony on September 18, the sixth annual National HIV/AIDS and Aging Awareness Day, from five witnesses testifying about the challenges facing aging HIV-infected people. Witnesses noted that states with large aging HIV-infected populations experienced greater impact than other states. According to Kenneth Miller, executive director of Maine’s Down East AIDS Network, older HIV-infected people who lived in rural areas faced complicated health issues, including lack of access to medical care and mental health treatment.

Miller stated that older, rural patients also isolated themselves because of stigma against those who were gay and had HIV. Other difficulties specific to rural HIV-infected people included transportation to physician’s appointments and lack of access to social support networks. Miller recommended ways to improve the system of care, including awareness and outreach. He advised that this population was vulnerable to depression and might not have access to mental health screening and care.

Although treatment advances had extended life expectancy for HIV patients, Sen. Susan Collins (R-Maine) cautioned older Americans not to stereotype HIV as a young person’s disease. Older Americans also were vulnerable to HIV and should “exercise the same kind of care” if they were engaging in high-risk behaviors.

**An AIDS Cure in Two Years? Prostratin Could Make It Possible**

*Healthline*, (09.09.2013)  By David Heitz

Scientists researching a cure for HIV have projected that a cure could be available in 18 to 24 months. The researchers were working on two natural compounds—prostratin and bryostatin—that they reproduced in the laboratory for medical purposes. Prostratin comes from the bark of the Samoan mamala tree. Paul Cox, an ethnobotanist and director of the Institute of Ethnomedicine in Wyoming, heard of the bark from a Samoan healer. Paul Wender, a chemist from California’s Stanford University, found in experiments with prostratin that it flushed out the virus from cells where it was hiding. Drugs are able to kill the virus when it is in the open, but not when it is hiding in cells. When patients stopped taking their medication, the virus resurfaced and quickly multiplied.

Wender was able to recreate the drug and design new variants and has made it 100 times more powerful than that obtained from the tree. The AIDS Research Alliance (ARA), a Los Angeles nonprofit dedicated to finding a cure for AIDS, is developing prostratin. Dr. Stephen Brown, medical director of
ARA, stated that the organization was two thirds of the way through necessary experiments before the drug would be ready for market. Researchers had performed initial tests on animals and now were conducting tests on blood from AIDS patients who had been on immunosuppressive therapy.

Bryostatin, a compound that comes from a sea creature called bryozoa, also has healing qualities. It was discovered by Robert Pettit, a University of Arizona chemistry professor. Wender created bryostatin variants 1,000 times more powerful at flushing HIV from cells than prostratin. However, additional work is necessary before it could be considered a successful drug candidate.

**Scientists discover possible way to turn fungus from foe to friend**

*Study shows how deadly Candida albicans might be rendered harmless*

*Candida albicans* is a double agent: In most of us, it lives peacefully, but for people whose immune systems are compromised by HIV or other severe illnesses, it is frequently deadly. Now a new study from Johns Hopkins and Harvard Medical School shows how targeting a specific fungal component might turn the fungus from a lion back into a kitten. Study results were reported this month in *The Journal of Biological Chemistry*.

"Treatment options for systemic *Candida* infections are limited, and a major difficulty in finding new drug targets is that fungi are closely related to us, so we risk hurting the patient as much as the pathogen," says Rajini Rao, Ph.D., a professor of physiology in the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine. "What we've identified is a function that is critical for virulence. If we could block this through medication, it would leave both the fungus and the host healthy while taking away *Candida*’s ability to harm." *Candida* lives in the guts of most people as one of many so-called "commensal microbes" — that is, harmlessly. It can sometimes cause local infections of the mouth or genitals, known as thrush, that are treatable with over-the-counter antifungals. But given the opportunity to breach our defenses, *Candida* can cross into the bloodstream and switch from peaceful coexistence to attack mode, producing long filaments that dig into tissues and destroy them.

Unfortunately, Rao says, "there are only a few antifungal drugs, so it's particularly dangerous when drug resistance develops in *Candida." For that reason, she says, "we're always looking for new chinks in its armor."

In her study, Rao and her collaborators looked for such a new chink in a part of *Candida*'s cells known as the vacuole. The vacuole's main function is as a recycling center that chews up cellular waste, so it was a surprise when a previous study from her group found that a well-known antifungal drug prevented the vacuole from becoming acidic. This led them to suspect that acidification of the vacuole was important for virulence. The research team focused on V-ATPase, the enzyme responsible for making many compartments of the cell, including the vacuoles, acidic. Because humans have a very similar enzyme, the scientists weren't looking to eliminate it altogether — "that would have been like taking a sledgehammer to cells," Rao explains. Rather, they homed in on just one of the enzyme's components, known as subunit a. Like many proteins in fungi and higher animals, there is more than one version of subunit a, which come from different genes — a duplication that gives the organism a backup in case a mutation disables one of the genes.

Rao said first they altered *Candida* cells so that they could only use one or the other version of the subunit a gene. As expected, they found that inactivating either one had no effect because the other compensates in every function — except one. It turned out that acidification of the vacuole exclusively depended on one version of the gene. This allowed them to test the importance of the vacuole's acidity on...
virulence, separate from the many other functions of the V-ATPase. Unable to acidify the vacuole, the fungus could no longer form the tentacle-like filaments that characterize its deadly form. When the researchers injected healthy Candida into the bloodstream of mice, nearly all died within a week. In contrast, mice injected with the strain of fungus that was unable to acidify the vacuole remained healthy and survived.

Rao says that this study reveals a vulnerability that could be exploited using drugs known to alter the pH of the vacuole, rendering Candida harmless while potentially posing little risk to infected patients. For example, previous studies from her lab showed that a drug already in use to treat a heart condition known as arrhythmia had the unexpected effect of blocking acidification of the fungal vacuole. The next step, she says, would be to screen drugs already approved by the U. S. Food and Drug Administration to increase the repertoire of antifungal agents to combat deadly fungal infections.

Cancer-Killing Cells Controlled by Epigenetic Process
Sep. 23, 2013 — Natural killer (NK) cells in the human body can kill and contain viruses and cancerous tumors, and a new study from the University of Southern California (USC) describes for the first time how those cells can be manipulated by epigenetics. The discovery, detailed in the Proceedings of the National Academy of Sciences, paves the way for developing more effective cancer drugs.

"Natural killer cells are very attractive targets for immunotherapy because they are able to kill tumor cells," said Si-Yi Chen, M.D., Ph.D., a faculty member of the USC Norris Comprehensive Cancer Center and senior author of the study. "While scientists all around the world are working on developing new drugs using NK cells, none of the drugs in development focuses on epigenetic regulation of the cells. Our study describes how an epigenetic process involving the enzyme MYSM1 plays a critical role in the development of natural killer cells."

Epigenetics involve biochemical changes in the body that directly affect DNA, turning some genes on and turning others off. MYSM1 is an enzyme in the body's immune system that turns genes on and off by modifying proteins called histones embedded in DNA.

Through a series of experiments in mice, Chen and his colleagues demonstrate that MYSM1 is required for natural killer cells to mature and function properly.

"We found that MYSM1 creates access to proteins that enhance gene transcription and, ultimately, the maturation of natural killer cells themselves," said Vijayalakshmi Nandakumar, a Ph.D. student at the Keck School of Medicine of USC and the study's first author. "To date, there are no elaborate reports linking an epigenetic phenomenon to natural killer cell development. More importantly, unlike conventional therapies, NK cell-based therapies have shown to be more effective against metastasis. We believe cancer drugs targeting this pathway could be a viable option for future immunotherapies."

Journal Reference:

Sep 25, 2013
PATH Evaluates Janssen’s Rilpivirine as HIV Infection Prophylactic
Janssen R&D Ireland has signed a license agreement with PATH to develop an injectable form of rilpivirine as a potential pre-exposure prophylaxis (PrEP) against HIV infection. It is believed that a long-acting injectable formulation of rilpivirine could address one of the primary challenges in HIV prevention—patient adherence to treatment.

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor. Currently, it is commercialized by Janssen for the oral, once daily treatment of HIV-1, in combination with other antiretroviral agents (ARVs), in ARV treatment-naïve adults, and in most countries, in patients with a viral load less than or equal to 100,000 HIV-1RNA copies/mL.

Under the agreement, PATH intends to conduct prophylaxis clinical trials in collaboration with its partners, the HIV Prevention Trials Network and the Division of AIDS at the NIH. Following the completion of the Phase II program, anticipated to begin in 2014, PATH and Janssen will evaluate entering into a late-stage development agreement covering the use of rilpivirine as PrEP for uninfected individuals at high risk of acquiring HIV.

Janssen Therapeutics, partner of Janssen R&D, currently markets three antiretroviral HIV medications. This license agreement with PATH does not impact the commercialization of rilpivirine by Janssen, and does not impact the use of rilpivirine in combination treatments, according to the company.
HPV type 39 linked to anal dysplasia, better screening needed for HIV+ men and women

Liz Highleyman
Published: 25 September 2013

About two-thirds of gay men and one-fifth of women tested in Spain were found to have cell or tissue abnormalities that could progress to anal cancer, and both groups could benefit from more widespread and accurate testing, researchers reported at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) last week in Denver. The men's study found that human papillomavirus (HPV) type 39 was a key risk factor.

HPV can trigger abnormal cell growth ranging from warts to cancer. Certain high-risk or oncogenic types including HPV 16 and HPV 18 cause anal, cervical, and other genital cancers. These typically begin as low-grade dysplasia (also known as squamous intraepithelial lesions or intraepithelial neoplasia) and can progress to high-grade lesions and carcinoma if left untreated. Low-risk types including HPV 6 and HPV 11 cause genital warts. However, high-risk types do not always cause dysplasia, low-grade neoplasia does always progress to high-grade lesions or cancer and lesions may regress on their own without treatment.

Anal cancer is more common amongst people with HIV than it is in the general population, and is especially high amongst men who have sex with men (MSM). Although cervical cancer is considered an AIDS-defining malignancy, anal cancer is not so classified. Regular cervical cytology (often referred to as Pap or smear tests) is recommended for both HIV-positive and HIV-negative women to catch abnormalities at an early stage, but clinical practices for screening, preventing and treating anal cancer vary widely.

Carmen Hidalgo from Hospital Universitario Virgen de las Nieves in Granada, Spain, and colleagues reported findings from studies looking at HPV infection, anal dysplasia, and predictive factors in men and women with HIV.

Men who have sex with men

The men's study, presented at an oral session, looked at prevalence of and risk factors for high-grade or stage 2 to 3 anal intraepithelial neoplasia (AIN) or anal cancer (carcinoma in situ) among HIV-positive MSM.

The researchers assessed the accuracy of HPV PCR testing for more than a dozen high- and low-risk types, cytology (testing for cell abnormalities, as done with a Pap smear) and anoscopy (examination of anal-rectal tissue with a magnifying device). They also compared anoscope-guided cytology vs cytology samples taken with swab.

The analysis included 103 participants in a prospective cohort study that screened HIV-positive MSM for anal dysplasia from April 2010 through to September 2012 using all three methods.

The average age was 36 years and the mean and nadir (lowest-ever) CD4 T-cell counts were 645 and 387 cells/mm³, respectively, indicating well-preserved immune function. Most (85%) used antiretroviral therapy (ART). Half were smokers – a known risk factors for HPV-related cancer – and about 40% had anal warts. All the men reported anal sex, they had a median of 1.5 sexual partners during the study, and 70% said they used condoms.

Overall, the researchers found that one-third to one-half of the men had low-grade squamous intraepithelial lesions (LSIL) or stage 1 AIN, and around 5 to 10% had high-grade squamous intraepithelial lesions (HSIL) or stage 2 to 3 AIN, depending on the method used:

**Anal cytology using swab:**
- LSIL: 53%
- HSIL: 5%
- Atypical squamous cells of undetermined significance (ASCUS): 5%
- Normal: 33%

**Anoscopy:**
- AIN 1: 44%
- AIN 2-3: 10%
- Carcinoma in situ: 11%
- Normal: 36%
Cytology with anoscope:
- LSIL: 36%
- HSIL: 7%
- ASCUS: 6%
- Normal: 50%

In a univariate analysis looking at separate risk factors, older age and infection with HPV types 6, 39 or 42 predicted high-grade AIN or anal cancer. However, in a multivariate analysis HPV 36 was the only independent risk factor to reach statistical significance, conferring more than a ten-fold higher risk (odds ratio 10.51; p=0.04). Neither smoking nor CD4 count were associated with greater risk in this study, in which CD4 cells were uniformly high.

For each testing method, the researchers calculated sensitivity (ability to detect true cases), specificity (ability to rule out if not present), positive predictive value (PPV, or proportion of correct positive diagnoses) and negative predictive value (NPV, or proportion of correct negative diagnoses):
- Anal swab cytology: 94%, 42%, 31% and 97%, respectively.
- Cytology with anoscope: 90%, 61%, 40% and 96%, respectively.
- High-risk HPV testing: 83%, 15%, 24% and 77%, respectively.
- Anal swab cytology and high-risk HPV: 79%, 41%, 28% and 88%, respectively.
- Anal swab cytology and/or high-risk HPV: 100%, 15%, 24% and 100% NVP.

"In our HIV-positive MSM cohort, the association of the oncogenic HPV genotype 39 with other [high risk] HPV genotypes was the main risk factor associated with high-grade AIN and/or carcinoma in situ," the researchers concluded.

With regard to testing methods, "anoscopy-guided cytology does not improve the diagnosis of the dysplastic lesions, and for this reason, we do not think that it should be included in the screening protocol."

HIV-positive MSM "should be systematically tested for dysplastic lesions with anal cytology and HPV PCR," they summarised.

If cytology is abnormal, irrespective of the grade of dysplasia, histologic evaluation of the lesion should be performed using anoscopy, they added. But if cytology is normal, HPV PCR screening should be done, and if high-risk HPV is found, the patient should also be referred for anoscopy.

Asked if anal screening could be done less often after a series of negative tests (as is the case for HIV-negative women undergoing cervical screening), Hidalgo Tenorio said she recommends ongoing screening every year for this population.

Session moderator Judith Aberg asked about the unexpectedly high rate of HPV 39, speculating whether vaccination against HPV types 16 and 18 might allow other types to take over as major causes of cancer. Hidalgo Tenorio did not have an answer, but to date HPV vaccines have mostly been given to young women, and more recently young men, so coverage is likely still low in this population of MSM. She noted that new vaccines are under study that will protect against more HPV types.

Women with HIV
Hidalgo Tenorio's team also presented a poster looking at the prevalence of and risk factors for anal dysplasia among a cohort of women in southern Spain, comparing rates to those of men who have sex with men.

While cervical abnormalities are a known risk for women with HIV, anal dysplasia may be equally or more common but is not regularly screened for. The researchers noted that HIV-positive women have a 14-fold higher risk of anal neoplasia than HIV-negative women.

This cross-sectional analysis looked at HIV-positive women and MSM receiving medical care at a single centre between December 2008 and December 2012. The men were the same group described above.

The 45 women were a bit older, with an average age of 43 years. Mean and nadir CD4 cell counts were 692 and 223, respectively, and most (93%) were taking ART. A majority (71%) were smokers, 22% had anal warts and 27% were coinfected with hepatitis C (compared with just 4% of the men). They reported a median of one sexual partner during the study, 53% said they used condoms and only 22% reported anal sex.

The researchers found that 23% of the women had low-risk HPV types and 34% had high-risk types, compared with 71 and 85%, respectively, amongst the men. Looking at high-risk types amongst women, 5% had HPV 16, 5% had HPV 18, 9% had HPV 51 and 2% had HPV 53. For men, the prevalence rates were 27, 17, 18 and 15%, respectively.
Turning to anal abnormalities, more than three-quarters of the women (79%) had normal cytology by anal swab, compared with one-third of the men. Eight women (19%) had low-grade SIL, none had high-grade SIL and one (2%) had ASCUS.

In a univariate analysis, significant risk factors for anal dysplasia were presence of either low-risk or high-risk HPV types, with HIV viral load and CD4 count being of borderline significance. However, in a multivariate analysis presence of anal or genital warts was the only independent risk factor (OR 11.5; p=0.046)

Rates of dysplasia and anal HPV infection in this cohort of HIV-positive women were significantly lower than those of HIV-positive MSM, but even so it is enough to justify screening regardless of virological or immunological status, the researchers concluded.

They did not answer the question put forth in their title – whether anal dysplasia among people with HIV is a matter of sexual behaviour or gender – but HPV is sexually transmitted, and the women in this study were much less likely than the gay men to have had anal sex.

References

'X-shape' not true picture of chromosome structure, new imaging technique reveals
First 3D pictures of chromosome structure revealed
A new method for visualising chromosomes is painting a truer picture of their shape, which is rarely like the X-shaped blob of DNA most of us are familiar with.

Scientists at the BBSRC-funded Babraham Institute, working with the University of Cambridge and the Weizmann Institute, have produced beautiful 3D models that more accurately show their complex shape and the way DNA within them folds up.

The X-shape, often used to describe chromosomes, is only a snapshot of their complexity. Dr Peter Fraser of the Babraham Institute explains: "The image of a chromosome, an X-shaped blob of DNA, is familiar to many but this microscopic portrait of a chromosome actually shows a structure that occurs only transiently in cells – at a point when they are just about to divide."

"The vast majority of cells in an organism have finished dividing and their chromosomes don’t look anything like the X-shape. Chromosomes in these cells exist in a very different form and so far it has been impossible to create accurate pictures of their structure."

Peter’s team has developed a new method to visualise their shape. It involves creating thousands of molecular measurements of chromosomes in single cells, using the latest DNA sequencing technology. By combining these tiny measurements, using powerful computers, they have created a three-dimensional
portrait of chromosomes for the first time. This new technology has been made possible thanks to funding from the Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC) and the Wellcome Trust.

Dr Fraser added: "These unique images not only show us the structure of the chromosome, but also the path of the DNA in it, allowing us to map specific genes and other important features. Using these 3D models, we have begun to unravel the basic principles of chromosome structure and its role in how our genome functions."

This latest research, published in *Nature*, puts DNA into its proper context in a cell, conveying the beauty and complexity of the mammalian genome in a far more effective way than volumes of text previously have. In doing so it shows that the structure of these chromosomes, and the way the DNA within them folds up, are intimately linked to when and how much genes are expressed, which has direct consequences for health, ageing and disease.

Douglas Kell, BBSRC Chief Executive, said: "Until now, our understanding of chromosome structure has been limited to rather fuzzy pictures, alongside diagrams of the all too familiar X-shape seen before cell division. These truer pictures help us to understand more about what chromosomes look like in the majority of cells in our bodies. The intricate folds help to unravel how chromosomes interact and how genome functions are controlled."

**Study: New Medical Device Extremely Effective at Preventing HIV in Women**

New intravaginal ring delivers drug effectively, guards against HIV for one month

Sep 27, 2013

It's often said that the HIV/AIDS epidemic has a woman's face. The proportion of women infected with HIV has been on the rise for a decade; in sub-Saharan Africa, women constitute 60 percent of people living with disease. While preventative drugs exist, they have often proven ineffective, especially in light of financial and cultural barriers in developing nations.

A new intravaginal ring filled with an anti-retroviral drug could help. Developed with support from the National Institute of Allergy and Infectious Diseases by Northwestern University visiting associate professor Patrick Kiser, the ring is easy to use, long lasting, and recently has demonstrated a 100 percent success rate protecting primates from the simian immunodeficiency virus (SHIV). The device will soon undergo its first test in humans.

"After 10 years of work, we have created an intravaginal ring that can prevent against multiple HIV exposures over an extended period of time, with consistent prevention levels throughout the menstrual cycle," said Kiser, an expert in intravaginal drug delivery who joined Northwestern from the University of Utah, where the research was conducted.

Kiser is a new faculty member in Northwestern’s McCormick School of Engineering’s Department of Biomedical Engineering and visiting associate professor of obstetrics and gynecology in the Feinberg School of Medicine.

The research was published September 16 in the *Proceedings of the National Academy of Sciences (PNAS)*.

Previous studies have demonstrated that antiviral drugs can prevent HIV infection, but existing methods for delivering the drug fall short. Pills must be taken daily and require high doses; vaginal gels that must be applied prior to each sex act are inconvenient, yielding poor usage rates.
The device contains powdered tenofovir, an anti-retroviral drug that is taken orally by 3.5 million HIV-infected people worldwide, but that has not previously been studied topically. But the ring’s strength stems from its unique polymer construction: its elastomer swells in the presence of fluid, delivering up to 1,000 times more of the drug than current intravaginal ring technology, such as NuvaRing, which are made of silicon and have release rates that decline over time.

The upcoming clinical trial, to be conducted in November at Albert Einstein College of Medicine in New York, will evaluate the ring in 60 women over 14 days. The trial will assess the ring’s safety and measure how much of the drug is released and the properties of the ring after use.

Other drugs could potentially be integrated into the ring, such as contraceptives or antiviral drugs to prevent other sexually transmitted infections — a feature that could increase user rates, Kiser said.

“The flexibility to engineer this system to deliver multiple drugs and change release rates is extraordinary and could have a significant impact on women’s health,” he said.

The paper is titled “Intravaginal Ring Eluting Tenofovir Disoproxil Fumarate Completely Protects Macaques from Multiple Vaginal Simian-HIV Challenges.”