October 2013 Epidemics and AIDS Update

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The Leprosy Bacillus, circa 1873
A scientist’s desperate attempts to prove that *Mycobacterium leprae* causes leprosy landed him on trial, but his insights into the disease’s pathology were eventually vindicated.

By Kate Yandell | October 1, 2013
Gerhard Armauer Hansen observed *Mycobacterium leprae* for the first time in infected nodules excised from leprosy patients. Barely distinct, rod-shaped bacteria (purple) became apparent under Hansen’s microscope. However, it took German bacteriologist Albert Neisser’s stain for the bacterium, developed after visiting Hansen in 1879, to make *M. leprae* clearly visible. Pictured are illustrations of *M. leprae*-infected cells from a testicle, taken from Hansen’s 1895 book *Leprosy: In its Clinical and Pathological Aspects*. WELLCOME LIBRARY, LONDON

Norwegian physician Gerhard Armauer Hansen first saw rod-shaped microbes in samples harvested from leprosy patients in 1873. Seven years later, Hansen, who worked in the leprosy hospital in the coastal town of Bergen, was on trial for attempting to infect a patient with bacteria without permission, using a cataract knife to inoculate a woman’s eye with material from leprous lesions.

Hansen resorted to such an extreme measure because he was having trouble proving his conviction that the microbes caused leprosy—which results in peripheral nerve damage and skin lesions—and that the disease was infectious. He had tried in vain to infect rabbits and to cultivate the microbe in vitro—evidence considered necessary to prove contagiousness. “Leprosy was afterwards called the least contagious of contagious diseases,” says Tony Gould, author of *A Disease Apart: Leprosy in the Modern World*, which might explain why Hansen had struggled to come up with the necessary proof.

Hansen’s unfortunate patient, a 33-year-old woman named Kari Nielsdatter, already had tuberculoid leprosy, one form of the disease, but Hansen hoped to infect her with a second form, called lepromatous leprosy. The infection did not take hold, but Hansen was punished for conducting the experiment. He was stripped of his position at the leprosy hospital but allowed to keep his position as Norway’s chief medical officer for leprosy, which he used to push through measures that kept leprosy patients in partial isolation. Despite his misdeeds, Hansen was later honored as the discoverer of *Mycobacterium leprae*, which was officially accepted as the cause of the disease at the first International Leprosy Conference, held in Berlin in 1897. Today, leprosy is often called Hansen’s disease.

Some of the early skepticism about the contagiousness of the disease came from Daniel Cornelius Danielssen, Hansen’s mentor and a preeminent leprosy expert of the day. Danielssen was convinced that leprosy could not be transmissible and instead thought it ran in families, or arose from poor living conditions. He had even inoculated himself and others with material from leprosy patients without causing illness, which bolstered his conviction.

While Hansen’s assertion that leprosy is infectious was ultimately vindicated, “there appears to be a very strong genetic predisposition to leprosy,” according to Richard Truman, acting chief of the laboratory
research branch at the National Hansen’s Disease Program in Baton Rouge, Louisiana. Only up to 5 percent of people are susceptible to leprosy, and susceptibility appears to run in families, but is additionally enhanced by malnutrition and conditions that compromise the immune system.

In the end, then, perhaps Hansen and Danielssen were both partly right: Hansen’s mysterious rods cause leprosy, but only in those with the poor luck to be genetically and environmentally susceptible.

A Farewell to Parasites

Despite a fierce civil war, scientists led a 14-year grassroots campaign that has eradicated a parasitic disease from northern Sudan.

By Nsikan Akpan | September 1, 2013

In 2002, they said it was impossible. At an international conference held in Atlanta, 64 experts on public health, human rights, and finance concluded that ridding Africa of river blindness—a parasitic disease more formally known as onchocerciasis—was unachievable.

Unlike in Central and South America, where certain regional pockets of onchocerciasis had been conquered, Africa’s disease burden was deemed too massive, with 99 percent of the world’s 17.7 million annual cases occurring on that continent. Furthermore, it had taken a legion of health workers to make the substantial progress witnessed in Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela—resources that aren’t available in many African countries.

Several attendees at the 2002 summit, which included reps from the World Health Organization (WHO), the National Institutes of Health (NIH), the Pan American Health Organization (PAHO), and the World Bank, argued that future efforts in Africa should focus on limiting the spread of onchocerciasis, rather than complete eradication. But a group of scientists at The Carter Center already had different plans in mind for Sudan.
The nematode responsible for onchocerciasis, *Onchocerca volvulus*, is spread from person to person via black flies, which prefer breeding near rivers. The larvae worm their way underneath the skin all over the body, where they mature in skin nodules, mate, and produce thousands of new larvae every day. The human immune system’s response to dead and dying larvae causes itchy skin rashes. “Onchocerciasis doesn’t kill you like HIV, tuberculosis, or malaria, but instead you itch and itch day and night,” says Moses Katabarwa, senior epidemiologist at The Carter Center.

Onchocerciasis is the world’s second leading cause of infectious blindness—which occurs when the worm larvae die in the victim’s eyes.

In 1998, Katabarwa and his team embarked on a mission to the northern Sudanese town of Abu Hamad, where one out of three residents had the disease’s telltale skin lesions. The researchers saw similar rates in surrounding villages, with an affected region spanning about 1,500 square kilometers.

The area’s remoteness and high incidence of disease made it ideal for trying new eradication tactics. It was isolated by natural barriers on both sides—the coursing Nile River and the arid Sahara Desert—and the nearest area where river blindness was endemic lay more than 800 kilometers away. Thus the researchers could precisely measure the effect of treating Abu Hamad residents with little danger of the disease spilling over from another heavily affected area.

Rather than assemble a giant contingent of health-care workers, the experts relied on community leaders as their workforce. For a decade and a half trained villagers administered Mectizan, Merck’s formulation of ivermectin, a broad-spectrum antiparasitic drug that had been successfully used to fight river blindness in the Americas. Ivermectin targets the immature stages of the worms’ development, but not adults, which can live as long as 15 years in humans, making lax drug compliance a barrier to completely stopping transmission.

A major turning point for this campaign came in 2006 when Katabarwa’s team stepped up the frequency of treatments from a single annual dose to two per year, a daunting but ultimately surmountable burden for community volunteers. “Twice-a-year, community-directed treatment for 15 consecutive years was critical to achieving the interruption of transmission of river blindness in Abu Hamad,” says Kamal Binnawi, director of Sudan’s Onchocerciasis Elimination/Control Program at the Federal Ministry of Health in Khartoum.

By 2011, the grassroots campaign had reached more than 90 percent of the 120,000-plus people at risk for the disease, educating and empowering whole communities to take responsibility for drug compliance. “A community-based, community-directed treatment is the standard approach developed by the African Program for Onchocerciasis Control (APOC), and this work vindicates this approach,” says Gilbert Burnham, an international health professor at Johns Hopkins University who was not involved in the project.

In May 2013, Katabarwa and his collaborators provisionally announced the eradication of onchocerciasis in Abu Hamad in the *American Journal of Tropical Medicine and Hygiene*. “Our team will spend the next 3 years on surveillance for the region,” says Tarig Higazi, an Ohio University epidemiologist and first author on the study. The WHO will take another 5–6 years to certify the elimination of the disease, but the researchers are confident that it is gone.

In 2011, Higazi and his colleagues screened blood samples from more than 6,000 Abu Hamad school children for Ov16 antibodies, the main blood marker for onchocerciasis. They all came back negative. Entomological analysis over 12 months failed to detect a single worm in 17,000 black flies, even during their peak season from November to May when they like to feed on humans. “And business is booming,” says Katabarwa, referring to the region’s renewed agricultural productivity, as disease-free farmers now have more time to spend on their harvests.

This initiative could serve as an inexpensive, sustainable model for other areas of Africa where onchocerciasis is endemic, although questions remain. Community-based programs require a large time commitment from villagers, and can negatively impact productivity and subsistence farming at first.
Following the success at Abu Hamad, Binnawi says semiannual treatment programs are being implemented in parts of eastern Sudan where onchocerciasis is endemic. Disease control efforts in southern Sudan, where the disease is most severe, were largely stymied by recent violent conflicts. Government-led control efforts have recommenced in war-torn regions that have remained part of Sudan, while the WHO’s APOC is aiding the new Republic of South Sudan. With the help of Merck, whose Mectizan donation program celebrated its 25-year anniversary in 2012, onchocerciasis researchers across the world are hopeful about the future. “The ambition to eliminate river blindness altogether is the vision and the mission of a lot of dedicated partners all over the globe,” Binnawi says.

Sources of MERS Still Unknown
As the death toll rises, scientists scour the Middle East respiratory syndrome coronavirus genome for clues as to how it first infected humans.
By Tracy Vence | September 23, 2013
The World Health Organization last week announced 18 new laboratory-confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, including three deaths. From September 2012 to date, the CoV has infected 132 people worldwide, killing 58 of them. As scientists continue to investigate the etiology and epidemiology of MERS, others are scouring the CoV genome for clues to its deadly potential and how it first infected humans.

In a report published last week (September 20) in *The Lancet*, researchers from the Saudi Arabian Ministry of Health and their international colleagues examined the viral genomes from 21 MERS cases, and analyzed the phylogenetic relationships among them, plus nine already published MERS-CoV genome sequences. Their analysis hinted at multiple chains of infection in humans, suggesting that in one particular outbreak—the Al-Hasa cluster—the MERS-CoV might have been introduced to people more than once. Further, the researchers found evidence to suggest that additional human or animal cases, which have gone undetected to date, may be sources of infection.

“The hypothesis now is [that] there were multiple introductions into the hospitals from the community, which gives us the clue that there is probably a community source of transmission,” the Ministry of Health’s Ziad Memish told NPR’s Shots blog. “My gut feeling is [that] there is some animal reservoir that is causing the transmission that is still to be found,” he added.

Nevertheless, “the source of the virus and mode of disease transmission remain unknown,” The Chinese University of Hong Kong’s David Hui noted in a *Lancet* commentary accompanying the genomic analysis. While researchers in August reported having isolated a small stretch of viral sequence in a bat that was nearly identical to that from the first human infection case, the finding has yet to be replicated. Others have also reported finding MERS-CoV neutralizing serum antibodies in dromedary camels. Still, neither bats nor camels are confirmed animal reservoirs.

Indeed, in *The Lancet* paper, Memish and his colleagues noted that “transmission within Saudi Arabia is consistent with either movement of an animal reservoir, animal products, or movement of infected people,” adding that “further definition of the exposures responsible for the sporadic introductions of MERS-CoV into human populations is urgently needed.”

That scientists are not yet sure of the source(s) of MERS has irked some. “We should have had this kind of information long ago,” the University of Minnesota’s Michael Osterholm, director of the Center for Infectious Disease Research and Policy, told NPR. “The fact that we have such incomplete information a year into this is just inexcusable.”

But Memish assured Shots that he and his colleagues are now working night and day to find potential animal reservoirs and previously unrecognized human-to-human cases that may be causing MERS to spread. “It won’t be too long before we find out what’s going on,” he told NPR.

Evolution of H7N9
Genetic diversity helped avian influenza A viruses make the leap from birds to humans, researchers report.
By Erin Weeks | September 20, 2013
A team of Chinese researchers has shed light on how avian influenza A viruses like H7N9 spread to humans by sequencing viral genomes and piecing together the pathogen’s evolutionary history. The study, published this week (September 19) in *Cell Host & Microbe*, suggests two reassortment events were likely responsible for the virus’s genetic diversity.
Since March, global health officials have been keeping a close eye on China, where H7N9 made its first-ever leap from domestic birds to humans. More than 130 cases of infection had been reported by July, about a fifth of which were fatal. Most cases were contracted through direct contact with infected poultry, as the virus remains inefficient at human-to-human transmission. Just one mutation could help the virus overcome that barrier, however, which underscores the importance of understanding avian flu’s genetic variability and evolutionary history.

“A deep understanding of how the novel H7N9 viruses were generated is of critical importance for formulating proper measures for surveillance and control of these viruses and other potential emerging influenza viruses,” said Taijiao Jiang, a senior author of the study from the Chinese Academy of Sciences, in a statement.

The team conducted whole-genome sequencing on 87 isolates of both the novel H7N9 virus and another strain, H9N2, including samples from humans, poultry, and wild birds. Their findings suggested that H7N9 may have mixed with other strains more than once—first in wild birds, and then again in domesticated birds. Such reassortment is common among influenza viruses and is thought to be behind the rapid emergence of new strains.

**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 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.”


Opinion: How HIV Became Positive

Immunotherapies, such as the re-engineered T cells that last year saved a 7-year-old girl’s life, continue to show promise as cancer treatments.

By JJ More | September 17, 2013

The scientific community witnessed an unexpected medical breakthrough last year, when a child with acute lymphoblastic leukemia (ALL) was treated with the help of HIV. Emily Whitehead, who was 7 at the time, underwent an experimental treatment in which millions of T cells were extracted from her body and re-engineered to target cancer cells. Researchers delivered new genes to the T cells through a disabled HIV strain that specifically targeted CD19 proteins on the surface of most B cells, immune cells that turn malignant in leukemia. Since the treatment, Emily has been in full remission and has gone back to school. She is now living a healthy and happy life.

After more than a decade’s worth of immunotherapy research and experimentation, approaches such as re-engineering T cells hold promise for conquering cancer. Still, it is too soon to jump to conclusions. Of the 11 other patients—10 adults and another child—treated with experimental immunotherapies in recent years, three with chronic leukemia had complete remissions; four showed improvements, but did not beat the disease completely; two saw no effect; one was treated too recently to be evaluated; and the child, who initially responded, eventually relapsed.

Soon after her treatment, Emily nearly died due to severe fever. Fortunately, the doctors found out that cytokine-release syndrome—or cytokine storm, when natural chemicals pour out of immune cells as they are activated—caused the fever and other symptoms, and were able to treat it quickly. Within hours, Emily’s temperature dropped and her blood pressure returned to normal.

“Three weeks after receiving the treatment, she was in remission,” The Children’s Hospital of Philadelphia’s Stephan Grupp, who led the team that performed Emily’s experimental treatment, said in a statement. “The cancer-fighting T cells are still there in her body.”

Emily’s dramatic response inspired hope the world over. Though the treatment, now known as CTL019, was initially only considered for patients who had run out of options, Grupp said that oncologists are now recognizing patients who might qualify for it early on in the disease process. Rather than using it as a last resort, he suggested that clinicians extract cells while the patients are healthier. “It’s an insurance policy for the future,” he said. Grupp is also looking into the possibility of using the CTL019 treatment to replace bone marrow transplantation, a risky and expensive procedure.

According to The New York Times, Novartis has shown interest in this recent development. The drug giant’s attention surprised many, as the treatment is a far cry from a traditional commercial process.
Because a new batch of T-cells must be produced for every patient, such treatments cannot be mass-produced. Currently, the CTL019 treatment costs around $20,000 per patient. While relatively cheaper than bone marrow transplantation, the price tag doesn’t yet include profit margin and other research-related costs. Though it would probably cost less if it were scaled up, there’s still a possibility of the procedure costing more down the line, considering its potential.

Still, there is no doubt that this approach has the potential to revolutionize current and future treatments of leukemia and related blood cancers. It could even mean that re-engineered T cells improve a patient’s immune system over the long term by continuously battling out cancer cells, improving recovery rates.

More patients are needed to test the safety, efficacy, and long-term success of experimental immunotherapies. Today, Grupp continues to collaborate with the team that originally designed and used the CTL019 cells, and his group is currently accepting qualified patients into its program.

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JJ More is a Detroit-based medical writer. He studied biology at Western Michigan University, and has been covering advances in clinical research, among other topics, since 2011.

**CDC Charts Antibiotic Resistance Threat**

The agency estimates that at least 23,000 people in the U.S. die each year as a result of antibiotic-resistant infections.

By Tracy Vence | September 16, 2013

Of the 2 million-plus people that are infected with antibiotic-resistant bacteria in the United States each year, at least 23,000 die as a result. That’s according to the Centers for Disease Control and Prevention, which today (September 16) released the first federal estimate of antibiotic-resistant infections in a comprehensive report on the subject.

“They have come up with hard numbers where it has been only guesswork,” Tufts University microbiologist Stuart Levy told The New York Times. “This sets a baseline we can all believe in.”

In its report, the CDC noted that about half of human antibiotic use is unnecessary, and such overuse could be leading to heightened resistance among circulating bacterial strains. The agency also noted that “antibiotic use in animals is unnecessary and inappropriate,” and might also contribute to increased drug resistance.

Elsewhere in the report, CDC listed antibiotic-resistant pathogens according to urgency—the extent to which researchers ought to focus their efforts and expand public attention to the existence of these bugs. Topping the list was carbapenem-resistant Enterobacteriaceae (CRE), members of which are highly resistant to most antibiotics. The CDC also marked Clostridium difficile and drug-resistant Neisseria gonorrhoeae as “urgent” threats, deemed 12 other microorganisms—including drug-resistant tuberculosis and methicillin-resistant Staphylococcus aureus (MRSA)—“serious” threats, and another three others “concerning.”

During a conference call with reporters, CDC Director Tom Frieden highlighted the importance of molecular detection and surveillance. “We think we will be able, over the coming years . . . to develop ways to detect resistant organisms much more quickly,” he said . . . “and to figure out how they are spreading, so we can prevent more effectively.” Better diagnostic tests, he added, “will be extremely important.”

**Sieving Through 'Junk' DNA Reveals Disease-Causing Genetic Mutations**

Oct. 3, 2013 — Scientists have revealed nearly 100 genetic variants implicated in the development of cancers such as breast cancer and prostate cancer.

The new method designed by the team, described in the journal Science, identified these variants in the under-explored regions of DNA that do not code for proteins, but instead influence activity of other genes. As even more whole genome sequences become available, this approach can be applied to find any potential disease-causing variant in the non-coding regions of the genome.

Researchers can now identify DNA regions within non-coding DNA, the major part of the genome that is not translated into a protein, where mutations can cause diseases such as cancer.

Their approach reveals many potential genetic variants within non-coding DNA that drive the development of a variety of different cancers. This approach has great potential to find other disease-causing variants.

Unlike the coding region of the genome where our 23,000 protein-coding genes lie, the non-coding region—which makes up 98% of our genome—is poorly understood. Recent studies have emphasised the biological value of the non-coding regions, previously considered ‘junk’ DNA, in the regulation of proteins.
This new information provides a starting point for researchers to sieve through the non-coding regions and identify the most functionally important regions.

"Our technique allows scientists to focus in on the most functionally important parts of the non-coding regions of the genome," says Professor Mark Gerstein, senior author from the University of Yale. "This is not just beneficial for cancer research, but can be extended to other genetic diseases too."

The team used the full set of genetic variants from the first phase of the 1000 Genomes Project, together with information about the non-coding regions generated by the ENCODE Project, and identified regions that did not accumulate much variation.

Protein-coding genes play a crucial role in human survival and fitness, and are under strong 'purifying' selection, which removes variation. The team found that some non-coding DNA regions showed almost the same low levels of variation as protein-coding genes, and called these 'ultrasensitive' regions.

Within the ultrasensitive regions, they looked at specific single DNA letters that, when altered, caused the greatest disturbance to the genetic region. If this non-coding, ultrasensitive region is central to a network of many related genes, variation can cause a greater knock-on effect, resulting in disease.

They integrated all this information to develop a computer workflow known as FunSeq. This system prioritises genetic variants in the non-coding regions based on their predicted impact on human disease.

"Our method is a practical and successful way to screen for purifying selection in non-coding regions of the genome using freely available data such as those from the ENCODE and 1000 Genomes Projects," says Dr Yali Xue, author from the Wellcome Trust Sanger Institute. "It really shows the value of these large-scale open access data-sets."

The team applied FunSeq to 90 cancer genomes including breast cancer, prostate cancer and brain tumours, and found nearly 100 potential non-coding cancer driving variants. In the breast cancer genomes, for example, they found a single DNA letter change that seems to have great impact on the development of breast cancer. This single letter change occurs in an ultrasensitive region that is central to a network of many related genes.

"Although we see that the first effective use of our tool is for cancer genomes, this method can be applied to find any potential disease-causing variant in the non-coding regions of the genome," says Dr Chris Tyler-Smith, lead author from the Wellcome Trust Sanger Institute. "We are excited about the vast potential of this method to find further disease-causing, and also beneficial variants, in these crucial but unexplored areas of our genome."

**Journal Reference:**


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**Three Signalling Pathways Regulate Gates to Powerhouses of the Cell**

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Oct. 4, 2013 — Freiburg researcher discovers three signalling pathways that regulate the gates to the powerhouses of the cell

Mitochondria burn sugar and supply the cell with energy. They were long thought to be structures that are relatively independent of the cell. However, Carolin Gerbeth, a PhD student from the trinational research training group "Membrane Proteins and Biological Membranes," has now identified no less than three signalling paths the cell uses to influence processes in the mitochondrion. In baker's yeast, she and her colleagues at the University of Freiburg found three enzymes that regulate the transport of proteins into the mitochondria. The team published its findings in the journal Cell Metabolism.

"Our work lays an important foundation for investigating signalling pathways like these in humans and determining what role they play in the development of illnesses. In tumour cells the mitochondrial energy metabolism is dysregulated, and it is possible that this reprogramming is conveyed over these newly discovered signalling paths," explains project head Prof. Dr. Chris Meisinger, Cluster of Excellence BIOSS Centre for Biological Signalling Studies and Institute of Biochemistry and Molecular Biology of the University of Freiburg.

Mitochondria resemble a cell within the cell: Separated by two membranes from the rest of the cell and with their own genome, they were long thought to be regulated for the most part independently of the nucleus. However, most mitochondrial proteins are read off from the DNA in the nucleus and need to be transported to the mitochondria following their synthesis in the cytosol, the liquid surrounding the cell components. The mitochondrial proteins need to be sorted precisely according to their destination. Not just anything is allowed to pass through the membrane of the cellular powerhouses: Only with a molecular mailing address can a protein pass through the central entrance gate in the outer mitochondrial membrane, the TOM complex. In addition to the molecular pore Tom40, the complex contains receptors like Tom22, which decides in the manner of a bouncer at a nightclub which proteins can enter and which can't. The right "outfit" for admission is a particular molecular structure.

Not only do proteins found in the mitochondrion enter from outside: The entrance gate is also regulated by cellular proteins, as Gerbeth discovered. She demonstrated that two of these so-called kinases can make the gate more or less permeable by connecting a phosphate to the precursor of the protein Tom22. The catalyst in this case is the sugar glucose, which uses the yeast as food and as a source of energy. This enables the yeast cell to adjust the energy metabolism in the mitochondrion to changes in the environment. When glucose is available in abundance, for example, the pores allow fewer proteins, which are necessary for energy production, to pass through—the mitochondria shift into economy mode and the cell obtains its energy from the cytosol. One of the kinases is even embedded directly in the outer membrane, right next to the TOM complex. Up to now, only few protein kinases have been found in mitochondria.

**Journal Reference:**

**Long-Acting HIV Antiretrovirals May Be Revolutionary. But Will They Be Worth It?**
By Myles Helfand
From TheBodyPRO.com
October 4, 2013

Once-a-month HIV antiretroviral dosing is no longer a fanciful dream. Long-acting antiretrovirals are currently in development, and the first glimpses of early safety/efficacy data are not terribly far away. So it's not outlandish for us to start thinking about where these drugs might fit into the HIV treatment armamentarium once they arrive.

It's within that context that Eric Ross, a research assistant at Massachusetts General Hospital's Medical Practice Evaluation Center, strode to the podium at IDWeek 2013 to offer the results of a "what if" simulation model.

Ross and his colleagues asked themselves: What if the U.S. Food and Drug Administration approved a once-a-month HIV antiretroviral—possibly GSΚ744 or TMC278 LA, both of which are presently in early development and have not yet been studied for efficacy in HIV-infected people? Heck, what if enough of them were approved that a complete, long-acting regimen could be formed? How might that regimen be...
utilized? How might it increase the lifespan of people with HIV? How much would it cost—and would that cost be worth the benefits it might provide?

To explore these questions, Ross et al fabricated an imaginary cohort of treatment-naive, HIV-infected patients and stratified it into four groups:

- control group (takes currently available, once-daily oral HIV treatment)
- multi-failure group (took two or more once-daily, oral HIV treatment regimens, and lost viral control on them all; then switched to a once-monthly regimen)
- second-line group (failed their first once-daily, oral HIV treatment regimen; then switched to a once-monthly regimen)
- first-line group (takes a once-monthly regimen as their initial antiretroviral therapy)

Ross et al also made a few assumptions about the baseline characteristics of their study population, based on recent research into the current demographics of the U.S. epidemic:

- mean baseline CD4+ cell count of 320 cells/mm$^3$
- mean baseline age of 43
- mean gender split of 84% men, 16% women
- mean adherence to oral antiretroviral therapy of 89% (vs. 100% on long-acting antiretrovirals)
- Estimates were also made regarding the effect of adherence on virologic suppression and loss to follow-up.

An estimated drug cost of $53,000 per patient per year for this as-yet-nonexistent, once-a-month drug was factored into this statistical model. The estimate was based on assessments of the costs of existing oral HIV medications, as well as the costs of novel, long-acting drugs developed for other diseases. (Ross noted that $53,000 was roughly 85% more expensive than oral regimens based on boosted protease inhibitors.)

When all of these data were plugged into their simulation, Ross et al found that—assuming generally good adherence—there was only a small benefit to life expectancy among patients receiving long-acting antiretroviral therapy (LA-ART) compared to patients receiving once-daily treatment: an additional .5 years for those with multiple prior treatment failures, an additional .6 years for those with one prior treatment failure and an additional .7 years for those who were taking LA-ART as their first regimen. The relative benefits increased significantly, to upwards of three years, among patients with the worst adherence to daily antiretroviral therapy, the simulation suggested.

Regardless, the exploratory analysis appeared to show a benefit to life expectancy. The remaining question was: Is that benefit high enough to make the drug cost-effective?

The answer was: maybe. Using generally approved measures for incremental cost-effectiveness, Ross et al determined that LA-ART would be a cost-effective option only for patients with multiple prior failures on standard, once-daily therapy. The cost of LA-ART would need to be $29,000 per patient per year—roughly the same as a typical boosted protease inhibitor-based regimen in the U.S.—for the regimen to be cost-effective in their simulation, they calculated.

Ross et al tinkered with some of their initial assumptions regarding baseline patient characteristics and other parameters (including adherence levels and loss to follow-up) in order to establish a better range of cost-effectiveness possibilities, but ultimately found similar results: LA-ART’s greatest value, and highest likelihood of cost-effectiveness, would be for patients who had already failed multiple once-daily regimens. For it to be "worth it" even as a second-line treatment option, the cost would need to be dramatically lower than estimated, in the $27,000 to $34,000 range.

Ironically (though logically), Ross noted that good adherence made LA-ART less cost-effective. This is why its appeal was so much greater in multi-failure scenarios: Those situations tend to assume that poor adherence was the reason for the failures (as it often is), and LA-ART eliminates daily adherence problems as a concern. Among patients who would normally be adhering just fine to once-daily treatment, LA-ART is—from a cold, calculating standpoint—merely an overly expensive nicety, although from a more subjective standpoint such regimens could be reasonably expected to have a tremendous amount of appeal.

Obviously, there are a tremendous number of possibly mistaken assumptions that went into Ross et al’s simulation. The exercise also completely ignores (by necessity) the extraordinary quality-of-life and psychological benefits that LA-ART would provide for people living with HIV. (Ross additionally noted that the analysis ignores any possible reduction in HIV transmission rates that may result from the ability of LA-ART to keep viral load more reliably suppressed in the patient population.) But the study provides valuable food for thought as we begin to ponder the future role of LA-ART alongside other treatment
options. It also provides some insight into the types of calculations that may go into drug-pricing decisions.

Oct 4, 2013, 2:54pm PDT

**Gladstone lab uncovers a potential HIV cure — and it's already a drug**

Monkeys' evolutionary protection against a virus similar to HIV may be mimicked by a drug sitting on a biotech company's shelf, says a Gladstone Institutes researcher who wants to take the drug into clinical trials.

The drug proved safe in a Phase II trial looking at chronic inflammation as the cause of seizures but did not reduce seizure activity to the point the unidentified company thought it would be commercially successful. But Dr. Warner Greene, director of virology and immunology research at the Gladstone Institutes in San Francisco, said the drug could offer a functional cure for deadly HIV.

Once Gladstone negotiates the right to use the drug with the U.S.-based company, Greene said, a clinical trial could be up and running within six to 12 months.

The potential treatment is one of the latest and greatest breakthroughs in the fight against the AIDS virus. Only last month, for example, Oregon Health & Science University reported that they are working on an HIV/AIDS vaccine that may clear the virus from the body.

In the short term, the drug looked at by Greene's 17-person lab could be a therapeutic bridge for the roughly 16 million people in the world — many of them in Africa — who need antiretroviral therapy, like those drugs developed by Foster City-based Gilead Sciences Inc. (NASDAQ: GILD). It also could help reduce inflammation in people already on so-called ARV therapy, Greene said.

"This drug would stop the progression of the disease and put them in a holding pattern until they can get into more definitive ARV therapy," he said.

Greene was one of three Gladstone scientists to win National Institutes of Health research awards toward the Sept. 30 end of the fiscal year, before the federal government shutdown. All three are working on approaches to HIV.

The Gladstone is an affiliate of the University of California, San Francisco.

Greene's work — supported by a nearly $5 million, five-year NIH Avante-Garde Award for high-impact research — is particularly interesting because of its implications for controlling and possibly eradicating the AIDS virus.

Scientifically, here's why Greene is excited:

After HIV enters certain white blood cells, called CD4 T cells, the cells commit suicide and trigger inflammation. This alerts other disease-fighting cells that rush to the scene, but they fall into a trap that causes them to kill themselves, too, which often leads to a vicious cycle of abortive infection, cell death, inflammation and recruitment of new cells that are destined to the same fate.

The process links the two signature events in HIV/AIDS, Greene said: the depletion of CD4 T cells and chronic inflammation.

Monkeys, however, have evolved so their bodies do not mount an attack on simian immunodeficiency virus but, instead, control the inflammatory response to the virus. The virus — even different versions of it — still is present, but it doesn’t set off the chain of events that cause inflammation.

Greene's lab believes there are existing drugs that could chemically reproduce this evolutionary jump in humans, blocking the inflammation pathway connected to T cell death. One drug, in particular, has caught Greene's eye.

The targeted drug inhibits an enzyme known as caspase 1. That enzyme is involved in pyroptosis, the process where the membrane of a T cell leaks its contents, triggering high-level inflammation.

By viewing biopsied lymph nodes of HIV patients at San Francisco General Hospital, Greene's 17-person lab confirmed that the process occurs in untreated HIV-infected subjects.

Greene's lab then went looking for already developed caspase 1 inhibitors. It found one in particular that had failed clinical trials for chronic seizures but was safe and well tolerated. Gladstone now is in negotiations with the company that controls the drug.

"These folks are not the only game in town," Greene said. "But we have safety data of their drug and we know their drug works in all of our assays beautifully."

The drug could reduce the need for HIV-infected individuals to take antiretroviral therapy. That is important since researchers are looking at whether ARV therapy or the virus — or both — contribute to accelerated aging in AIDS patients. What’s more, millions people in Africa, for example, don’t have access to antiretroviral drugs like those from Gilead.
Yet even with antiretroviral therapy, HIV patients see low levels of chronic inflammation that may cause them to develop heart problems and other diseases as much as 20 years earlier than people who don’t carry HIV.

"But even more exciting, it could be used with other agents to cure people of HIV," Greene said, "so they would never, ever need antiretrovirals at all."

**Computer Scientists Develop New Approach to Sort Cells Up to 38 Times Faster**

Oct. 2, 2013 — A team of engineers led by computer scientists at the University of California, San Diego, has developed a new approach that marries computer vision and hardware optimization to sort cells up to 38 times faster than is currently possible. The approach could be used for clinical diagnostics, stem cell characterization and other applications.

The approach improves on a technique known as imaging flow cytometry, which uses a camera mounted on a microscope to capture the morphological features of hundreds to thousands of cells per second while the cells are suspended in a solution moving at approximately 4 meters per second. The technique sorts cells into different categories, for example benign or malignant cells, based on their shape and structure. If these features can be calculated fast enough, the cells can be sorted in real-time.

"Previous techniques simply could not keep up with the image data streaming off of this high speed camera," said Ryan Kastner, a professor of computer science at the Jacobs School of Engineering at UC San Diego. "This has to potential to lead to a number of clinical breakthroughs, and we are working closely with UCLA and their industrial partners to commercialize our technology."

Other researchers had previously discovered that the physical properties of cells could provide useful information about cell health, but previous techniques had been confined to academic research labs because measuring the cells of interest could take hours or even days. The new approach brings imaging flow cytometry closer to being used in a clinical setting.

The microscope-mounted camera used in imaging flow cytometry operates at 140,000 frames per second. But algorithms currently in use take anywhere from 10 seconds to 0.4 seconds to analyze a single frame, depending on the programming language used—making the technique impractical.

The researchers' new approach speeds processing speeds up to 11.94 milliseconds and 151.7 milliseconds depending on the type of hardware used. For the fastest results, engineers developed a custom hardware solution using a field-gate programmable array, or FPGA, which speeds up the process considerably. The slower results, which are still much faster than what's currently available, were obtained using a graphics processing unit, or GPU.

The researchers’ ultimate goal is to analyze the cell properties in real-time, and use that information to sort the cells. To do so, the sorting decision must be made in less than 10 milliseconds.

The computer scientists presented their findings in September at the International Conference on Field Programmable Logic and Applications in Portugal.
Computer vision algorithm and hardware optimization

The ultimate goal of the algorithm is to determine the radius at every angle of the cell. This provides the necessary information to determine the cell's key features. Ideally this process needs to be performed on every frame in about 7 microseconds per frame. The algorithm must first detect the presence of the cell, then find the center of the cell, and finally determine the distance from this center to the cell wall for every angle, finding the cell's radius. To do this reliably, yet still meet stringent timing requirements, the algorithm was carefully modified to run faster on the FPGA.

The Blob Search module analyzes the images to detect the cell's area. It then converts the black and white image of the cell into a digital image called a binary image, where each pixel carries either a zero or non-zero value. In this case, only the pixels representing the cell are highlighted. The system then constructs a graphical representation of the distribution of data in the image, known as a histogram. It then crops a 20 by 20 pixel image around the cell.

The Interpolation step resizes the picture up to 200 by 200 pixels. It also generates a higher-contrast image of the cell. Then the Find Center module finds the center of the cell by converting the higher contrast images to binary images. It then counts the pixels with a non-zero value in each row and column of the image. The module averages the data from the two images produced by the Interpolation module to find the cell's center point. Finally, the algorithm determines the cell's shape and morphological properties by finding the darkest pixels on a line from the cell center at each angle of the image, which are considered to be part of the cell's wall.

The researchers then carefully analyzed each step in the algorithm, and made modifications to the algorithm when necessary to implement it efficiently on the FPGA. When mapping to custom hardware, the designer must carefully consider the complexity of the algorithm versus the accuracy of the result. Certain algorithmic features, such as algorithms with larger number of decisions points or those requiring multiple passes over the data, make for a slow and inefficient hardware solution.

They found that they obtained much better results with FPGA than with GPU. That’s because FPGAs, unlike GPUs, can be configured so that they match the algorithm exactly. All operations occur at lightning-fast speeds. It takes the system under 500 microseconds to detect a cell and calculate its radius.

Zambian government continues prosecution of gay-rights activist

October 9, 2013
Jonathan Dockney

On 15 August 2013 the Zambian High Court refused to hear a constitutional application by Paul Kasonkomona regarding his right to freedom of expression being violated by police charges against him.

Kasonkomona was arrested on 7 April 2013 after he appeared on television calling on the Zambian government to recognize the rights of sexual minorities including LGBTI people and sex workers in order for the government to effectively curb HIV infections. He was arrested as he left the TV station and charged with “inciting the public to take part in indecent activities”.

The court ruled that no violation of his rights had taken place and the criminal case against Kasonkomona will now proceed on 16 and 17 October 2013 in the Lusaka Magistrate’s Court.

High Court Judge N.A. Sharpe-Phiri ruled, "that there was no constitutional issue concerning the contravention of fundamental rights of the accused and there was no ground for the court below to make this reference to the High Court."

According to Anneke Meerkotter of the Southern Africa Litigation Centre (SALC), “what is important is that the concerns about violations of constitutional issues are now on the court record and the Magistrate’s referral of Kasonkomona’s application to the High Court shows that the Magistrate dealing with the criminal case against Kasonkomona is thinking about these issues. The issue of freedom of expression underlies all of the cases against Kasonkomona”.

Kasonkomona is represented by Sunday Nkonde SC, William Ngwira and Bwalya Mubanga from SBN Legal Practitioners. SALC is providing legal support in the People v Kasonkomona case.

The state argued that no constitutional issues were violated and therefore that Kasonkomona’s constitutional application was "vexatious and frivolous". The prosecution further argued that the right to freedom of expression has limitations and that section 178 (g) of the Penal Code (under which Kasonkomona has been charged) is such a limitation.

The prosecution argued that Zambia is defined as a Christian country in its Constitution and therefore certain behavior such as sex work and homosexuality is not socially acceptable.
Kasonkomona’s lawyers have filed a constitutional petition to the High Court dealing with the vagueness of the section with which he is charged and violations of his right to a fair trial. The petition will be heard in the High Court on 1 November 2013.

**Genes Protect Themselves Against Being Silenced**
Oct. 10, 2013 — Harvard Stem Cell Institute (HSCI) researchers have settled a century-old debate over whether occurrence of DNA methylation acts to silence gene expression, or if genes are turned off by other means before they are methylated.

As explicated today in the journal *Nature*, methylation in fact enforces gene silencing, and it is levels of a newly identified form of RNA produced by individual genes that determines whether they are turned off by the addition of a methyl (CH$_3$) group by the enzyme DNA methylase 1 (DNMT1).

The study, led by HSCI Principal Faculty member Daniel Tenen, MD, found that during transcription of DNA to RNA, a gene produces a small amount of what the investigators named "extracoding RNA," which stays in the nucleus and binds to DNMT1, blocking its ability to methylate, or silence the gene. The discovery of RNA’s new function has therapeutic potential as an on-off switch for gene expression.

"We have demonstrated, at least for one gene in detail, and probably thousands more, that extracoding RNA serves to protect the gene from methylation," said Tenen, who heads laboratories at Beth Israel Deaconess Medical Center and the Cancer Science Institute of Singapore, where he is director, at the National University of Singapore. "When the RNA is shut off, which we did by various means, the gene becomes methylated."

Postdoctoral fellow Annalisa Di Ruscio, MD, PhD, and laboratory staff member Alexander Ebralidze, PhD, were major contributors to the work.

The biological irony is that DNMT1 has long been considered a DNA-binding enzyme, so it is surprising that it is able to bind so well to extracoding RNA, Tenen explained.

"If you put extracoding RNA into a cell, you can actually inhibit the ability of DNMT1 to maintain methylation patterns of that gene and induce demethylation in a gene-selective manner," Tenen said. "The reason this is interesting is the cancers and other disease are treated using demethylation agents, so this gives us the opportunity to try to direct gene-specific demethylation."

**Journal Reference:**

**The Stone** October 10, 2013, 10:00 pm

**The Dangers of Pseudoscience**
By **Massimo Pigliucci** and **Maarten Boudry**

Philosophers of science have been preoccupied for a while with what they call the “demarcation problem,” the issue of what separates good science from bad science and pseudoscience (and everything in between). The problem is relevant for at least three reasons.

What happens when a theory adopts the external trappings of science, but without the substance? The first is philosophical: Demarcation is crucial to our pursuit of knowledge; its issues go to the core of debates on epistemology and of the nature of truth and discovery. The second reason is civic: our society spends billions of tax dollars on scientific research, so it is important that we also have a good grasp of what constitutes money well spent in this regard. Should the National Institutes of Health finance research on “alternative medicine”? Should the Department of Defense fund studies on telepathy? Third, as an ethical matter, pseudoscience is not — contrary to popular belief — merely a harmless pastime of the gullible; it often threatens people’s welfare, sometimes fatally so. For instance, millions of people worldwide have died of AIDS because they (or, in some cases, their governments) refuse to accept basic scientific findings about the disease, entrusting their fates to folk remedies and “snake oil” therapies.

It is precisely in the area of medical treatments that the science-pseudoscience divide is most critical, and where the role of philosophers in clarifying things may be most relevant. Our colleague Stephen T. Asma raised the issue in a recent Stone column (“The Enigma of Chinese Medicine”), pointing out that some traditional Chinese remedies (like drinking fresh turtle blood to alleviate cold symptoms) may in fact work, and therefore should not be dismissed as pseudoscience.

This, however, risks confusing the possible effectiveness of folk remedies with the arbitrary theoretical-metaphysical baggage attached to it. There is no question that some folk remedies do work.
The active ingredient of aspirin, for example, is derived from willow bark, which had been known to have beneficial effects since the time of Hippocrates. There is also no mystery about how this happens: people have more or less randomly tried solutions to their health problems for millennia, sometimes stumbling upon something useful. What makes the use of aspirin “scientific,” however, is that we have validated its effectiveness through properly controlled trials, isolated the active ingredient, and understood the biochemical pathways through which it has its effects (it suppresses the production of prostaglandins and thromboxanes by way of interference with the enzyme cyclooxygenase, just in case you were curious).

Asma’s example of Chinese medicine’s claims about the existence of “Qi” energy, channeled through the human body by way of “meridians,” though, is a different matter. This sounds scientific, because it uses arcane jargon that gives the impression of articulating explanatory principles. But there is no way to test the existence of Qi and associated meridians, or to establish a viable research program based on those concepts, for the simple reason that talk of Qi and meridians only looks substantive, but it isn’t even in the ballpark of an empirically verifiable theory.

Read previous contributions to this series.

In terms of empirical results, there are strong indications that acupuncture is effective for reducing chronic pain and nausea, but sham therapy, where needles are applied at random places, or are not even pierced through the skin, turn out to be equally effective (see for instance this recent study on the effect of acupuncture on post-chemotherapy chronic fatigue), thus seriously undermining talk of meridians and Qi lines. In other words, the notion of Qi only mimics scientific notions such as enzyme actions on lipid compounds. This is a standard modus operandi of pseudoscience: it adopts the external trappings of science, but without the substance.

Asma at one point compares the current inaccessibility of Qi energy to the previous (until this year) inaccessibility of the famous Higgs boson, a sub-atomic particle postulated by physicists to play a crucial role in literally holding the universe together (it provides mass to all other particles). But the analogy does not hold. The existence of the Higgs had been predicted on the basis of a very successful physical theory known as the Standard Model. This theory is not only exceedingly mathematically sophisticated, but it has been verified experimentally over and over again. The notion of Qi, again, is not really a theory in any meaningful sense of the word. It is just an evocative word to label a mysterious force of which we do not know and we are not told how to find out anything at all.

Philosophers of science have long recognized that there is nothing wrong with positing unobservable entities per se, it’s a question of what work such entities actually do within a given theoretical-empirical framework. Qi and meridians don’t seem to do any, and that doesn’t seem to bother supporters and practitioners of Chinese medicine. But it ought to.

Still, one may reasonably object, what’s the harm in believing in Qi and related notions, if in fact the proposed remedies seem to help? Well, setting aside the obvious objections that the slaughtering of turtles might raise on ethical grounds, there are several issues to consider. To begin with, we can incorporate whatever serendipitous discoveries from folk medicine into modern scientific practice, as in the case of the willow bark turned aspirin. In this sense, there is no such thing as “alternative” medicine, there’s only stuff that works and stuff that doesn’t.

Second, if we are positing Qi and similar concepts, we are attempting to provide explanations for why some things work and others don’t. If these explanations are wrong, or unfounded as in the case of vacuous concepts like Qi, then we ought to correct or abandon them. Most importantly, pseudo-medical treatments often do not work, or are even positively harmful. If you take folk herbal “remedies,” for instance, while your body is fighting a serious infection, you may suffer severe, even fatal, consequences. That is precisely what happens worldwide to people who deny the connection between HIV and AIDS, as superbly documented by the journalist Michael Specter. Indulging in a bit of pseudoscience in some instances may be relatively innocuous, but the problem is that doing so lowers your defenses against more dangerous delusions that are based on similar confusions and fallacies. For instance, you may expose yourself and your loved ones to harm because your pseudoscientific proclivities lead you to accept notions that have been scientifically disproved, like the increasingly (and worryingly) popular idea that vaccines cause autism.

Philosophers nowadays recognize that there is no sharp line dividing sense from nonsense, and moreover that doctrines starting out in one camp may over time evolve into the other. For example, alchemy was a (somewhat) legitimate science in the times of Newton and Boyle, but it is now firmly pseudoscientific (movements in the opposite direction, from full-blown pseudoscience to genuine science, are notably rare). The verdict by philosopher Larry Laudan, echoed by Asma, that the demarcation
problem is dead and buried, is not shared by most contemporary philosophers who have studied the subject.

Even the criterion of falsifiability, for example, is still a useful benchmark for distinguishing science and pseudoscience, as a first approximation. Asma’s own counterexample inadvertently shows this: the “cleverness” of astrologers in cherry-picking what counts as a confirmation of their theory, is hardly a problem for the criterion of falsifiability, but rather a nice illustration of Popper’s basic insight: the bad habit of creative fudging and finagling with empirical data ultimately makes a theory impervious to refutation. And all pseudoscientists do it, from parapsychologists to creationists and 9/11 Truthers.

Asma’s equating of Qi energy with the “sacrosanct scientific method,” as if both are on the same par, is especially worrisome. Aside from comparing a doctrine about how the world works (Qi) with an open-ended method for obtaining knowledge, what exactly is “sacrosanct” about a method that readily allows for the integration of willow bark and turtle blood, provided that they hold up to scrutiny? The open-ended nature of science means that there is nothing sacrosanct in either its results or its methods.

The borderlines between genuine science and pseudoscience may be fuzzy, but this should be even more of a call for careful distinctions, based on systematic facts and sound reasoning. To try a modicum of turtle blood here and a little aspirin there is not the hallmark of wisdom and even-mindedness. It is a dangerous gateway to superstition and irrationality.

Unravelling the mystery of the vaccine trials
Gus Cairns
Published: 11 October 2013

There have been thousands of small vaccine trials in the history of HIV – the first one took place in 1986 – but only six large efficacy trials, and the results of these have been puzzling. Many presentations at the 13th AIDS Vaccine conference were dedicated to understanding what went on in them and how we can use their findings to guide better vaccine design.

The efficacy trials

The history of HIV vaccine research has been one of both disappointment and one apparent success. The first trials were the two VAX trials, which used AIDSVAX, a protein from the envelope (surface) of HIV, gp120 (which forms the ‘knobs’ on HIV that act as its cell-contacting mechanism) with the aim of stimulating the humoral branch of the immune system to make antibodies against HIV. The protein did stimulate antibody responses in both trials, but in neither one were they effective in reducing the rate of HIV infection in participants. It became clear that HIV can quickly mutate to shrug off antibodies formed against it.

The two second-generation trials were STEP and Phambili. These used a quite different form of vaccine, HIV genes (respectively tailored for the types most common in the USA and southern Africa) carried into cells inside the shell of an infectious but non-reproducing form of an adenovirus, a common cold virus, called Ad5. Three shots of this Ad5 vector vaccine were given. This method, it was hoped, would stimulate the other, cellular branch of the adaptive immune system to produce CD8 cells that would kill off HIV-infected cells. Phambili, which had started later, was stopped when the STEP results were announced. The failure of these trials was a low point in vaccine development, as not only did they fail to stop HIV, but there was some evidence at the point the trials were unblinded that they may have increased the risk of HIV infection to participants who had pre-existing immunity to Ad5, and also to uncircumcised men.

Meanwhile two other vaccine trials had started. The first one, RV144, combined the methods seen in the three first studies. It ferried HIV genes into cells inside the shell of a different virus, a canarypox virus called MVA, and then finished off with two doses of the AIDSVAX gp120 vaccine. Expectations for it were not high as it involved one component, AIDSVAX, that had already shown no efficacy, and one group of vaccine researchers even wrote a letter saying its scientific rationale was weak and it should be discontinued. So it was a surprise when, in 2009, it was announced that it reduced HIV infections in recipients by 31%, compared to placebo.

The one further efficacy trial was another disappointment, however. HVTN 505 consisted of two shots of ‘naked’ HIV DNA followed by a shot of HIV DNA inside an Ad5 shell – the same vector as in STEP and Phambili. It was conducted in the US with gay men and transgender women and because of the STEP trial result, participants had to have no pre-existing immunity to Ad5 and to be circumcised. The study was stopped in April 2013 and full results were published just before the AIDS Vaccine conference opened, on 7 October.
What worked in RV144?
Merlin Robb of the US Military Research Program presented findings on the correlates of protection (factors associated with efficacy) in RV144. Initially it was hard to find anything that could explain the vaccine’s apparent efficacy: it did not produce a CD8 cell response, and it produced fewer of the supposedly essential broadly neutralising antibodies to HIV – antibodies that block infection by a wide variety of HIV viruses – than AIDSVAX. It did produce weaker binding antibodies, but these, it had been supposed, were too weak and too specific to have a protective effect.

However, it became clear that the vaccine generated two types of binding antibodies to HIV. One type was called immunoglobulin A (IgA) – a type of antibody that mainly lurks in mucous membranes. High levels of anti-HIV IgA had an unhelpful effect: they were associated with increased susceptibility to HIV. The other type was immunoglobulin G (IgG) – a type that mainly circulates in the blood. High levels of IgG were helpful – they were associated with protection against HIV.

It had been thought that antibodies protective against HIV would most likely be formed against a region of the gp120 protein called the V3 loop, but the helpful antibodies were formed in reaction to two other parts, the V1 and V2 loops – indeed antibodies to V3 seemed to be associated with risk. The participants with the highest ratio of IgG to IgA had a 60% reduced risk of HIV infection. Interestingly, if RV144 had been stopped after a year, 60% would also have been the efficacy observed: however the antibody protection appeared to fade quite quickly and by 3.5 years it was the observed 31%.

Why did IgA and IgG matter? The first blocked, and the second facilitated, a process called ADCC – antibody-dependent cellular cytotoxicity. Antibodies are Y-shaped molecules and it is the two short branches of the Y that are their ‘keys’ – they are produced in an amazing variety of shapes, a few of which are able to stick to specific components of foreign invaders in the body and proliferate when they encounter them. However, the stem of the Y also has a purpose in some antibodies. When the short branches encounter the foreign material they are keys to, the long stem can send out signals to other parts of the immune system and alert them to come over and kill the foreign invaders.

In this case, the anti-HIV IgGs sent out their signal to the third and oldest part of the immune system, the innate immune system, an unspecific but fast force of cells and chemicals, including the powerful natural killer cells. These rushed to infection sites in response to the IgG antibodies’ ‘distress call’ and quelled infection. In contrast, the IgAs specifically blocked off natural killer cells from reacting to the invading HIV.

The researchers found that anti-V1 and V2 IgG antibodies in the RV144 recipients were reactive to a broad variety of HIV viruses whereas IgG antibodies from AIDSVAX recipients were reactive to a much narrower group and belonged to a different subgroup that did not send a strong ADCC signal.

Why didn’t HVTN 505 work?
The above findings also seem to explain why HVTN 505 vaccine didn’t work. It produced high levels of antibodies to the V3 loop and virtually none to V1 and V2. Furthermore, while it did produce high levels of IgG antibodies, most were not in reaction to any part of the gp120 protein. Instead, 90% were antibodies to gp41, the ‘stem’ of the knobs on the surface of HIV, and the part which actually fuses with the cell.

These antibodies were very non-specific: in fact they reacted to many common bacteria, including the ones most people carry around in their gut. The 10% of antibodies to gp120 were mainly IgA antibodies. What this meant was that while the RV144 vaccine was capable of stimulating an immune reaction that could neutralise 20 to 90% of a selection of less exotic and immune-resistant HIV viruses in the test tube (the type that normally get transmitted), the HVTN 505 immune response could only neutralise 3 to 28% of the same viruses.

Taken together, this meant that the antibody response generated by HVTN 505 actually disabled the ADCC process that might have helped to protect against HIV.

Did the Ad5 vaccines increase susceptibility to HIV?
One of the most worrying questions about the vaccine trials is whether some of them really did increase participants’ susceptibility to HIV. A new meta-analysis by Peter Gilbert of the Fred Hutchinson Cancer Research Center in Seattle, USA attempted to shed some light on this. It looked at all 8500 participants in the STEP, Phambili and HVTN 505 trials and established that, over the whole group, participants who were given a vaccine were 33% more likely to become infected with HIV than placebo recipients. However, the increased risk in HVTN 505 was only 9% and this was not remotely statistically significant (p = 0.7).

There was a 41% raised risk of acquiring HIV for vaccine recipients over placebo recipients in STEP and Phambili taken together. This was statistically significant (p = 0.005). However, if STEP was taken by itself, the raised risk for all participants was only 22% and this was not significant. So in terms of whole
trials, it was Phambili, where vaccine recipients were 74% more likely to acquire HIV than placebo recipients, which remained significant.

This is to ignore the fact that it was already known that only certain groups – men, especially uncircumcised men, and people with pre-existing immunity to adenoviruses – had a raised risk of HIV in STEP. So based on the results at the end of the blinded phase of vaccine trials, when participants did not know whether they were on vaccine or placebo (which is what has been published before) – pre-existing adenovirus immunity, especially in uncircumcised men, seemed to be implicated (being male and having Ad5 immunity raised your risk by 68%).

Both trials, however, continued after unblinding: participants were followed for three years after they found out whether or not they had actually been on the vaccine. During the unblinded phase, a very odd thing started to happen: while the increased risk of vaccine over placebo remained, especially in Phambili, and the risk for men over women persisted in that trial too, the risks associated with adenovirus immunity and circumcision actually reversed. In fact this started happening before unblinding: after 18 months from their first vaccine or placebo shot, people without immunity to Ad5 and circumcised men became more likely to acquire HIV than Ad5-immune and uncircumcised participants.

So it appeared that, whatever was causing the excess infections in vaccine recipients, it either wasn’t Ad5 immunity after all, or the Ad5 risk only contributed to the overall risk in the first 18 months after people were given the vaccine, for some unknown biological reason – and it would be very unusual for a vaccine to suddenly start producing a biological risk that hadn’t happened before after as long as 18 months.

It may have been behaviour in the unblinded phase. Trials are blinded so that knowledge of whether they are on the treatment or the placebo does not influence participants’ behaviour; as a result, it is much more difficult to tease out influences on outcomes in the unblinded phase. The continuing difference in infection rates in the unblinded phase of STEP and more markedly in Phambili was characterised by another odd thing: the difference later on was not so much driven by vaccine recipients acquiring more HIV so much as placebo recipients ceasing to acquire it. In Phambili in particular, in the last year of follow-up no infections were seen in the placebo group.

What was happening? Did placebo recipients reduce their risk behaviour after unblinding, or vaccine recipients increase theirs? Conversely, what about people who dropped out of the study? Somewhat more placebo recipients dropped out of the study after it had been unblinded than vaccine recipients, a common phenomenon in vaccine trials. What if the high-risk placebo recipients had been the ones that dropped out? That would also keep infections in the remaining placebo group down. Conversely, high-risk vaccine recipients might have been more likely to stay in the study.

Glenda Gray, Principal Investigator of the Phambili trial, said that self-reported behaviour did not differ between vaccine and placebo recipients and that even if there was differential drop-out in high-risk placebo recipients, it would only make a single infection’s difference to the Phambili result.

Peter Gilbert said that based on the drop-out rates in all three trials, there would have to be 33% more infections in placebo drop-outs than those who stayed in the trials, and 28% fewer in vaccine drop-outs than in those who stayed, to even out the vaccine/placebo difference seen during the unblinded phases of the trials.

For now, then, the explanation for the higher rates of infection seen in some groups in the STEP and Phambili trials remains mysterious.

References

Eviplera works well regardless of viral load or CD4 count, may improve lipid levels

Liz Highleyman
Published: 11 October 2013
The single-tablet regimen Eviplera (rilpivirine/tenofovir/emtricitabine) worked as well as Atripla (efavirenz/tenofovir/emtricitabine) for treatment-naive people across a range of viral load and CD4 T-cell
levels, researchers reported at the Second IDWeek conference last week in San Francisco. Another study found that switching from a boosted protease inhibitor to Eviplera lowered cholesterol and triglyceride levels

Calvin Cohen from the Community Research Initiative of New England reported findings from the open-label STA R trial, the first head-to-head comparison of Eviplera vs Atripla in people starting antiretroviral therapy (ART) for the first time.

Unlike the earlier ECHO and THRIVE trials, which compared the same drug combinations taken as separate pills plus placebos—requiring multiple daily pills with different food requirements—all participants in STA R took a single tablet once-daily.

The study included 786 participants. More than 90% were men, about two-thirds were white, one-quarter were black and the median age was 36 years. At baseline the mean CD4 count was approximately 390 cells/mm³. Two-thirds started treatment with a viral load at or below 100,000 copies/ml, about 27% had 100,000 to 500,000 copies/ml and about 7% had above 500,000 copies/ml at baseline.

Overall, both single-tablet regimens produced good virological suppression: 86% of participants in the Eviplera arm and 82% in the Atripla arm achieved undetectable viral load (<50 copies/ml) at 48 weeks in a ‘snapshot’ analysis. Virological failure occurred in 8% and 6%, respectively, and CD4 gains were similar (200 vs 191 cells/mm³).

Cohen reported results from a sub-analysis looking at response rates according to baseline viral load and CD4 count. Amongst people with 100,000 copies/ml or less at baseline, 89% taking Eviplera and 82% taking Atripla had undetectable viral load at week 48, a statistically significant difference. Amongst those with viral load above 100,000 copies/ml, response was lower overall but similar for the two regimens, 86% vs 82%, respectively.

A similar pattern emerged for CD4 counts. Amongst people with greater than 200 cells/mm³, response rates were 88% for Eviplera and 83% for Atripla. Response rates were lower overall for people who started treatment with 200 cells/mm³ or less but similar for the two regimens, 72% and 71%, respectively. These differences were not significant.

Turning to adherence as determined by pill counts, people with 95% or better adherence had high response rates with either Eviplera or Atripla: 90% and 88%, respectively. Response rates dropped amongst people with less than 95% adherence, to 75% and 66%, respectively. But neither difference between the two regimens was significant.

Looking at these factors together, in an analysis that excluded patients with missing data, virological response rates were statistically similar amongst Eviplera and Atripla recipients with all combinations of baseline viral load, CD4 count and adherence levels. Amongst people with the least favourable combination—high viral load, low CD4 count and sub-optimal adherence—only 50% achieved viral suppression with either single-tablet regimen.

Turning to virological failure, rilpivirine appeared to fare a bit more poorly, especially amongst people with low CD4 counts. In the lower viral load/lower CD4, strata, two out of 10 people (20%) with excellent adherence and three out of nine (33%) with lower adherence experienced virological failure on Eviplera, compared with none (0%) on Atripla. However, patterns were not consistent and the number of failing patients was small and affected by missing data, so differences were not significant.

People with at least 95% adherence reported better tolerability of both regimens. In particular, highly adherent patients taking Atripla reported fewer efavirenz-associated central nervous system side effects such as abnormal dreams or depression, but this study could not determine the direction of cause and effect. Although rilpivirine has been associated with fewer CNS adverse events than efavirenz in clinical trials, this sub-group analysis showed that in people with CD4 counts above 200 and greater than 95% adherence, the difference in tolerability was much less pronounced.

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Cohen noted that this analysis was intended in part to see if rilpivirine is more vulnerable than efavirenz to resistance and treatment failure if patients miss doses. The findings indicated that although "both drugs suffered from missed doses," rilpivirine did not appear to do worse.

**Lipid improvements**

Pablo Tebas from the University of Pennsylvania reported findings from the phase 3 SPIRIT study, which looked at outcomes amongst people with suppressed viral load who simplified treatment by switching from a ritonavir-boosted protease inhibitor plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) to Eviplera.
The study included 476 participants. About 90% were men, three-quarters were white, about 16% were black, the median age was just over 40 years and they had been on ART for nearly three years. The mean CD4 count was high, approaching 600 cells/mm³. At baseline about one-third each were taking boosted atazanavir (Regaturaz) and lopinavir/ritonavir (Kaletra) whilst 20% were on boosted darunavir (Prezista). For NRTIs, 81% used tenofovir/emtricitabine (the drugs in Truvada) and 13% used abacavir/lamivudine (the drugs in Kivexa or Epzicom). Participants were randomly assigned to switch to Eviplera either immediately or after six months.

Eviplera was shown to be non-inferior overall: 94% of participants who switched right away, 92% in the delayed switch arm and 90% who stayed on their protease inhibitor regimen maintained virological suppression (<50 copies/ml) at 24 weeks. At 48 weeks, 89% in the immediate switch arm still had undetectable viral load.

Tebas' report focused on changes in blood lipids, which are known to affect cardiovascular risk.

Total cholesterol levels fell by -25 mg/dl following either an immediate or delayed switch to Eviplera, whilst LDL 'bad' cholesterol fell by about -16 mg/dl. HDL 'good' cholesterol fell by only a small amount (-2 to -4 mg/dl). People who stayed on a protease inhibitor essential saw no change in any of these parameters. Triglyceride levels in the immediate switch arm fell by -54 mg/dl at 24 weeks and by -65 mg/dl at 48 weeks; the delayed switch arm saw a -81 mg/dl drop. In contrast, triglycerides rose slightly whilst patients remained on protease inhibitors (+3 mg/dl).

These changes resulted in overall improvement in lipid profiles after switching to Eviplera. The researchers used the US National Cholesterol Education Program (NCEP) system, which classifies people as having desirable/optimal, borderline or high lipid levels based on their risk of developing cardiovascular disease.

At baseline, 59% of participants were classified as having desirable total cholesterol levels. At 24 weeks, this rose to 84% in the immediate switch group whilst remaining about the same for people who remained on protease inhibitors. The before-and-after percentages were the same for triglycerides.

The proportion of people with optimal LDL rose after the switch (from 29% to 45%) whilst the percentage with high HDL fell a bit (from 27% to 17%). This resulted in an increased proportion of switchers achieving a favourable total cholesterol-to-HDL ratio (from 41% to 55%), compared with no change (38% to 37%) amongst those continuing on protease inhibitors.

"Simplifying from a [protease inhibitor/ritonavir] regimen to [Eviplera] in HIV-1 RNA suppressed patients may be an effective therapeutic choice for maintaining virologic suppression...[and] improving lipid profiles," the researchers concluded.

References

HIV Rate Could Reach 50% Among IDUs of Lahore and Karachi by 2015
Author: Mark Mascolini
09 October 2013
Half of injection drug users (IDUs) in Karachi and Lahore, Pakistan could have HIV infection by 2015, according to modeling projections. One in five male sex workers (MSW) and transgenders in Karachi could have HIV by 2015.

HIV transmission is high among IDUs in Pakistan, and recent evidence indicates rising HIV transmission among MSW, transgenders (hijra), and female sex workers (FSW). UNAIDS estimates an HIV prevalence below 0.1% in 15- to 49-year-olds in Pakistan, but HIV rates may be much higher in some urban high-risk populations.

Using 2011 mapping data, researchers calculated densities of key populations per 1000 adult men in Karachi, Lahore, Faisalabad, Larkana, Peshawar, and Quetta. They used surveillance data to assess bridging between these populations. And they used the UNAIDS Estimation and Projection Package model to estimate and project HIV epidemics among these key populations in Karachi, Lahore, Faisalabad, and Larkana.

Modeling determined that Lahore had the largest FSW population (at 11.5 FSWs per 1000 adult men) but the smallest IDU population (at 1.7 per 1000 adult men). Quetta had the most sexual and drug
injecting bridging between sex workers and IDUs, at estimated rates of 6.7% of FSWs, 7.0% of MSW, and 3.8% of transgenders.

The models suggested that by 2015 HIV prevalence will reach 17% to 22% among MSW and transgenders in Karachi, 44% to 49% among IDUs in Lahore, and 46% to 66% among IDUs in Karachi. By 2025, modeling indicates that 65% to 75% of IDUs in Faisalabad could have HIV infection.

The model estimated that 2.6% to 5.4% of FSWs in Larkana would have HIV by 2015, and 11.9% to 20.3% would be infected by 2025. The model determined that HIV prevalence is also rising quickly among FSWs in Karachi.

“Prevention among key populations remains a key challenge for Pakistan’s efforts to curtail the HIV epidemic,” the authors stress. “Without intervention or behaviour change, the HIV prevalence is expected to continue to rise among key populations in cities across Pakistan over the next 10-15 years.”


Study: Herbal products omit ingredients, contain fillers
Consumers of natural health products beware. The majority of herbal products on the market contain ingredients not listed on the label, with most companies substituting cheaper alternatives and using fillers, according to new research from the University of Guelph.

The study, published today in the open access journal BMC Medicine, used DNA barcoding technology to test 44 herbal products sold by 12 companies. Only two of the companies provided authentic products without substitutions, contaminant or fillers. Overall, nearly 60 per cent of the herbal products contained plant species not listed on the label. Researchers detected product substitution in 32 per cent of the samples. More than 20 per cent of the products included fillers such as rice, soybeans and wheat not listed on the label.

"Contamination and substitution in herbal products present considerable health risks for consumers," said lead author Steven Newmaster, an integrative biology professor and botanical director of the Guelph-based Biodiversity Institute of Ontario (BIO), home of the Canadian Centre for DNA Barcoding.

"We found contamination in several products with plants that have known toxicity, side effects and/or negatively interact with other herbs, supplements and medications."

One product labelled as St. John’s wort contained Senna alexandrina, a plant with laxative properties. It’s not intended for prolonged use, as it can cause chronic diarrhea and liver damage and negatively interacts with immune cells in the colon.

Several herbal products contained Parthenium hysterophorus (feverfew), which can cause swelling and numbness in the mouth, oral ulcers, and nausea. It also reacts with medications metabolized by the liver. One ginkgo product was contaminated with Juglans nigra (black walnut), which could endanger people with nut allergies.

Unlabelled fillers such as wheat, soybeans and rice are also a concern for people with allergies or who are seeking gluten-free products, Newmaster said.

"It’s common practice in natural products to use fillers such as these, which are mixed with the active ingredients. But a consumer has a right to see all of the plant species used in producing a natural product on the list of ingredients."

Until now, verifying what’s inside capsules or tablets has posed challenges, Newmaster said. His research team developed standard methods and tests using DNA barcoding to identify and authenticate ingredients in herbal products.

"There is a need to protect consumers from the economic and health risks associated with herbal product fraud. Currently there are no standards for authentication of herbal products."

Medicinal herbs now constitute the fastest-growing segment of the North American alternative medicine market, with more than 29,000 herbal substances sold, he said.

More than 1,000 companies worldwide make medicinal plant products worth more than $60 billion a year.

About 80 per cent of people in developed countries use natural health products, including vitamins, minerals and herbal remedies.

Canada has regulated natural health products since 2004. Regulators face a backlog of licence applications, and thousands of products on the market lack a full product licence. Globally, regulatory problems involving natural health products continue to affect consistency and safety, Newmaster said.
“The industry suffers from unethical activities by some of the manufacturers.”
The study also involved research associate Subramanyam Ragupathy, U of G student Meghan Gruric and Sathishkumar Ramalingam of the Bharathiar University in India.

**Badgers ultimately responsible for around half of TB in cattle, study estimates**
by Sam Wong 11 October 2013

Badgers are ultimately responsible for roughly half of tuberculosis (TB) in cattle in areas with high TB prevalence, according to new estimates.

However, only around six per cent of infected cattle catch TB from badgers, with onward transmission between cattle herds accounting for the remainder, the study suggests.

The findings are published in the journal *PLOS Currents: Outbreaks*.

Badgers ultimately responsible for around half of TB in cattle, study estimates

has been debated intensely as part of discussions about whether badgers should be culled to control the disease.

The Randomised Badger Culling Trial, which ran from 1998 to 2005, found evidence that culling could reduce TB in herds inside culled areas, while increasing TB in areas nearby.

Mathematical models based on data from the trial were previously used to calculate an estimate of the proportion of TB in cattle that could ultimately be attributed to transmission from badgers.

The new paper, by scientists at Imperial College London, provides a more detailed analysis. It estimates that badgers ultimately account for 52 per cent of cattle TB in areas where prevalence in cattle is high. There is considerable uncertainty around this estimate, but the authors say that 38 per cent is a robust minimum value for the estimate. There is no robust maximum value.

Professor Christl Donnelly, from the Medical Research Council Centre for Outbreak Analysis and Modelling at Imperial, said: “These findings confirm that badgers do play a large role in the spread of bovine TB. These figures should inform the debate, even if they don’t point to a single way forward.”

The mathematical model suggested that 5.7 per cent* of transmission to cattle herds is from badgers to cattle, with the rest of the contribution from badgers resulting from onward transmission between cattle herds.

*The 95% confidence interval for this estimate is 0.9% to 25%.

Reference
Christl A Donnelly and Pierre Nouvellet. ‘The contribution of badgers to confirmed tuberculosis in cattle in high-incidence areas in England.’ *PLOS Currents: Outbreaks*, 10 October 2013. View

**Immune system discovery could lead to EBV vaccine to prevent mono, some cancers**
October 11, 2013

Development of a vaccine against Epstein-Barr virus (EBV) has taken a step forward with the Canadian discovery of how EBV infection evades detection by the immune system.

EBV causes infectious mononucleosis and cancers such as Hodgkin’s lymphoma and nasopharyngeal carcinoma, which is the most common cancer in China, as well as opportunistic cancers in people with weakened immune systems. A member of the herpes virus family that remains in the body for life, the virus infects epithelial cells in the throat and immune cells called B cells.

The researchers discovered that the virus triggers molecular events that turn off key proteins, making infected cells invisible to the natural killer T (NKT) immune cells that seek and destroy EBV-infected cells.

“If you can force these invisible proteins to be expressed, then you can render infected cells visible to NKT cells, and defeat the virus. This could be key to making a vaccine that would provide immunity from ever being infected with EBV,” says Dr. Rusung Tan, the study’s principal investigator. Dr. Tan is a
scientist and director of the Immunity in Health & Disease research group at the Child & Family Research Institute at BC Children’s Hospital, and a professor in the Department of Pathology at the University of British Columbia.

The findings were published this week in the print edition of the scientific journal Blood.

For this study, the researchers looked at cells from infected tonsils that had been removed from patients at BC Children’s Hospital by Dr. Frederick Kozak. The researchers infected the tonsillar B cells with EBV, and then combined some of these cells with NKT cells. They found that more NKT cells led to fewer EBV-infected cells, while an absence of NKT cells was associated with an increase in EBV-infected cells.

Outside influence: Genes outside nucleus have disproportionate effect

October 11, 2013

New research from the University of California, Davis, shows that the tiny proportion of a cell’s DNA that is located outside the cell nucleus has a disproportionately large effect on a cell’s metabolism. The work, with the model plant Arabidopsis, may have implications for future treatments for inherited diseases in humans.

Plant and animal cells carry most of their genes on chromosomes in the nucleus, separated from the rest of the cell. However, they also contain a small number of genes in organelles that lie outside the nucleus. These are the mitochondria, which generate energy for animal and plant cells, and chloroplasts, which carry out photosynthesis in plant cells.

The influence of genes outside the nucleus was known to an earlier generation of field ecologists and crop breeders, said Dan Kliebenstein, professor in the UC Davis Department of Plant Sciences and Genome Center and senior author on the paper published Oct. 8 in the online journal eLife. This is the first time that the effect has been quantified with a genomic approach, he said.

Bindu Joseph, a postdoctoral researcher in Kliebenstein’s lab, and Kliebenstein studied how variation in 25,000 nuclear genes and 200 organellar genes affected the levels of thousands of individual chemicals, or metabolites, in leaf tissue from 316 individual Arabidopsis plants.

They found that 80 percent of the metabolites measured were directly affected by variation in the organellar genes — about the same proportion that were affected by variation among the much larger number of nuclear genes. There were also indirect effects, where organellar genes regulated the activity of nuclear genes that in turn affected metabolism.

"At first it’s surprising, but at another level you almost expect it," Kliebenstein said. "These organelles produce energy and sugar for cells, so they are very important."

Similar effects could also occur in mammalian cells, Kliebenstein said. That has implications for in vitro fertilization therapies aimed at preventing diseases caused by faulty mitochondria being passed from mother to child. The British government recently proposed draft regulations for "three-parent embryos," created by taking a the nucleus from a fertilized egg and putting it into an egg cell from a third donor with its own set of mitochondria. The technique has so far only been tested in animals.

"From what we can see in plants, there might be an issue, but it needs testing," Kliebenstein said. Large population surveys that aim to link conditions such as obesity to specific genes should also take more account of organellar genes, he said.

Single Gene Mutation Linked to Diverse Neurological Disorders

Oct. 9, 2013 — A research team, headed by Theodore Friedmann, MD, professor of pediatrics at the University of California, San Diego School of Medicine, says a gene mutation that causes a rare but devastating neurological disorder known as Lesch-Nyhan syndrome appears to offer clues to the developmental and neuronal defects found in other, diverse neurological disorders like Alzheimer’s, Parkinson’s and Huntington’s diseases.
The findings, published in the October 9, 2013 issue of the journal *PLOS ONE*, provide the first experimental picture of how gene expression errors impair the ability of stem cells to produce normal neurons, resulting instead in neurological disease. More broadly, they indicate that at least some distinctly different neurodevelopmental and neurodegenerative disorders share basic, causative defects.

The scientists say that understanding defects in Lesch-Nyhan could help identify errant processes in other, more common neurological disorders, perhaps pointing the way to new kinds of therapies. Lesch-Nyhan syndrome is caused by defects in the HPRT1 gene (short for hypoxanthine guanine phosphoribosyltransferase, the enzyme it encodes), a gene that is well-known for its essential "housekeeping duties," among them helping generate purine nucleotides—the building blocks of DNA and RNA.

Mutations in the gene result in deficiencies in the HPRT enzyme, leading to defective expression of the neurotransmitter dopamine and subsequent abnormal neuron function. HPRT mutation is known to be the specific cause of Lesch-Nyhan, an inherited neurodevelopmental disorder characterized by uncontrollable repetitive body movements, cognitive defects and compulsive self-mutilating behaviors. The disorder was first described in 1964 by medical student Michael Lesch and his mentor, William Nyhan, MD, professor emeritus at UC San Diego School of Medicine.

Using mouse embryonic stem cells modified to be HPRT-deficient, Friedmann and colleagues discovered that the cells do not develop normally. Instead, they differentiate from full-fledged neurons into cells that resemble and partially function as neurons, but also perform functions more typical of glial cells, a kind of supporting cell in the central nervous system. In addition, they noted that HPRT deficiency causes abnormal regulation of many cellular functions controlling important operational and reproduction mechanisms, DNA replication and repair and many metabolic processes.

"We believe that the neural aberrations of HPRT deficiency are the consequence of these combined, multi-system metabolic errors," said Friedmann. "And since some of these aberrations are also found in other neurological disorders, we think they almost certainly play some role in causing the neurological abnormalities in diseases like Alzheimer's, Parkinson's, Huntington's and possibly others. That makes them potential therapeutic targets for conditions that currently have limited or no treatments, let alone cures."

The task now is to further parse and better understand the many pathways that cause abnormal brain and brain cell development, and how those pathways are also disturbed in other neurological disorders. Those defects will probably not affect HPRT directly, said Friedmann, but rather will correspond to some of the same metabolic and genetic errors that occur as a result of HPRT deficiency. Once those pathways are identified, they may become good targets for more effective forms of therapy.

**Journal Reference:**

Innovative Concept for Knee Cartilage Treatment

Oct. 9, 2013 — Researchers have developed a material that can be used for the controlled release of a substance when subjected to cyclic mechanical loading. This work, carried out within the context of the National Research Programme "Smart Materials" (NRP 62), offers a potential treatment method for specific tissues such as knee cartilage.

In order to regenerate, knee cartilage, paradoxically, needs to be placed under mechanical stress, as happens whenever we take a step and our knees take our weight. When stimulated in this way, the cartilage cells develop receptors that are sensitive to the growth factors produced by the organism. It is also at this very moment that they would be most receptive to medication. Working on this basis, Dominique Pioletti and Harm-Anton Klok from EPF Lausanne have developed a smart material that only releases a substance when the material is mechanically loaded.

**Threshold effect**

As they describe in a recent publication, their material takes the form of a hydrogel matrix, liposome-type nanoparticles and, finally, a payload—in this case a dye. When subjected to cyclic mechanical loading, the hydrogel matrix heats up. Once subjected to heat, the diameter of the liposomes shrinks significantly. This frees up space in the matrix, increasing its permeability and facilitating the release of the dye from the matrix. "One of the main difficulties has been the development of nanoparticles that respond to our specification," explains Dominique Pioletti. "Basically, for the concept to work, their response to the
heating process must have a very clear threshold between the two to three degrees that separate the static and stimulated states.”

The researchers then wanted to verify that it was actually the heating process resulting from the repetition of the mechanical loading that caused the dye to be released. During an initial experiment, the material was subjected to cyclic mechanical loading but the heat produced was evacuated in order to prevent any local temperature increase in the material. "This test enabled us to exclude a sponge-type function, whereby the dye was only being released as a result of the pressure," explains Dominique Pioletti. During a second experiment, the nanoparticles were removed. The matrix heated up as expected due to the cyclic mechanical loading but none of the dye was released. The researchers concluded that the three elements of the composite material were required for the system as a whole to function as intended.

Long-term prospects Whilst the researchers have been able to demonstrate the validity of their concept, Dominique Pioletti stresses that a future treatment is still a long way off. "First of all we need to develop a hydrogel and nanoparticles that are safe and biodegradable, before progressing to clinical trials. And, above all, we need to find partners interested in investing in our project.”

**Journal Reference:**

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Only a fifth of pregnancies among women living with HIV in the US are planned

Michael Carter
Published: 15 October 2013

Only a fifth of pregnancies among women living with HIV in the United States are planned, research published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes* shows. The majority of women were ambivalent about their pregnancy and planned pregnancies were associated with patient-initiated discussions about conception and pregnancy.

“Our findings suggest that family planning – including discussions of effective contraception, pregnancy intentions and safer contraception methods – alongside HIV prevention education – is needed in this population...in the primary HIV care setting,” comment the authors. “Our goal should be to maximize the number of planned pregnancies.”

Improvements in HIV treatment and care mean that the risk of vertical (mother-to-child) transmission of HIV can be reduced to below 1%. Moreover, use of antiretroviral therapy can minimise the risk of sexual transmission of HIV in couples wishing to conceive.

The number of pregnancies among women living with HIV in the US increased by 30% between 2000 and 2006. However, relatively little is known about pregnancy planning among women in the US. Investigators from the HIV and Obstetrics Pregnancy Education Study (HOPES) therefore designed a cross-sectional study involving women with HIV who received care at twelve sites in 2012.

All the women knew they were living with HIV before becoming pregnant and were aged 18 or over. They completed the London Measure of Unplanned Pregnancy (LMUP), a validated questionnaire designed to assess the pregnancy intentions of women who are already pregnant. The LMUP categorises pregnancies as unplanned, ambivalent pregnancy or planned. The women were also asked about their engagement with HIV care in the year before they became pregnant and if they had had any discussions with a healthcare provider about conception and pregnancy.

A total of 172 women were recruited to the study. Their median age was 28 years and 78% were black. The majority (86%) reported that they had seen a healthcare provider in the year before their pregnancy, including 77% who had seen an HIV specialist and 47% who had received interdisciplinary care (combination of HIV care, primary care and/or obstetrics and gynaecology). Most (81%) were taking antiretroviral therapy in the year before conceiving.

Approximately half (45%) of participants reported that they had initiated a conversation with a healthcare provider about their interest in pregnancy and 60% said that a healthcare provider had raised this subject with them. Conversations with healthcare staff about conception and birth control were reported by 81% of women and 97% said they had been informed about condom use to prevent the transmission of HIV and sexually transmitted infections.

Analysis of the LMUP scores showed that 19% of participants had planned their pregnancy, 58% were ambivalent and 23% had an unplanned pregnancy. Over half (52%) indicated that they had not intended
to become pregnant and a similar proportion (54%) stated that when they became pregnant they did not want the baby.

Factors associated with a reduced risk of an unplanned or ambivalent pregnancy included a previous pregnancy since diagnosis with HIV (aRR = 0.67; 95% CI, 0.47-0.94, p = 0.02).

“We speculate that this may be related to increased knowledge regarding the low risk of transmission of HIV during pregnancy from past experience and, therefore, less ambivalence or fear regarding planning for a future pregnancy,” comment the authors.

Having seen a healthcare provider (aRR = 0.60; 95% CI, 0.46-0.77, p < 0.001) and having a patient-initiated pregnancy discussion (aRR = 0.63; 95% CI, 0.46-0.77, p < 0.001) also significantly reduced the risk of unwanted or ambivalent pregnancies.

The investigators conclude that interventions that increase the engagement of women living with HIV with health care and the incorporation of pregnancy discussions and counselling into routine HIV care may decrease rates of unplanned or ambivalent pregnancies among women with HIV.

Reference

Fungus targets HIV patients—study
October 15 2013 at 09:33am
By Vuyo Mkize
Johannesburg—Local researchers have discovered a new fungus that causes a potentially deadly disease in HIV-positive South Africans.

The study – titled A Dimorphic Fungus Causing Disseminated Infection in South Africa – was led by Chris Kenyon from Groote Schuur Hospital in Cape Town and Dr Nelesh Govender from the National Institute of Communicable Diseases (NICD), and was published on Thursday in the New England Journal of Medicine, a widely read and influential medical periodical.

From July 2008 to July 2011, the researchers and their team conducted an enhanced surveillance to identify the cause of systemic, dimorphic fungal (fungi that can exist as mould or yeast) infections in patients at Groote Schuur and other hospitals affiliated with the University of Cape Town.

The infection was caused by a newly described, but unnamed, opportunistic fungus in the type Emmonsia, and was fatal in three patients.

It was probably acquired after inhalation of fungal spores from the environment. However, how it got into the body and how the immune system responded to it still needed to be researched.

“No person-to-person transmission occurs with this infection and, fortunately, it can be treated successfully in most cases,” the NICD said.

Researchers collected clinical and laboratory data on 13 patients – who were aged between 29 and 38 – and had disseminated Emmonsia disease and other dimorphic fungal infections.

Eight of the patients were men and all 13 presented with “evidence of clinically advanced HIV disease and with very low CD4 counts”. They were also anaemic and had widespread skin lesions.

The NICD said that until antiretroviral treatment was started and recovery of the immune system occurred, many HIV-infected patients were at risk of bacterial, viral and fungal infections.

“Onece the diagnosis had been made, most patients experienced dramatic and rapid responses to antifungal treatment. In most patients, the skin lesions healed almost completely, they gained weight and their lungs recovered.”

According to the study, five patients were on antiretroviral treatment – two had virologic and immunologic failure; the other three – who had presented at four, seven, and 11 weeks after starting
antiretrovirals – had a more pronounced inflammatory infiltrate in the dermis than the patients not receiving antiretrovirals.

Govender said on Friday: “So far, it (the fungus) has only been discovered in South Africa, but the most important way to prevent it is to get diagnosed for HIV early. It’s a great honour for us for our study to be published in this very prestigious journal, but it’s also an important discovery because it will impact on how patients are treated and also how doctors diagnose patients with suspected opportunistic infections more carefully.” – The Star

October 14, 2013
Research at the medico-legal borderland: perspectives on HIV and criminal law
By Alex McClelland
In recent years, the criminalization of HIV transmission, exposure and non-disclosure has become a hot topic among those working within the global AIDS milieu. Social scientists have become increasingly attentive to the complex and varied consequences and impacts of HIV criminalization. Not surprisingly, at this year’s Association of the Social Science and Humanities on HIV (ASSHH) Conference there was a wide variety of innovative work on the issue. A majority of the research was presented from social scientists working in the two countries with some of the greatest number of per-capita criminal charges and prosecutions related to HIV non-disclosure and exposure: the United States and Canada.

The conference held two formal sessions highlighting new work in this area entitled: Viral Politics: HIV Criminalization & Social Inquiry and Social Science, Criminal Law and HIV Transmission Risks: Novel Research Perspectives. In this article I summarize highlights and key findings from these presentations, and examine some of the methodological approaches and theories employed by social scientists working on the ‘medico-legal borderland’. I also provide a brief critical analysis in order to pose questions for future potential inquiry.

The medico-legal borderland
Social research into HIV criminalization is most often situated within the theoretical and discursive space described by Timmermans and Gabe (2003) as the ‘medico-legal borderland’. The medico-legal borderland emerges from the intersection of the medical and the legal wherein both forms of knowledge and power join together to constitute new regimes of knowledge; ones that produce hybrid legal and medical subjects who are governed through normative knowledge on health and illness, as well as legal regulation, discipline and forms of social control (Mykhalovskiy, 2011). This intersection of crime and health contains elements of both realms but cannot be simply reduced to either one. The medico-legal borderland itself constitutes a hybrid disciplinary environment in which state institutions mobilize medical knowledge for legal purposes, and where the medical becomes intertwined with other mechanisms of power – both legal and extra-legal. As highlighted by HIV criminalization scholar Eric Mykhalovskiy (2011), Timmermans and Gabe use the term medico-legal borderland to “decry the absence of dialogue between criminology and medical sociology and to encourage critical analyses of sites in which health care and criminal-legal practices intersect” (pg. 674, 2011).

Day One: Deviance, Advocacy & Model Laws
During the first session at the ASSHH conference, Trevor Hoppe presented his doctoral work titled: ‘From Sickness To Badness: Punishing, Regulating, and Controlling HIV in Michigan’. Michigan is one of the 24 American states to have enacted criminal laws requiring that people living with HIV disclose their HIV status prior to engaging in sexual acts with partners. In the presentation, Hoppe employs sociological theories of social control and mobilizes the work of Conrad and Schneider (1980) to examine how people with HIV are constituted as deviants to be punished within the juridical apparatus of Michigan, USA. Conrad and Schneider’s ‘Deviance and Medicalization: From Badness to Sickness’ (1980), elaborates how the medicalization of deviant behaviour has been organized socially. This includes how issues such as attention deficit, learning disabilities, drug use and alcoholism have been transformed from being understood as acts of deviance, to those that are regulated through medical ways of knowing.

In an attempt to build on the work of Conrad and Schneider, Hoppe’s research reveals that medicalized knowledge of HIV has no traction in Michigan courts where legal decisions are guided by fear, stigma and moralistic judgements, thus: “From Sickness to Badness”. Hoppe argues that the decisions made under Michigan’s HIV disclosure law are not formed through benevolent medical or public health considerations (i.e. to prevent further HIV transmissions), but rather, they are formed by punitive and moralizing narratives that frame people living with HIV as social deviants who need to be
under state control. Hoppe’s theoretical engagement ends there and one is left thinking: has HIV not always been akin to badness?

Additionally, it is unclear in Hoppe’s project what is to be achieved theoretically through the polarization of sickness and deviance. Under a regime of medicalization, are people living with HIV not also governed by law? Hoppe’s work suggests that a more nuanced investigation is required of the ways in which medical and legal knowledges intersect to create complex hybrid rationalities of governance.

Hoppe’s work primarily consists of a case-by-case thematic analysis of prosecutorial documents to highlight the court’s perpetration of moralizing tropes towards positive people as the violent criminal “other”. However, Hoppe makes up for what is lacking in the project’s theoretical rigour with his greatest contribution to the field: bringing to light detailed evidence from 58 felony HIV non-disclosure convictions in Michigan through undertaking extensive research from police data and media archives. Hoppe’s research constitutes 95% of all convictions between 1992-2010 in the state. In many of these cases, in sentencing, HIV is taken into account by judges in the same way as the use of a violent weapon. Hoppe presents a number of disheartening scenarios in which people living with HIV are charged and prosecuted for variety of sex acts, even an act of vaginal to nasal penetration in which a stripper was prosecuted for rubbing her labia on an undercover police officer’s nose.

The injustices that Hoppe’s work reveals leave one wanting more in terms of understanding what drives such punitive and state-sponsored stigma. There is no doubt that the work of social scientists is to document the forces that marginalize so as to interrogate and reveal oppressive power structures. But if our work is merely descriptive and not aimed at revealing how such events have come to be in the first place, at what point does such straightforward documentation become gratuitous? Since the beginnings of the epidemic, people living with HIV have been framed as social outcasts, deviants and criminals. What new contributions can we make to the body of social research in this area to advance understandings of how and why regimes of medical and legal governance are historically, socially, culturally and economically constituted?

The following presentations in the session were by Canadian researcher, Eric Mykhalovskiy, an Associate Professor at York University, and by Daniel Grace, a post-doctoral researcher with the University of British Columbia and visiting fellow at the London School of Hygiene and Tropical Medicine. Both researchers employ forms of feminist sociologist Dorothy Smith’s (1987) institutional ethnographic inquiry to examine how relations with institutions structure people’s everyday lives. Because of its focus on mundane everyday activity, as well as broader social, economic, political and cultural power relations, institutional ethnographic inquiry can offer both a useful and critical micro and macro analysis to explore aspects of the criminalization of HIV transmission, exposure and non-disclosure.

In the presentation: HIV, Criminalization, and the Limits of Science: Rethinking Activism, Eric Mykhalovskiy explored the Canadian activist milieu in reaction to the recent Supreme Court R v. Mabior decision and disjuncture that occurred between biomedical knowledge of HIV and judicial decision-making. Building on the work of sociologist George Smith, Mykhalovskiy’s intervention elaborated a reflective ethnographic analysis of activists who mobilized in reaction to the 1998 Supreme Court R v. Cuerrier decision, and the consequences of the promotion of “science-based” law reform. In “Political Activist as Ethnographer”, George Smith (1990) proposed grass-roots political organizing as a research method aimed at providing communities living with HIV an opportunity to step outside of their current realities in order to change the harmful social conditions that lead to structural violence and forms of oppression. The work of the activist ethnographer is then to extend and promote knowledge to help themselves and others understand how “a ruling regime works with a view to transforming it” (Smith, 1990). Mykhalovskiy follows this tradition in the Canadian AIDS activist milieu where his work aims to counter the increasing punitive nature of legal governance of people with HIV. Most recently he has been working on an Ontario-wide campaign to call on the Attorney General to develop guidelines for prosecutors in HIV non-disclosure cases.

In 2012, the highest court in Canada extended the role of law in relation to HIV non-disclosure: now legally requiring the use of a condom and a ‘low viral load’ if someone does not tell a sex partner their HIV-positive status. Without both a condom and a ‘low viral load’ consent is legally vitiated. This ruling ignores the fact that many people are not able to use condoms for complex reasons, or achieve a ‘low viral load. Interpreted by activists, this ruling over-extends the law, puts the legal burden solely on people living with HIV, and is inconsistent with years of HIV prevention work.

Previously, the law had been murkier: the 1998 Supreme Court decision required that someone with HIV must disclose if the sexual behaviour they engaged in posed a “significant risk” of transmitting HIV to their partner(s). But the court did not define “significant risk” and this led to years of uncertainty for
people living with HIV and many inconsistent charges and prosecutions. Growing rapidly since the early 1990s, Canada has seen approximately 150 charges faced by 140 defendants in relation to non-disclosure – with a disproportionately high conviction rate. Those who are prosecuted are often added to a lifetime sex offender registry and have known to be held in what is called ‘protective custody’ or ‘administrative segregation’.

As Mykhalovskiy elaborates, to quell the growing number of charges and prosecutions, activists’ had strategically called for “science-based” law reform aiming to ensure more consistency and greater restraint from the courts. An example of such reform would be ensuring that charges could only be laid when there was a scientific basis for transmission to have occurred and where there was willful intent or reckless behaviour involved. However, what resulted is that the Supreme Court’s 2012 decision interpreted scientific knowledge of HIV risk and transmission using a legal rationality that views non-disclosure as sexual assault. Such logic can be only understood through looking back to the legacy of second wave feminist legal scholars, who invoked ‘consent’ as a locus of governance, thus expanding the role of the state juridical and punitive apparatus so as to protect women from rape and sexual assault. Mykhalovskiy thus calls into question the activist strategy of mobilizing scientific knowledge on HIV in the context of this legal rationality because of the way it backfired in the Canadian context, resulting in a new legal test that is inconsistent with years of transmission science and HIV prevention work.

Another contribution of this presentation is the examination of the person with a low viral load (and conversely the person who cannot achieve a low viral load) as new medico-legal subjects that the Supreme Court’s decision constitutes. Or what the session discussant Martin French noted as the emergence of “techno-scientific identify profiles cloaked in jurisprudence”. As a technique of governance, the judicial management of viral load will be increasingly important to understand for social researchers, especially in the context of ‘treatment as prevention’ regimes, viral load mapping projects, and with the development of new technologies of therapeutic surveillance.

Mykhalovskiy’s reflexive approach is encouraging in the wake of the discouraging Supreme Court decision. More work like this is needed to interrogate and evaluate strategies to counter the increasingly punitive climate for people with HIV. Mykhalovskiy’s work on the strategy of law reform employed by activists in the HIV social movement suggests that a number of questions remain. With the current reality of the negative consequences of second wave feminist legal reform related to how consent now legally frames HIV non-disclosure, what are the unforeseen impacts that could result from AIDS activists-led legal reform for prosecutorial guidance? Who could get left behind with the new prosecutorial guidelines? And will such guidance for prosecutors help draw a further dividing line between the sick and the well, or the virally detectable and the virally undetectable?

In the case of Daniel Grace’s doctoral thesis work: ‘Best Practice as Coordinating Genre in the Criminalization of HIV Transmission’, the researcher proposes a form of transnational institutional ethnography through examining the proliferation of USAID-written omnibus model laws on HIV that were adopted across 15 west and central African nations between 2005-2010. The model laws include a provision for criminalizing the transmission of HIV and are known as the USAID/Action for West African Region (AWARE) legislation. In Grace’s work, the researcher notes that the laws act as a “pre-operative” and “harmonizing” text that were claimed to be “best practice” grounded in “human rights”. As a legal instrument the model legislation was also promoted as a simple ‘one-size fits all’ solution for legislators working to address HIV/AIDS. Grace calls into question the mobilization of “best-practice” and “human rights” language and elaborates that through his international fieldwork, many policy actors view these transnational legislative practices as harmful and are now actively working to counter them.

A critical analysis of the transnational macro-level coordinating and governance function of “best practices” in the global AIDS response is refreshing. However, the presentation left me wondering how these model laws are so easily adopted. I was left wanting a better sense of the geopolitics, political economy and colonial aspects of this practice, particularly in the context of the American neo-colonial project aimed at exporting forms of morality to African nations and at continuing forms of aid dependency. Grace’s project is a large scale one, and it is likely these analyses are in the work but just did not come out in the short span of the conference presentation. It will be important for social scientists to continue to track the social impact of this legislation in the region to better understand the consequences of this American legislative “best practice” on the lives of people living with HIV.
**Day Two: Service Provider Perspectives & Viropolitics**

The following day of the conference saw the second session during which research was presented from the USA and the UK. The UK is an interesting case, as England and Wales only prosecute ‘intentional’ and ‘reckless’ transmission of HIV. In 2008, the Crown Prosecution Service established policy guidance for prosecutions, which only allows for prosecutions in cases for which a transmission has occurred. As such, there are notably fewer prosecutions (a total of 17 prosecutions as of 2010) than in countries such as Canada and the USA. For some, the example of the UK is regarded as a progressive law reform achievement and has resulted in the push for prosecutorial guidance in other countries.

Catherine Dodds, researcher from the UK’s Sigma Research and the London School of Hygiene and Tropical Medicine presented her team’s research entitled *Keeping Confidence: HIV and Criminal Law From Service Provider Perspectives*. Dodd examines the medico-legal borderland from the perspective of service providers who support people living with HIV. As a result of the legal environment, Dodd’s qualitative research with 75 service providers reveals a conflict between the professional liability and the ‘duty of care’ for those they work with, and the ‘duty to the law’, or the legal liability to report a client if they fear they could be having unprotected sex. Dodd’s work shows how many providers had a basic understanding of the law, but they lacked a nuanced understanding so as to effectively communicate legal obligations to clients.

With this project, the roles of providers have become conflicted which, Dodd notes, creates professional uncertainty around service provision and the potential new burden that has emerged for them to communicate accurate legal information. In some cases, providers now see themselves as having to enforce the law and/or build legal literacy (re: people living with HIV’s criminal law obligations), as well as providing care and support. This has complicated service provider/client relations and has potentially negative consequences for the delivery of care. In a small number of instances this issue has directly impacted how people do their jobs, as a few providers noted that they have stopped detailed note-taking during client sessions to avoid the potential for health records to be subpoenaed.

As service providers’ jobs are becoming entangled with new legal obligations, Dodd’s work is important in expanding understandings of the impacts of criminalization on the services that people living with HIV access to support their health and wellbeing. Additionally, this project is an important step toward revealing how the day-to-day juridical management of people living with HIV is increasingly diffused throughout extra-legal actors in society.

Martin French ended the session with his presentation titled *The Viropolitics of HIV Testing: Counselling and Criminalization in Tennessee*. French – a new faculty member in the Sociology Department at Montreal’s Concordia University – presented on his fieldwork in the American state of Tennessee with HIV voluntary testing and counselling providers. The state leads all other American jurisdictions with 48 prosecutions related to various forms of HIV criminalization between 2008-2010. French’s work concerns a number of issues specific to the negative impact that HIV criminalization has on public health outcomes. This includes examining how hybrid legal and medical principles result in promoting HIV stigma, and examine what occurs when public health knowledge, such as health records, are “recoded” in a juridical context.

In his work, French reveals how the macro level punitive legal environment negatively impacts the micro level practice of voluntary HIV testing and counselling. Through qualitative interviews with Tennessee service providers, French describes the emerging sense of anomie produced by the apparatus of criminalization. French notes that the counselling milieu has been theorized in the past as a site of normalization, in which medical knowledge from across populations is measured against the individual to evaluate the “normal” and “abnormal”. Under criminalization, this emerging anomie environment of normlessness leaves people living with HIV and service providers who work with them in a state of increasing stress, confusion and uncertainty.

Seeking to advance conceptions of the biopolitical, French is proposing what he has labelled “viropolitics”, or the “latent indeterminacy prior to biopolitics”. Biopolitics aims to describe a situation in which human biological life becomes the “object of political strategy” (Foucault, 2007, pg. 1). In the early 2000s Achille Mbembe took biopower to the grave by elaborating the concept of ‘necropolitics’. With necropolitics, Mbembe seeks to elaborate “under what practical conditions is the right to kill, to allow to live, or to expose to death exercised?” (Mbembe, 2003, pg. 2). For French, viropolitics is at the analytic margins of biopolitics and necropolitics. His work seeks to further develop and mobilize this concept, which would be a theoretically and analytically useful tool for revealing and understanding the emerging hybrid forms of medico-legal governance that people living with HIV face.
The second ASSHH conference provided a useful platform for taking forward the concept of the medico-legal borderland. It promises to be a useful tool for thinking about how the complex intersection of regimes of medical and legal knowledge shape responses to the HIV epidemic. Social scientists play an important role in this area and by examining the criminalization of HIV at the medico-legal borderland our field will continue to expand and interrogate these complex relations so as to understand how criminal law shapes the social relations of people living with HIV, health care workers, service providers, other actors in the global response to HIV.

References:

Scientists Unravel Mechanisms in Chronic Itching

Oct. 15, 2013 — Anyone who has suffered through sleepless nights due to uncontrollable itching knows that not all itching is the same. New research at Washington University School of Medicine in St. Louis explains why.

Working in mice, the scientists have shown that chronic itching, which can occur in many medical conditions, from eczema and psoriasis to kidney failure and liver disease, is different from the fleeting urge to scratch a mosquito bite.

That’s because chronic itching appears to incorporate more than just the nerve cells, or neurons, that normally transmit itch signals. The researchers found that in chronic itching, neurons that send itch signals also co-opt pain neurons to intensify the itch sensation.

The new discovery may lead to more effective treatments for chronic itching that target activity in neurons involved in both pain and itch. The research is reported online Oct. 15 in The Journal of Clinical Investigation and will appear in the November print issue.

"In normal itching, there’s a fixed pathway that transmits the itch signal," said senior investigator Zhou-Feng Chen, PhD, who directs Washington University’s Center for the Study of Itch. "But with chronic itching, many neurons can be turned into itch neurons, including those that typically transmit pain signals. That helps explain why chronic itching can be so excruciating."

Chen, a professor of anesthesiology, and his colleagues generated mice in which a protein called BRAF always is active and continually sends signals inside itch neurons. The BRAF gene and the protein it makes are involved in the body’s pain response, but scientists didn’t know whether the gene also played a role in itch.

"We thought the animals might be prone to feeling pain rather than itching," Chen explained. "To our great surprise, the mice scratched spontaneously. At first, we didn’t know why they were scratching, but it turns out we developed a mouse model of chronic itch."

Further studies discovered that the BRAF protein could turn on many itch genes, and they showed similar changes of gene expression in mice with chronic itch induced by dry skin and in mice with allergic contact dermatitis, two of the skin conditions that frequently cause people to scratch incessantly.
The findings suggest that targeting proteins in the BRAF pathway may open new avenues for treating chronic itch, a condition in which few therapies are effective. One possibility includes using drugs that are prescribed to treat pain.

"Certain drugs are used to inhibit some of the same targets in patients with chronic pain, and those medications also may quiet down itch," Chen said.

In earlier studies, Chen identified gastrin-releasing peptide (GRP), a substance that carries itch signals to a gene called GRPR (gastrin-releasing peptide receptor) in the spinal cord. In the new study, GRP and GRPR activity was doubled in the genetically altered mice, which could account for some of the increase in the intensity of itching. But other genes that normally are activated by pain also were turned on in the itch pathway, further intensifying the itch sensation.

Surprisingly, however, the mice had a normal response to pain, indicating that the pain and itch pathways are very different.

Unlike scratching a mosquito bite, which usually is only a temporary sensation, chronic itch can persist much longer, according to Chen, also a professor of psychiatry and of developmental biology. His team found that the mice in this study not only scratched spontaneously but also had more severe responses when exposed to substances that normally would induce acute itching.

"In people, chronic itching can last for weeks, months or even years," Chen said. "These mice are helping us to understand the pathways that can be involved in transmitting itch signals and the many contributors to chronic itching. There are many pathways leading from BRAF, and all of these could be potential targets for anti-itch therapies."

Journal Reference:

Pandoravirus: Missing Link Discovered Between Viruses and Cells
Oct. 14, 2013 — With the discovery of Mimivirus ten years ago and, more recently, Megavirus chilensis[1], researchers thought they had reached the farthest corners of the viral world in terms of size and genetic complexity. With a diameter in the region of a micrometer and a genome incorporating more than 1,100 genes, these giant viruses, which infect amoebas of the Acanthamoeba genus, had already largely encroached on areas previously thought to be the exclusive domain of bacteria. For the sake of comparison, common viruses such as the influenza or AIDS viruses only contain around ten genes each.

In the article published in Science, the researchers announced they had discovered two new giant viruses:
• Pandoravirus salinus, on the coast of Chile;
• Pandoravirus dulcis, in a freshwater pond in Melbourne, Australia.

Detailed analysis has shown that these first two Pandoraviruses have virtually nothing in common with previously characterized giant viruses. What’s more, only a very small percentage (6%) of proteins encoded by Pandoravirus salinus are similar to those already identified in other viruses or cellular organisms. With a genome of this size, Pandoravirus salinus has just demonstrated that viruses can be more complex than some eukaryotic cells[2]. Another unusual feature of Pandoraviruses is that they have no gene allowing them to build a protein like the capsid protein, which is the basic building block of traditional viruses.

Despite all these novel properties, Pandoraviruses display the essential characteristics of other viruses in that they contain no ribosome, produce no energy and do not divide.
This groundbreaking research included an analysis of the *Pandoravirus salinus* proteome, which proved that the proteins making it up are consistent with those predicted by the virus' genome sequence. Pandoraviruses thus use the universal genetic code shared by all living organisms on the planet.

This shows just how much more there is to learn regarding microscopic biodiversity as soon as new environments are considered. The simultaneous discovery of two specimens of this new virus family in sediments located 15,000 km apart indicates that Pandoraviruses, which were completely unknown until now, are very likely not rare.

It definitively bridges the gap between viruses and cells—a gap that was proclaimed as dogma at the very outset of modern virology back in the 1950s.

It also suggests that cell life could have emerged with a far greater variety of pre-cellular forms than those conventionally considered, as the new giant virus has almost no equivalent among the three recognized domains of cellular life, namely eukaryota (or eukaryotes), eubacteria, and archaea.

**Notes**


*New Analysis of US Elementary School Mathematics Finds Half-Century of Problematic 'Strands' Structure*

Oct. 15, 2013 — During the "New Math" movement of the 1960s, a team of mathematicians developed a new structure for elementary mathematics. Instead of having a single subject, namely, school arithmetic, as its central core, this new structure instead had eight "strands" that were supposed to tie together elementary mathematics content. The strands structure has persisted to this day. In an article in the November 2013 issue of the *Notices of the American Mathematical Society*, Liping Ma argues that the strands structure has significantly weakened U.S. school mathematics.

In her article, Ma notes that, in many countries where students do well in mathematics, elementary mathematics has school arithmetic as its main organizing structure. School arithmetic is developed as a self-contained subject consisting of whole numbers and fractions, with the whole numbers forming the basis for understanding of fractions. Other components of elementary mathematics, such as measurement or geometry, are not presented as self-contained subjects but are taught in relation to the main subject of school arithmetic.

In the U.S., by contrast, the organizing structure for elementary mathematics has no self-contained structure at its core but rather consists of several strands that are juxtaposed but not explicitly connected. Over the decades, the strands have been given different names—such as "strands," "content areas," or "standards"—and their number, form, and content have varied many times.

Examining developments in U.S. mathematics education going back to the 19th century, Ma notes that although U.S. scholars made significant contributions to school arithmetic, the U.S. never had, as some other countries do, a well-developed school arithmetic. Nevertheless, arithmetic was the core of elementary mathematics in the U.S. for almost one hundred years. Ma describes how this began to change during the 20th century with the advent of the "New Math" of the 1960s and the NCTM Standards of the 1990s. Among the effects of the strands structure are instability of curricular content, discontinuity in instruction, and incoherence in concepts.

In the United States, "the potential of school arithmetic to unify elementary mathematics is not sufficiently known," Ma argues. "This is a blind spot for current U.S. elementary mathematics." Too often school arithmetic is equated with basic computational skills that require only inferior cognitive activity such as rote learning. Although many people in mathematics education view arithmetic as an ugly duckling—that is, a collection of algorithms to be learned by rote—Ma notes that "in the eyes of mathematicians it is often a swan" because of the mathematical structure mathematicians see in arithmetic.
Liping Ma became well known among mathematicians for her 1999 book *Knowing and Teaching Elementary Mathematics* (the book was reviewed by Roger Howe in the *Notices*; see http://www.ams.org/notices/199908/rev-howe.pdf). In this book, Ma studied the understanding of mathematics possessed by school teachers and described a quality called "profound understanding of fundamental mathematics." Ma found that about 10 percent of very experienced teachers in China have this quality. Their profound understanding was acquired not by studying advanced mathematics, but by studying and teaching school mathematics with arithmetic as its core. In an ironic twist, she finds that today China seems to be moving toward adopting a more strand-like structure for its school mathematics standards.

**Journal Reference:**

**New HIV Strain in Russia Spreading Rapidly – Scientists**
MOSCOW, October 16 (RIA Novosti) – A scientific research center in Siberia said Wednesday that it has discovered a new strain of HIV in Russia and that the virus is spreading “at a rapid rate.”

The subtype, known as 02_AG/A, was first detected in the Siberian city of Novosibirsk in 2006 and now accounts for more than 50 percent of new HIV infections in the region, Novosibirsk’s Koltsovo science city said in a statement.

The number of HIV-positive people living in the Novosibirsk Region has leaped from about 2,000 in 2007 up to 15,000 in 2012, the statement said, citing Russia’s Federal AIDS Center.

02_AG/A might be the most virulent form of HIV in Russia, said Natalya Gashnikova, head of the retroviruses department at the Vektor state biotechnology research center at Koltsovo, whose specialists discovered the strain.

She said the virus could spread much faster than Russia’s current leading HIV strain, subtype A(I). The new strain is not limited to the vast area of Siberia. It has been detected in Russia’s southern republic of Chechnya, as well as the former Soviet republics of Kyrgyzstan and Kazakhstan, the institute said.

HIV, a retrovirus that causes slow failure of the immune system, has two types: HIV-1 and HIV-2. The latter is considered less virulent and transmissible.

Scientists say HIV-1 is the most common strain, and divide it into subtypes based on various forms that are grouped in geographic regions around the world.

According to the United Nations, Eastern Europe and Central Asia are the only regions in the world where the HIV infection is clearly on the rise. Fifty-two percent of the HIV-positive people that live across that area are in Russia.

The disease remains poorly understood in Russia and, according to experts at Koltsovo, research into the spread and properties of new HIV strains is underfunded.

Russian schools generally offer little or no sex education, a factor that is believed to contribute to a high HIV infection rate from lack of awareness about sexually transmitted diseases.

Pavel Astakhov, Russia’s children’s rights advocate, said in September that he opposed teaching teenagers about sexual health in school, adding that Russian literature is “the best sex education there is.”

**Study shows how Staph toxin disarms the immune system**
Findings point the way to new class of antibiotics
Researchers at NYU Langone Medical Center have discovered a new mechanism by which the deadly *Staphylococcus aureus* bacteria attack and kill off immune cells. Their findings, published today in the journal *Cell Host & Microbe*, explain a critical survival tactic of a pathogen that causes more skin and heart infections than any other microbe, and kills more than 100,000 Americans every year.

"What we’ve found is that Staph unleashes a multi-purpose toxin capable of killing different types of immune cells by selectively binding to surface receptors," says Victor J. Torres, PhD, assistant professor of microbiology, and senior author of the study. "Staph has evolved the clever ability to target the immune system at different stages."

Scientists have long known that Staph releases an arsenal of toxins to puncture immune cells and clear the way for infection. But only recently have they begun to understand exactly how these toxins work. Earlier this year, Dr. Torres and his team published a paper in Nature explaining how one of those toxins, a protein called LukED, fatally lyses T-cells, macrophages and dendritic cells, all types of white blood cells that help fight off infection. The LukED toxin, they showed, binds to a surface receptor called CCR5 (the same one exploited by HIV). "It attaches to the surface receptor and then triggers pore
formation," says Dr. Torres. But their discovery failed to explain how the bacterial toxin kills other types of white blood cells, such as neutrophils, that lack the CCR5 receptor.

Their most recent work solves this puzzle, showing for the first time how receptors on neutrophils (a common type of white blood cell) also enable binding of the LukED toxin. The researchers found that LukED latches onto surface receptors called CXCR1 and CXCR2, creating the same deadly pores that it does when it latches onto CCR5 receptors. "The mechanism is the same," says Dr. Torres. "The strategy makes Staph deadlier in mice."

Neutrophils are the first responders. Upon infection, they race through the bloodstream to kill off the invading pathogen. "They're like the marines of the immune system," Dr. Torres says. T-cells, macrophages and dendritic cells rush in later, mounting a secondary attack to help the body clear the pathogen and remember it in the future. "Killing off the first responders completely disarms the immune system," Dr. Torres says.

LukED is just one piece of the puzzle, and more research is needed to understand other Staph toxins and how they work together to make the microbe deadlier. However, these recent insights hold promise for new medications that target LukED. Better treatments against Staph are desperately needed. In 2005, the Centers for Disease Control and Prevention estimated that more than half of the 478,000 people hospitalized for staph infections were resistant to methicillin, one of the most potent antibiotics available.

One therapeutic strategy is to block CCR5 receptors and spare the secondary immune response. "We know we can block CCR5 receptors without crippling the rest of the immune system. Some people lack CCR5 and they are perfectly healthy and immune to HIV as well," Dr. Torres says. "But just blocking CCR5 isn't enough." Drugs are available to block CXCR1 and CXCR2 receptors, but those will impair neutrophil recruitment and function. "The lesson is to target the toxin itself and prevent it from attaching to any receptors," Dr. Torres adds. "We have to think globally."

**Genetic errors identified in 12 major cancer types**

Examining 12 major types of cancer, scientists at Washington University School of Medicine in St. Louis have identified 127 repeatedly mutated genes that appear to drive the development and progression of a range of tumors in the body. The discovery sets the stage for devising new diagnostic tools and more personalized cancer treatments.

The research, published Oct. 17 in *Nature*, shows that some of the same genes commonly mutated in certain cancers also occur in seemingly unrelated tumors. For example, a gene mutated in 25 percent of leukemia cases in the study also was found in tumors of the breast, rectum, head and neck, kidney, lung, ovary and uterus.

Based on the findings, the researchers envision that a single test that surveys errors in a swath of cancer genes eventually could become part of the standard diagnostic workup for most cancers. Results of such testing could guide treatment decisions for patients based on the unique genetic signatures of their tumors.

New insights into cancer are possible because of advances in genome sequencing that enable scientists to analyze the DNA of cancer cells on a scale that is much faster and less expensive today than even a few years ago. While earlier genome studies typically have focused on individual tumor types, the current research is one of the first to look across many different types of cancer.

"This is just the beginning," said senior author Li Ding, PhD, of The Genome Institute at Washington University. "Many oncologists and scientists have wondered whether it's possible to come up with a complete list of cancer genes responsible for all human cancers. I think we're getting closer to that."

The new research analyzed the genes from 3,281 tumors – a collection of cancers of the breast, uterus, head and neck, colon and rectum, bladder, kidney, ovary, lung, brain and blood. In addition to finding common links among genes in different cancers, the researchers also identified a number of mutations exclusive to particular cancer types.

Looking at a large number of tumors across many different cancers gives the researchers the statistical power they need to identify significantly mutated genes. These genetic errors occur frequently in some cancers and rarely in others but are nevertheless thought to be important to cancer growth. The research was conducted as part of The Cancer Genome Atlas Pan-Cancer effort, funded by the National Cancer Institute and the National Human Genome Research Institute, both at the National Institutes of Health (NIH).

While the average number of mutated genes in tumors varied among the cancer types, most tumors had only two to six mutations in genes that drive cancer. This may be one reason why cancer is so
common, the researchers said. "While cells in the body continually accumulate new mutations over the years, it only takes a few mutations in key driver genes to transform a healthy cell into a cancer cell," noted Ding.

The scientists, which included co-first authors Cyriac Kandoth, PhD, and Michael McLellan, both at Washington University, along with collaborator Benjamin Raphael, PhD, from Brown University, were also able to identify genes that have a significant effect on survival.

TP53, an already well-known cancer gene, occurred most commonly across the different tumor types. It was found in 42 percent of samples and routinely was associated with a poor prognosis, particularly in kidney cancer, head and neck cancer and acute myeloid leukemia.

Another gene, BAP1, also was linked with an unfavorable prognosis, especially in patients with kidney and uterine cancer.

However, mutations in the breast cancer gene BRCA2 were associated with improved survival in ovarian cancer, while errors in IDH1 were linked to an improved prognosis in glioblastoma, a particularly aggressive brain tumor, and in other cancer types.

Research to find additional cancer genes is ongoing at Washington University's Genome Institute, one of the large-scale genome sequencing centers supported by NIH, and at other academic institutions. Identifying a more comprehensive list of cancer genes could provide the backdrop to improve the diagnosis of cancer and to guide treatment decisions.

"Because we now know, for example, that genes mutated in leukemia also can be altered in breast cancer and that genetic errors in lung cancer also can show up in colon and rectal cancer, we think one inclusive diagnostic test that includes all cancer genes would be ideal," Ding said. "This would provide a more complete picture of what's going on in a tumor, and that information could be used to make decisions about treatment."


Tracking viral DNA in the cell

The medical, humanitarian and economical impact of viral diseases is devastating to humans and livestock. There are no adequate therapies available against most viral diseases, largely because the mechanisms by which viruses infect cells are poorly known. An interdisciplinary team of researchers from the University of Zurich headed by cell biologist Prof. Urs Greber now presents a method that can be used to display viral DNA in host cells at single-molecule resolution. The method gives unexpected insights into the distribution of viral DNA in cells, and the reaction of cells to viral DNA.

Click chemistry detects viral DNA

For their studies, Greber and his team with PhD students I-Hsuan Wang, Vardan Andriasyan and senior research scientist Dr. Maarit Suomalainen used cell cultures and human adenoviruses causing respiratory disease and conjunctivitis, herpes viruses and vaccinia virus, the latter in collaboration with Dr. Jason Mercer and his PhD student Samuel Kilcher from the ETH Zurich. To label the DNA of an intact virus, the scientists turned to click chemistry – widely applicable chemical reaction types. Prof. Nathan Luedtke from the Institute of Organic Chemistry at the University of Zurich, and PhD student Anne Neef developed a new class of "clickable" chemical molecules. "Our molecule is incorporated into viral DNA without affecting the biological functions of the DNA, and it can be used to label the DNA for fluorescence microscopy," says Luedtke.

Defense response of infected cells visible for the first time

Greber and his team infected human cells in culture with the chemically labeled viruses, and observed the behavior of the viral DNA during entry into cells. "Using this elegant method, we can reveal that not all the incoming viral DNA enters the cell nucleus as originally expected, but a significant fraction remains in the cytosol, the fluids of the cytoplasm," explains Greber. According to the scientists, this phenomenon may be part of the antiviral defense reaction. "For the first time, we can display the localization of incoming viral DNA, and link it to anti-viral defense or infection mechanisms," says Greber. The researchers show that cells of the same type take up different amounts of viral DNA into their nucleus.

Greber suspects that the nucleus has antiviral defense reactions, akin to the cytosol, and these defense reactions are variable between cells. With the new method in hand, this is now subject to future studies. The scientists suggest that their procedure can be applied to other DNA viruses, or the HI virus (HIV).

Experts debate whether HIV cure is 'hype or hope'

Liz Highleyman
Published: 17 October 2013

Is a functional cure for HIV feasible within the foreseeable future or is it a hopeless quest robbing resources from more practical approaches to improve the lives of people living with HIV? This question was the crux of a mock trial held yesterday on the opening day of the 14th European AIDS Conference in Brussels.

The debate was part of a satellite session sponsored by Bristol-Myers Squibb (BMS) to mark the launch of its new Partnering for Cure initiative, which will support education and research into novel treatment and cure strategies for chronic viral diseases including HIV and hepatitis B and C.

Christine Katlama of Pierre and Marie Curie University in Paris, playing the 'judge', noted the recent increase in attention to the possibility of an HIV cure at scientific meetings and in the popular media, spurred in part by 'proof-of-concept' cases like that of Timothy Ray Brown (the 'Berlin patient') and that of the Mississippi baby.

Speaking in defence of the proposition that an HIV cure is possible, Carlo Federico Perno of the University of Rome gave the example of hepatitis C as a virus that can be eradicated.

Whilst traditional interferon-based therapy relied on stimulating the immune response, new direct-acting agents work by interfering with various steps of the hepatitis C virus (HCV) lifecycle, much like combination antiretroviral therapy (ART) for HIV. Two highly effective and well-tolerated compounds – Janssen's simeprevir and Gilead Sciences' sofosbuvir – are scheduled for US approval by the end of the year (assuming the federal government shutdown does not disrupt the work of the Food and Drug Administration).

The inclusion of this argument was no doubt intended as an opportunity to educate about hepatitis C, which is increasingly making its way into HIV conferences. Many people with HIV have hepatitis C co-infection, and HIV clinicians are increasingly called upon to treat it. BMS has some promising hepatitis C direct-acting agents in the pipeline including the NS5A inhibitor daclatasvir, the HCV protease inhibitor asunaprevir and the non-nucleoside polymerase inhibitor BMS-791325.

But no one, including Perno, really thinks hepatitis is a good model for an HIV cure. HCV remains confined to a cell's cytoplasm, where it must either "replicate or die", Perno explained. If it does not do so immediately, HCV RNA is rapidly degraded; drugs that fully halt replication can therefore offer a permanent cure. Perhaps the main scientific barrier to hepatitis C treatment is that the virus is highly variable – much more so than HIV – which means different drugs work best against different HCV genotypes and combination therapy is needed to prevent resistance.

HIV, in contrast, enters host cell chromosomes where it may remain latent for decades and perhaps even a lifetime. Speaking for the 'prosecution', José Alcamí of the European University of Madrid said that viral latency, existence of viral reservoirs and destruction of the immune system by the virus are the three main barriers to a cure.

HIV DNA in resting CD4 T-cells can awaken when these cells become activated as part of an immune response, leading to renewed viral replication, he explained. For this reason people with HIV must remain on ART – as far as we know for life – to guard against viral rebound.

HIV cure researchers are testing several different strategies to reverse latency and flush the virus out of hiding. The so-called 'shock and kill' approach involves using agents such as HDAC inhibitors to awaken latent virus coupled with immune-boosting therapies to kill infected cells. But current anti-latency drugs trigger only weak viral reactivation and target only a small proportion of the viral reservoir.

In addition to long-lived memory T-cells, the HIV reservoir also includes anatomical sites such as the lymph nodes, gut lymphoid tissue and central nervous system. HIV preferentially targets CD4 cells – the "brain of the immune system" – and persistent immune activation caused by the virus leads to immune senescence and eventual exhaustion of immune function, Alcamí said.

"I would like to give good news, but we face a virus we are not able to cure with drugs we have available or even drugs we may have in the future," he concluded. "The destruction of the immune system remains a barrier to a cure."

Returning to the 'defence', Giuseppe Pantaleo of Centre Hospitalier Universitaire Vaudois in Lausanne countered that we should not feel too depressed as "there is a lot to be optimistic about."

Pantaleo outlined the important proof-of-concept cases, previously reported on aidsmap.com, that indicate that a cure is possible at least in principle. These include the Berlin patient who was cured after a
bone marrow stem cell transplant for leukaemia, an American baby who shows no evidence of remaining virus after starting ART within a day after birth; two Boston stem cell transplant patients with sustained viral suppression after antiretroviral interruption; and the French VISCONTI cohort of individuals who appear HIV-free after ART initiation during acute infection.

Pantaleo argued that continuing residual viral replication despite ART is "probably responsible" for replenishment of latent reservoirs and better antiretroviral drugs that fully suppress replication may offer hope for a functional cure. Data on this point are mixed, however, and some researchers think that at least current classes of antiretrovirals already provide maximum suppression.

Summing up, Pantaleo noted that only 25% of people with HIV in the US have achieved undetectable viral load on ART and that even excellent current therapy remains "very hard to take" especially over the long term.

A combination of strategies will be the secret of an HIV cure, he concluded. "We're just at the beginning," he said. "A functional cure is possible if there is the right investment in these new approaches."

Perno added that there is "clear evidence that persistent virus is harmful." Even if 'undetectable', the virus is not absent in the body and even a few copies may be detrimental, for example by maintaining a state of persistent immune activation. "In the long term we will pay a price for this," he cautioned.

But the effectiveness of modern antiretroviral treatment was the gist of Georg Behrens argument against pursuing a cure. Behrens, of Hannover Medical School, explained that current ART is so good that attempts to cure HIV are not worth the risk. Donor stem cell transplants, for example, can be fatal and are only appropriate for people with life-threatening conditions such as leukaemia or lymphoma.

Furthermore, better antiretrovirals are in the works including agents that target HIV attachment and maturation, the "very ends of the replication cycle." Treatment dramatically extends survival of people with HIV and the relatively small percentage who do not do well on current ART – due to co-morbidities or adherence problems, for example – are "not the best candidates" for risky cure approaches.

Behrens concluded that research should focus on improving ART for the broad population of people with HIV, not on curing a few exceptional patients. "We should ask not only is a cure possible, but what is the real benefit for patients," he said. "We may be able to fly to the moon, but that doesn't solve our problems with traffic here [on earth]."

After hearing the arguments on both sides the audience 'jury' rendered its verdict. Among the more than 100 participants, opinion was nearly evenly divided as to whether a cure for HIV is an achievable and worthwhile goal.

Elusive secret of HIV long-term immunity
Discovery offers hope of new, shorter HIV treatment if drugs are started right away

CHICAGO -- Scientists have discovered a critical new clue about why some people are able to control the HIV virus long term without taking antiviral drugs. The finding may be useful in shortening drug treatment for everyone else with HIV.

These rare individuals who do not require medicine have an extra helping of a certain type of immune protein that blocks HIV from spreading within the body by turning it into an impotent wimp, Northwestern Medicine® scientists report. The new finding comes from analyzing cells from these rare individuals and HIV in the lab.

Scientists have been trying to solve the mystery of why 1 percent of people with HIV—called "controllers"—have enduring control of the virus without medications, in some cases for life. The controllers' early defense against HIV is quickly extinguished by the virus, so how do they have long-term immunity? The Northwestern discovery represents what scientists have long sought: a second line of defense deep in the immune system backing up the short-lived early defense.

This discovery suggests a novel approach involving much earlier treatment that could potentially make every HIV-infected person into a controller for the long term by protecting the reserves of this defensive immune protein. The goal would be for them to eventually be free from anti-retroviral drugs.

Currently most HIV patients need to take powerful anti-retroviral drugs every single day for life. If the medicines are stopped, the virus quickly reactivates to harmful levels even after years of treatment.

"Preserving and even increasing this defense in cells may make more HIV-infected persons into controllers and prevent HIV from rebounding to high and damaging levels when anti-HIV medications are stopped," said Richard D’Aquila, M.D., the director of the Northwestern HIV Translational Research Center. He is the senior author of the study, which will be published Oct. 16 in the journal PLOS ONE.
D'Aquila also is the Howard Taylor Ricketts Professor of Medicine at Northwestern University Feinberg School of Medicine and a physician at Northwestern Memorial Hospital.

D'Aquila and colleagues now are working to develop a medicine that would boost this defensive immune protein called APOBEC3G, or A3 for short.

**The Missing Second Defensive Line**

Much is known about how the immune system of controllers initially fights the virus. But HIV quickly escapes from that first line of defense by mutating and evading the adaptive immune system. How these individuals control HIV long term without medications to keep from developing AIDS has been under study by many researchers. It seemed there must be a second defensive line in the immune system.

**Turning HIV Into a Wimp**

In the new study, D'Aquila and his team have found that controllers, long after they have acquired HIV, have a more abundant supply of the critical immune protein A3 in specific white blood cells called resting memory T cells. This is where the virus lies silently in an inactive form and roars back when anti-retroviral drugs are stopped. In controllers, though, their bounty of A3 means that any new HIV made from those cells inherits a helping of A3, which turns the new viruses into harmless wimps that can't infect other cells.

**You Can't Fool A3**

The feisty A3 is a critical part of the newly characterized intrinsic immune system, and it resides in many cells of the immune system including resting T cells. Unlike the adaptive immune system, which fails to recognize the virus once it mutates its pieces, the intrinsic immune system can't be fooled.

"The intrinsic immune system recognizes the basic guts of the virus—the nucleic acids—that HIV can't change and then damages those nucleic acids," D'Aquila said. D'Aquila theorizes that the controllers' first line of defense slows down the ability of HIV to destroy all the A3.

"Perhaps starting anti-HIV drugs very soon after HIV is caught, rather than the current practice of waiting until later to start, would work like the controllers' first line of defense," D'Aquila suggested. "If we preserve A3, it could minimize HIV's spread through the body as this protein seems to do in controllers."

Otherwise, D'Aquila theorizes, all reserves of the protein are wiped out if HIV replicates unchecked for several months.

**Babies and Other Controllers**

D'Aquila pointed to several recent examples of early treatment sometimes resulting in lasting control of HIV in humans that are consistent with this theory.

In January 2013, a baby was born to an HIV-positive woman in Memphis who didn't take preventive medicines that are routinely given to these women. The baby got infected, and doctors began anti-HIV drug treatment within 36 hours of birth. After some treatment, the baby is now off anti-HIV medicines and appears to be cured of HIV.

Two studies published earlier this year show the protective effect of starting the medicines within three to four months after infection for a relatively short course, resulting in a lower level of HIV in the blood and better control of the virus for some who stopped the anti-retroviral medication.

A group of patients in a European study were started on anti-HIV drugs very early after infection. Their medications were stopped after three years but some continued to have a suppressed virus at such low levels it did not cause any damage.

**Earlier Detection Just Got Easier**

"Early-as-possible detection—much easier with our new technology—and early drug treatment will be the future of HIV therapy," D'Aquila said. He added that the Affordable Care Act mandates that insurance companies pay for routine HIV testing, which they did not always cover in the past.

**D'Aquila Helped Developed Personalized Approach to HIV Medicine**

D'Aquila is a leading HIV scientist who began investigating AIDS in 1982, the first year it was identified. He was a senior resident in Philadelphia when the early cases appeared at the hospital where he was working. D'Aquila began investigating, calling other area hospitals to see if they had seen similar cases. He discovered there were lots of them. The same month, Morbidity and Mortality Weekly Report sounded the first alarm that a new disease had erupted.

Over the last 30 years, D'Aquila has helped develop anti-HIV medicines and resistance testing for HIV—the latter is the first widely used clinical application of DNA sequencing in personalized medicine. Since the 1990s, HIV patients have their virus sequenced to determine which medicines are going to work best for them at that time—a result of research done by D'Aquila and others.
D'Aquila was also a leader and virologist for many NIH-supported clinical trials in the AIDS Clinical Trials Group. His laboratory studies were also among the first to characterize effects of resistance mutations on HIV's replicative fitness and to show that resistant virus persisted in HIV's latent reservoir. The new study was done in collaboration with MariaPia De Pasquale and Yordanka Kourteva, formerly at Vanderbilt University School of Medicine, where D'Aquila did the experiments.

**Pioneering use of oral cholera vaccine during outbreak**

In a report publishing October 17th, 2013 in *PLOS Neglected Tropical Diseases*, the international medical humanitarian organization Doctors Without Borders/Médecins Sans Frontières (MSF) and its scientific research arm, Epicentre, present results of one of the first-ever, large-scale use of an oral cholera vaccine during a cholera outbreak – a major breakthrough in the understanding and future control of deadly cholera epidemics.

Using results from a mass vaccination campaign of more than 300,000 people conducted in Guinea last year, MSF and Epicentre show the feasibility of implementing a mass vaccination campaign with oral cholera at the onset of an outbreak, similar to the way reactive vaccination campaigns are conducted when diseases such as measles or meningitis are reported in an area.

Last year, MSF teams in Guinea noticed cases of cholera months ahead of the rainy season. These early cholera cases and other factors, including the lack of a cholera epidemic in Guinea for several years, and the ongoing cholera epidemic in neighboring Sierra Leone, were strong indications to MSF and the Ministry of Health that a major cholera epidemic was imminent.

Starting in April of last year the Guinean Ministry of Health and MSF administered 316,250 doses of vaccine during two vaccination rounds in the coastal districts of Boffa and Forecariah, Guinea over six weeks. All individuals older than 12 months were eligible for vaccination in both rounds. The vaccination campaign was well accepted by the local community and MSF achieved high coverage rates. The two doses vaccine coverage was 75.8% in Boffa and 75.9% in Forecariah, respectively. Almost all people surveyed after the campaign, 98.9 percent, reported that they would be vaccinated again in a future cholera campaign.

Oral cholera vaccine was added to the WHO recommendation for cholera treatment in 2010, but so far has not been commonly used as a public health tool for control of the disease. Concerns about its feasibility, timeliness and acceptability by population, as well as fear of diverting resources from other medical programs have discouraged the use of an oral cholera vaccine.

"With this study, we show that with proper planning and outreach in the communities, it is indeed possible to vaccinate hundreds of thousands of people in a remote area, with a highly mobile population, in a relatively short period of time, against cholera," said Dr. Francisco Luquero, the paper’s principal investigator. "However, more evidence is still needed about the feasibility of reactive campaigns in densely populated urban areas. Oral cholera vaccines should not be viewed as a long-term solution for global cholera control. They should be integrated as an additional tool in the global response to cholera outbreaks."

**GSK1265744 rapidly suppresses HIV and appears safe at selected dose**

Liz Highleyman
Published: 20 October 2013

The experimental HIV integrase inhibitor GSK1265744 demonstrated rapid and potent antiviral activity and good tolerability for treatment-naive patients in the LATTE study, according to a report at the 14th European AIDS Conference this week in Brussels.

Integrase inhibitors are among the most well tolerated antiretroviral medications. GSK1265744 (or GSK744 for short), being developed by GlaxoSmithKline, is similar to the recently approved dolutegravir. It is being tested both as a once-daily oral drug and as a long-acting injectable that may allow for once-monthly administration. A recently presented analysis of eight studies showed that it is safe with no notable safety concerns.

David Margolis from GlaxoSmithKline and colleagues evaluated the safety, tolerability and efficacy of GSK744 in previously untreated people with HIV.

The phase 2b LATTE trial started with a 24-week induction phase comparing three oral doses of GSK744 plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) to inform selection of an optimal dose for further development. At week 24 participants with stable viral suppression discontinued NRTIs and switched to a simplified dual maintenance regimen of GSK744 plus oral rilpivirine (Edurant).
The primary endpoint of this partially-blinded, dose-ranging, multicentre study is undetectable HIV viral load (<50 copies/ml) at 48 weeks. Margolis reported interim 24-week findings.

This analysis included 243 treatment-naive patients. Almost all were men; Margolis explained that the lack of women was in part due to a restriction on use of hormonal contraception since drug interactions with GSK744 are not yet known. A majority of participants (about 60%) were white, about 30% were black and the median age was about 34 years. The median CD4 T-cell count was approximately 410 cells/mm$^3$ and 16% had high baseline viral load (>100,000 copies/ml). About 5% were coinfected with hepatitis C.

Participants were randomly assigned to receive GSK744 at doses of 10mg, 30mg or 60mg, or 600mg efavirenz, all once daily. They also started on two investigator-selected NRTIs, about 60% taking tenofovir/emtricitabine (Truvada) and 40% taking abacavir/lamivudine (Kivexa).

At 24 weeks 87% of participants taking GSK744 achieved undetectable viral load (all dose arms combined) compared with 74% of those taking efavirenz in a 'snapshot' analysis. Response was similar with all GSK744 doses (88%, 85% and 87%). There was no significant difference according to NRTI backbone.

Viral load fell rapidly after starting treatment in all GSK744 dose groups. People taking GSK744 achieved viral suppression significantly sooner than those taking efavirenz, with 76% vs 24%, respectively, having undetectable HIV RNA by week 4.

CD4 T-cell gains were similar for GSK44 and efavirenz recipients at week 24 (185 and 159 cells/mm$^3$), though the increase was faster in the GSK744 arms (123 vs 59 cells/mm$^3$ at week 8).

Virological failure rates in the snapshot analysis were 6% with GSK744 (all arms combined) and 15% with efavirenz. Protocol-defined virological failure—the narrower criteria used to determine who was eligible for the maintenance phase—was uncommon, with six total cases: one in each GSK744 dose arm (2% combined) and three in the efavirenz arm (5%). All these patients underwent genotypic or phenotypic resistance testing and no integrase, NRTI or NNRTI mutations were detected.

People taking GSK744 were about half as likely to withdraw from the study as those taking efavirenz (12% vs 26%), with no notable differences across GSK744 dose groups. This was mainly driven by a significantly lower dropout rate due to adverse events amongst GSK744 recipients (2% vs 11%, respectively).

Overall rates of grade 2-4 adverse events were similar, 18% with GSK744 and 16% with efavirenz. As expected, people taking efavirenz had more neuropsychiatric or central nervous system side-effects. Headache, usually mild to moderate, was more common with GSK744 (<3% vs 0%). Six people taking GSK744 had serious adverse events (none considered drug-related), as did three people taking efavirenz (one deemed drug-related, a suicide attempt).

Laboratory abnormalities occurred with similar frequency amongst GSK744 and efavirenz recipients overall. However, abnormalities were more common with the highest GSK744 dose. One-quarter of people in the 60mg group developed ALT liver enzyme elevations; these were usually mild, but there were two transient grade 4 (severe) elevations in people with pre-existing liver disease. Lipase elevation occurred in 8% in this arm but there were no cases of pancreatitis.

"Oral [GSK744] administered once daily with two NRTIs was associated with a good treatment response," the researchers concluded.

Based on these findings the 30mg GSK744 dose was selected. The maintenance phase of LATTE testing GSK744 plus rilpivirine maintenance therapy is currently underway. Results from that part of the trial will prepare the way for a phase 2b study of combined long-acting injectable formulations of both drugs, which may one day be used as monthly maintenance therapy or pre-exposure prophylaxis (PrEP).

Reference

Dual therapy with Kaletra and 3TC works well regardless of viral load
Liz Highleyman
Published: 20 October 2013
A dual combination of lopinavir/ritonavir (Kaletra or Aluvia) plus 3TC (lamivudine or Epivir) as first-line therapy produced good virological suppression regardless of baseline viral load and was well tolerated in the multinational GARDEL study, according to a late-breaking report at the 14th European AIDS Conference this week in Brussels.
Three-drug regimens that contain two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are the standard of care for antiretroviral therapy, but many NRTIs can cause side-effects and simplifying treatment may improve adherence and reduce cost. Lopinavir/ritonavir as monotherapy has been shown to be inferior to standard therapy, but adding one NRTI may be adequate.

Pedro Cahn from Fundacion Huesped in Buenos Aires and fellow investigators with the GARDEL Study Group compared the safety and effectiveness of a dual combination versus triple therapy for treatment-naive patients.

This randomised open-label phase 3 study included 426 previously untreated patients in Argentina, Chile, Mexico, Peru, Spain and the US. Nearly 85% were men (about 60% who have sex with men and 35% heterosexual) with a median age of about 35 years.

The median baseline CD4 T-cell count was approximately 325 cells/mm$^3$, 43% had high viral load (HIV RNA >100,000 copies/ml) and only 3% had a history of AIDS. People with NRTI or protease inhibitor resistance mutations at baseline were excluded.

Participants were randomly assigned to receive 400/100mg lopinavir/ritonavir plus 150mg 3TC, both taken twice daily, or a standard regimen of lopinavir/ritonavir plus two NRTIs in a fixed-dose combination. About 9% used Abacavir/3TC (Kivexa), 37% used tenofovir/emtricitabine (Truvada) and the rest (54%) used AZT/3TC (Combivir).

Cahn explained that NRTI choice was based on national treatment guidelines in the various countries. Whilst Combivir is no longer considered a preferred option in Europe and the US it is still used in middle- and lower-income countries.

Ten participants withdrew before receiving any therapy. Among those who started treatment, about half as many discontinued prematurely in the double-therapy arm compared with the triple therapy arm (8% vs 14%).

At 48 weeks 88% of people taking dual therapy and 84% taking triple therapy had undetectable viral load (<50 copies/ml) in the primary intention-to-treat 'snapshot' analysis, indicating that the simplified single-NRTI regimen was non-inferior to standard therapy. In an observed or as-treated analysis, response rates were 96% and 97%, respectively. CD4 cell gains were also similar in both arms at 227 and 217 cells/mm$^3$.

Dual therapy also performed at least equally well amongst people with high baseline viral load, with response rates of 87% and 78% in the two arms, allaying one of the concerns about a potentially less potent regimen.

Virological failure rates were similar in the dual and triple therapy groups at 5% and 6%, respectively. However, fewer people in the dual arm discontinued early due to adverse events or death (1% vs 5%). Two people in the dual arm and eight in the triple arm never achieved viral suppression, whilst eight and four, respectively, experienced viral rebound.

Amongst the small number of viral samples that were amplified and sequenced (in most cases virus levels were too low), two patients in the dual therapy arm, but none in the triple therapy arm, had emergent NRTI resistance mutations (M184V); no one in either group had primary protease resistance mutations.

Both regimens were generally safe and well tolerated with most side-effects being mild to moderate. There were significantly fewer grade 2-3 adverse events in the dual compared with the triple therapy arm (65 and 88 events, respectively). One person taking dual therapy and ten taking triple therapy discontinued due to adverse events.

The most common side-effects were elevated lipid levels (11% and 8%) and diarrhoea (7% in both arms). Nausea and dyspepsia were more common in the triple therapy arm (<1% vs 3-4%). Laboratory abnormalities were uncommon and similar in both arms. There was one serious adverse event considered probably drug-related, a case of gastritis in the dual therapy arm.

"Our results demonstrate that dual therapy with lopinavir/ritonavir + 3TC was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load," the researchers concluded. "The dual therapy regimen showed fewer discontinuations due to safety and tolerability."

"Virologic failure, occurring at similarly low levels in both treatment arms, did not result in protease inhibitor resistance development, preserving a wide range of drugs for 2nd line antiretroviral therapy," they added.

Amongst NRTIs, 3TC is very well tolerated. Cahn noted that the dual regimen does not require monitoring for kidney, liver or blood cell toxicities, making it a useful option in settings with limited monitoring capacity.
Flu virus wipes out immune system's first responders to establish infection
CAMBRIDGE, Mass. (October 20, 2013) — Revealing influenza’s truly insidious nature, Whitehead Institute scientists have discovered that the virus is able to infect its host by first killing off the cells of the immune system that are actually best equipped to neutralize the virus.

Confronted with a harmful virus, the immune system works to generate cells capable of producing antibodies perfectly suited to bind and disarm the hostile invader. These virus-specific B cells proliferate, secreting the antibodies that slow and eventually eradicate the virus. A population of these cells retains the information needed to neutralize the virus and takes up residence in the lung to ward off secondary infection from re-exposure to the virus via inhalation.

On the surface of these so-called memory B cells are high-affinity virus-specific receptors that bind virus particles to reduce viral spread. While such cells should serve at the body's first line of defense, it turns out that flu virus exploits the specificity of the cells' receptors, using them to gain entry, disrupt antibody production, and ultimately kill the cells. By dispatching its enemies in this fashion, the virus is able to replicate efficiently before the immune system can mount a second wave of defense. This seemingly counter-intuitive pathway to infection is described this week in the journal Nature.

"We can now add this to the growing list of ways that the flu virus has to establish infection," says Joseph Ashour, a co-author of the Nature paper and a postdoctoral researcher in the lab of Whitehead Member Hidde Ploegh.

"This is how the virus gains a foothold," adds Ploegh lab postdoc Stephanie Dougan, also a co-author of the study. "The virus targets memory cells in the lung, which allows infection to be established—even if the immune system has seen this flu before."

Discovering this dynamic of the virus was no small task, in part because virus-specific B cells are found in exceedingly small numbers and are extremely difficult to isolate. To overcome these challenges, Dougan together with students Max Popp and Roos Karssemeijer leveraged a protein-labeling technology developed earlier in the Ploegh lab to attach a fluorescent label to influenza virus, thus identifying flu-specific B cells by their interaction with fluorescent flu micelles. This step was essential because no flu protein can be tagged in the conventional manner with green fluorescent protein (GFP) in the context of an infectious virus. Dougan then introduced the B cells' nuclei into enucleated mouse egg cells via somatic cell nuclear transfer (SCNT)—a cloning technique she learned in Whitehead Founding Member Rudolf Jaenisch’s lab—to generate a line of mice with virus-specific B cells and cell receptors.

Though complicated, the generation of mice with B cells specific for a known pathogen allowed Dougan and Ashour to track the virus's interactions with the cells in unprecedented fashion. Because the infectious process they discovered is likely not exclusive to influenza virus, these scientists believe their approach could have implications for other viruses as well.

"We can now make highly effective immunological models for a variety of pathogens," says Dougan. "This is actually a perfect model for studying memory immune cells."

Adds Ashour: "This is research that could help with rational vaccine design, leading to more effective vaccines for seasonal flu. It might even suggest novel strategies for conferring immunity."

Full Citation: Nature, October 20, 2013; "Antigen-specific B-cell receptor sensitizes B cells to infection by influenza virus", Stephanie K. Dougan (1), Joseph Ashour (1), Roos A. Karssemeijer (1), Maximilian W. Popp (1,2), Ana M. Avalos (1), Marta Barisa (1), Arwen F. Altenburg (1), Jessica R. Ingram (1), Juan Jose Cragnolini (1), Chunguang Guo (3), Frederick W. Alt (3), Rudolf Jaenisch (1), and Hidde L. Ploegh (1,2)

20 October 2013, 8.16pm BST
Australia’s HIV infection rates at 20-year high
The rate of newly diagnosed HIV infections in Australia has risen by 10% in 12 months – the largest increase in 20 years, a new report shows. Last year, 1,253 cases of HIV were diagnosed, with unprotected sex among men the most common mode of transmission. The number of new diagnoses has been gradually...

The rate of newly diagnosed HIV infections in Australia has risen by 10% in 12 months – the largest increase in 20 years, a new report shows.
Last year, 1,253 cases of HIV were diagnosed, with unprotected sex among men the most common mode of transmission. The number of new diagnoses has been gradually increasing over the past 14 years, from 719 cases in 1999.

The data is outlined in the Kirby Institute’s Australia Annual Surveillance Report, which will be released today at the Australasian HIV/AIDS Conference 2013 in Darwin.

The report shows that over the past four years, two-thirds (67%) of new HIV diagnoses have occurred among men who have sex with men, 25% were attributed to heterosexual contact and 2% to injecting drug use.

Of the newly diagnosed heterosexual infections, 58% were among people born in Sub-Saharan Africa or Southeast Asia, or those who had partners from these regions.

Between 28,600 and 34,300 Australians have been diagnosed with HIV since the epidemic began.

Changing trends
Professor John de Wit, Director of the National Centre in HIV research said the key factor behind the rise was the “likelihood of being exposed to the virus through unprotected anal sex”.

Professor de Wit co-authored the Annual Report of Trends in Behaviour 2013, which will also be released today.

The report found that over the past decade, the number of gay men having unprotected casual sex has grown. In 2012, almost 40% of gay men with casual partners report having unprotected sex, with the trend most pronounced among HIV positive men and those aged under 25 years.

These young men are “less likely to have been exposed to HIV prevention”, Professor de Wit said, which means that they know condoms are important but haven’t quite got the message that when it comes to age, HIV doesn’t discriminate.

“What we need to do is to get across to people that they are personally at risk, which is very difficult because it also activates all the defences,” he said.

“But through testimonials and working with stories of people who are similar, we can achieve that.”

Professor de Wit said his report also contained some good news: men who were newly diagnosed with HIV were increasingly likely to take up treatment.

“Over the past decade, the number of HIV positive men initiating antiretroviral therapies increased from 60% to about 80%, which is wonderful news,” he said.

Reducing transmission
Infectious diseases expert Associate Professor Edwina Wright from the Alfred Hospital, Monash University and Burnet Institute said starting treatment early could play an important role in reducing transmission of HIV by dropping the carrier’s viral load.

“As soon as you drop your viral load to an undetectable level in the blood, within three to six months of treatment ... your chance of transmission to your sexual partner is reduced by 96%,” Professor Wright said.

“Treatment has this amazing double benefit of improving an individual’s health and reducing their risk of transmitting HIV to their partners.”

But current restrictions mean HIV positive people who are well and have above 500 CD4+ cells cannot access subsidised antiretroviral treatment and face an annual bill of around A$15,000.

Professor Wright and her colleagues have made a submission to Australia’s Pharmaceutical Benefits Advisory Committee, which decides who gets access to subsidised medication, to lift the current restriction.

“There’s enough evidence to show that starting treatment early would deliver health benefits and would be cost-effective,” she said, particularly taking “into account that fewer partners would be infected”.

Professor Wright said another key area for reform was to increase access to rapid HIV testing, which could deliver a result within 20 minutes.

“We don’t yet have widespread, routine access to rapid testing, but we’ve made some gains,” she said, with 32 sites in cities around the Eastern seaboard and Perth offering the service.

“I think that’s important because up to 10,000 Australians do not know that they’re HIV positive and a lot of them are going to need incentives to face it, or think about it, or find the time to be tested. So the easier we make it, the better.”

Professor Wright is President of Australasian Society for HIV Medicine, which delivers its report card on Australia’s progress on HIV in Darwin today. The overall score is 21 out of 40.
Tea party leader proposes ‘class action lawsuit’ against ‘homosexuality’

By David Edwards
Friday, October 18, 2013 9:08 EDT

A tea party leader and former Baptist pastor — who believes that AIDS is God’s judgement against LGBT people — this week proposed filing a “class action lawsuit” against “homosexuality.”

At a Tea Party Unity event on Thursday, LGBT activist Peter LaBarbera told group Chairman Rick Scarborough that Fox News should be pushed to cover “these wonderful stories of happy men and women who have left the homosexual lifestyle” like they covered African-American conservatives.

“We need to work on our conservative, alternate media and say, ’Look, don’t do the pro-gay thing, why don’t you rather step out and support these ex-gays?’ We should encourage Fox News to tell their stories,” LaBarbera said. “Fox is now telling the stories of black conservatives because the other media is not doing that, we should all get on Fox and say, ’Come on, tell these stories, these wonderful stories of happy men and women who have left the homosexual lifestyle.’”

Scarborough, however, had a different plan for fighting what LaBarbera had called “the pro-gay thing.”

“Peter, the whole issue of a class action lawsuit, you and I have talked about this a little bit,” Scarborough pointed out. “I just wonder if you’ve explored that, talked to anyone about it.”

The former Baptist pastor opined that “homosexuality much more likely leads to AIDS than smoking leads to cancer. And yet the entire nation has rejected smoking, billions of dollars are put into a trust fund to help cancer victims and the tobacco industry was held accountable for that.”

“Yeah I think that’s great,” LaBarbera agreed. “I would love to see it. We always wanted to see one of the kid in high school who was counseled by the official school counselor to just be gay, then he comes down with HIV. But we never really got the client for that.”

New ‘Virulent’ HIV Strain Spreading Rapidly Through Siberia Identified by Russian Scientists; Accounts for 50 Percent of New Infections

Medical Daily, (10.19.2013) By Lecia Bushak

Russian scientists believed they discovered a new, more easily transmitted type of HIV, according to local news reports. The new strain, first identified in 2006 and known as 02_AG/A, was being transmitted at a “rapid rate” in Russia, Chechnya, Kyrgyzstan, and Kazakhstan. A regional science city statement said this strain might account for more than 50 percent of new HIV cases.

Worldwide, new HIV infection numbers dropped by 30 percent since 2001, but according to the United Nations, Eastern Europe/Central Asia was the only region where HIV prevalence was on the rise, with the majority of cases located in Russia. Approximately 1 million of Russia’s 143 million residents were HIV-positive. According to Russia’s Federal AIDS Center, the number of infected people in Novosibirsk, Russia, rose from 2,000 in 2007 to 15,000 in 2012. “Russia has experienced the fastest-spreading HIV/AIDS epidemics in any one country in history, but there remains a lack of effective preventative measures to slow it down—in large measure because the people most affected are also the country’s most reviled,” wrote Gregory Gilderman of the Pulitzer Center. The World Bank estimated that by 2020, nearly 21,000 Russians per month could die because of HIV/AIDS.

HIV virus is categorized into two groups: HIV-1, which is more infectious; and HIV-2. Researchers believe the 02_AG/A strain, a subtype of HIV-1, is transmitted even more easily than other strains of the virus.
Breast milk protein may be key to protecting babies from HIV infection

DURHAM, N.C. – A substance in breast milk that neutralizes HIV and may protect babies from acquiring HIV from their infected mothers has been identified for the first time by researchers at Duke Medicine.

The protein, called Tenascin-C or TNC, had previously been recognized as playing a role in wound healing, but had not been known to have antimicrobial properties. The discovery could lead to potential new HIV-prevention strategies.

Reporting in the journal *Proceedings of the National Academy of Sciences* during the week of Oct. 21, 2013, the researchers describe how the TNC protein in breast milk binds to and neutralizes the HIV virus, potentially protecting exposed infants who might otherwise become infected from repeated exposures to the virus.

"Even though we have antiretroviral drugs that can work to prevent mother-to-child transmission, not every pregnant woman is being tested for HIV, and less than 60 percent are receiving the prevention drugs, particularly in countries with few resources," said senior author Sallie Permar, M.D., Ph.D., assistant professor of pediatrics, immunology and molecular genetics and microbiology at Duke. "So there is still a need for alternative strategies to prevent mother-to-child transmission, which is why this work is important."

Worldwide in 2011, an estimated 330,000 children acquired HIV from their mothers during pregnancy or birth, or through breastfeeding according to UNICEF. As international health organizations have set a goal of eliminating mother-to-child infections, researchers have worked to develop safe and affordable alternatives to antiretroviral therapy that can be used to block HIV transmission to infants.

Permar and colleagues focused on breast milk, which has long been recognized as having some protective quality that inhibits mother-to-child transmission despite multiple daily exposures over months and even years of nursing. Earlier studies had identified some antiviral properties in breast milk, but the majority of the HIV-neutralizing activity of breast milk remained unexplained. More recent studies pointed to a large protein that had yet to be identified.

In their study, the Duke team screened mature milk samples from uninfected women for neutralizing activity against a panel of HIV strains, confirming that all of the detectable HIV-neutralization activity was contained in the high molecular weight portion. Using a multi-step protein separation process, the researchers narrowed the detectable HIV-neutralization activity to a single protein, and identified it as TNC.

"TNC is a component of the extracellular matrix that is integral to how tissues hold themselves together," Permar said, noting that co-author Harold Erickson, Ph.D., professor of cell biology at Duke, was among the first to identify and describe TNC in the 1980s. "This is a protein involved during wound healing, playing a role in tissue repair. It is also known to be important in fetal development, but its reason for being a component of breast milk or its antiviral properties had never been described."

Further analysis described how TNC works against HIV by blocking virus entry. The protein is uniquely effective in capturing virus particles and neutralizes the virus, specifically binding to the HIV envelope. These properties provide widespread protection against infection.

"It's likely that TNC is acting in concert with other anti-HIV factors in breast milk, and further research should explore this," Permar said. "But given TNC's broad-spectrum HIV-1-binding and neutralizing activity, it could be developed as an HIV-prevention therapy, given orally to infants prior to breastfeeding, similar to the way oral rehydration salts are routinely administered to infants in developing regions."

Permar said TNC would also appear to be inherently safe, since it is a naturally occurring component of breast milk, and it may avoid the problem of HIV resistance to antiretroviral regimens that complicate maternal/infant applications.

"The discovery of the HIV inhibiting effect of this common protein in breast milk provides a potential explanation for why nursing infants born to HIV-infected mothers do not become infected more often than they do," said Barton F. Haynes, M.D., director of the Duke Human Vaccine Institute. "It also
provides support for inducing inhibitory factors in breast milk that might be even more protective, such as antibodies, that would completely protect babies from HIV infection in this setting."

**Low CD4 cell count increases heart attack risk for people with HIV**

Michael Carter  
Published: 28 October 2013

Immunodeficiency is an important risk factor for heart attack in people living with HIV, results of a large US study published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes* show. People with recent and nadir (lowest-ever) CD4 cell counts below 200 cells/mm³ were significantly more likely to have a heart attack compared to matched controls. But people living with HIV with nadir or recent CD4 cell counts above 500 cells/mm³ were no more likely to have a heart attack than the HIV-negative controls.

“Our results suggest that immunodeficiency is a key MI [myocardial infarction, or heart attack] risk factor,” write the authors. “While we found an increased risk of MI among HIV+ subjects with low CD (e.g. < 200) compared with HIV- subjects, we found no increased risk among HIV+ subjects with recent or nadir CD4 ≥500 cells/mm³ compared with HIV- subjects.”

Cardiovascular risk is an increasingly important cause of death among people with HIV. A number of reasons are thought to contribute to this elevation in risk, including a high prevalence of traditional risk factors such as smoking, the side-effects of some antiretroviral drugs and the inflammatory effect of HIV itself.

A team of US investigators wanted to disentangle these factors and see which were increasing the risk of heart attack.

They designed a case-controlled study involving people who received care through the Kaiser Permanente California health plan between 1996 and 2009.

The study population comprised 22,081 people living with HIV who were matched with 230,069 HIV-negative individuals of the same sex, age and who also received care at the same treatment centres.

The risk of heart attack was compared between the people with HIV and the controls, and the investigators conducted a series of analyses to identify specific risk factors for heart attack among the people with HIV.

The people with HIV were followed for a mean of 4.5 years and contributed 99,090 person-years for analysis. The mean duration of follow-up for people in the control group was 5.4 years and they provided 1,253,550 person-years. The overwhelming majority of study participants were men (90%) and aged between 30 and 49 years (70%).

There were 283 recorded heart attacks among the people living with HIV, an incidence rate of 283 per 100,000 person-years. A total of 2064 heart attacks were documented in the control patients, an incidence rate of 165 per 100,000 person-years.

In unadjusted analysis, the people with HIV were found to have a 70% increase in the risk of heart attack compared to the controls (RR = 1.7; 95% CI, 1.5-1.9).

The association between HIV and a higher risk of heart attack persisted after the investigators controlled for traditional risk factors and other confounders (aRR = 1.44; 95% CI, 1.27-1.64). People with HIV who were taking antiretroviral therapy were also shown to have a higher heart attack risk than the controls (aRR = 1.5; 95% CI, 1.3-1.7).

The authors then examined the association between immune status and heart attack risk for the people with HIV.

In their adjusted model, people with a current CD4 cell count below 200 cells/mm³ (aRR = 1.76; 95% CI, 1.31-2.37) or a nadir CD4 cell count below this level (aRR = 1.74; 95% CI, 1.47-2.06) had a higher risk of heart attack than the controls.

However, people with current and nadir CD4 cell counts above 500 cells/mm³ had a heart attack risk comparable to that of the control patients.

“That nadir CD4 acts as a risk factor for MIs is biologically plausible since atherosclerosis is considered a consequence of chronic inflammatory processes,” note the investigators.

Traditional risk factors including older age, male sex, smoking, prior diabetes and prior lipid-lowering medication were also independently associated with heart attack risk.

A sub-analysis included people with HIV who had well-documented antiretroviral treatment histories. Its initial results showed that each additional year of therapy with a protease inhibitor increased the risk...
of heart attack (RR = 1.14; 95% CI, 1.04-1.26). However, this association disappeared in the adjusted model.

The investigators believe their findings “argue for increased efforts to diagnose and treat HIV as early as possible, which if combined with aggressive traditional CVD risk factor management, might result in a similar MI burden as the general population.”

Reference

People With HIV Accounted for One Quarter of TB Deaths in 2012: WHO
Author: Mark Mascolini
25 October 2013
Tuberculosis developed in an estimated 8.6 million people worldwide in 2012, according to a World Health Organization report. Of the 1.3 million people who died of TB, 320,000—or one quarter—had HIV infection.

WHO’s Global Tuberculosis Report 2013 details findings from 197 countries and territories that account for more than 99% of TB cases worldwide. TB mortality fell 45% from 1990 to 2012, and the target to reach the Millennium Development Goal of a 50% reduction by 2015 is within reach, WHO projects.

Among 22 countries with the world’s highest TB burdens, 7 have already met 2015 targets to reduce TB incidence, prevalence, and mortality and 4 countries are on track to meet those goals by 2015. But by 2012 global TB prevalence had dropped only 37% since 1990, and WHO does not expect to meet the global goal of a 50% drop in TB prevalence by 2015.

The proportion of TB patients who knew their HIV status rose from 40% in 2011 to 46% in 2012. In WHO’s African Region, 74% of TB patients knew their HIV status, up from 69% in 2011. In 41 countries with the highest HIV/TB burdens, more than 85% of TB patients knew their HIV status in 15 countries, and in 7 of those countries more than 90% of TB patients knew their HIV status.

Among global TB patients known to have HIV infection, 57% were taking antiretroviral therapy in 2012, a gain from the 49% taking antiretrovirals in 2011. About 80% of HIV-positive patients were receiving cotrimoxazole prophylaxis.

Whereas 3.5 million people enrolled in HIV care got screened for TB in 2011, an estimated 4.1 million were screened for TB in 2012. Among 1.6 million people who began care for HIV infection in 2012, a half million (31%) received isoniazid preventive therapy.

The WHO report lists five priority actions to accelerate progress toward reaching 2015 TB goals:
1. Reach the missed TB cases.
2. Address multidrug-resistant TB as a public health crisis.
3. Accelerate the response to TB/HIV.
4. Increase financing to close all resource gaps.
5. Ensure rapid uptake of innovations.

For the Global Tuberculosis Report 2013

High prevalence of osteoporosis and osteopenia in young men with HIV
Exercise ‘strongly recommended’ for young people with HIV to counteract bone density decline
Michael Carter
Published: 29 October 2013
There is an increased prevalence of osteoporosis and osteopenia in young HIV-positive men, Spanish researchers report in the online edition of the Journal of Acquired Immune Deficiency Syndromes. The study also showed that a low nadir CD4 cell count and therapy with a protease inhibitor were associated with lower peak bone mass.

“HIV-infected men showed lower hip T score and a higher prevalence of osteopenia and osteoporosis than HIV-uninfected controls,” write the authors. “Peak bone mass was inversely associated with nadir CD4 T-cell counts and the use of protease inhibitors, but directly associated with fat and lean mass.”

Low bone mineral density is a recognised complication of HIV infection. Causes are thought to include traditional risk factors such as smoking and drug use, the inflammatory effects of HIV itself, and the side-effects of some antiretroviral drugs.
Bone mass reaches a peak at the end of skeletal maturation. Up to 90% of bone mass is acquired by the age of 18 in females and the age of 20 in males. By age 30, everyone has reached their peak bone mass. It is well known that low peak bone mass is associated with an increased risk of osteoporosis and bone fractures.

Given the accumulating evidence that HIV infection is associated with low bone mineral density and an increased risk of fractures, a team of Spanish investigators designed an observational study comparing bone mineral density and T-scores in the lumbar spine and femur between HIV-positive young adults and age- and sex-matched HIV-negative controls. They also examined the risk factors for low bone mineral density in the HIV-positive participants.

Bone mineral density was measured using dual-energy X-ray absorptiometry (DEXA) scanning. The study population comprised 232 HIV-positive participants and 75 HIV-negative controls. All were aged between 20 and 30 years and approximately three-quarters were male. Individuals with a very low (16 kg/m² or below) or a very high (above 28 kg/m²) body mass index were excluded from participation, as were those with comorbidities known to increase the risk of bone metabolism problems.

Data concerning risk factors for low bone mineral density were available for 50% of the participants and 40% of the controls. As expected, individuals with HIV were more likely to be smokers than the HIV-negative controls (57 vs 13%, p =0.012), and were also more likely to use drugs (15 vs 3%) and drink alcohol (20 vs 3%, p = 0.04). HIV-positive women were more likely to report the use of hormonal contraception (20 vs 0%, p = 0.05). Similar proportions of HIV-positive and HIV-negative participants reported regular exercise (48 vs 40%), which is known to protect again low bone mineral density.

Two-thirds of the HIV-positive participants were gay men and 94% were receiving antiretroviral therapy.

No differences in bone mineral density were found at any site between the HIV-positive and the HIV-negative individuals. The authors were “surprised” by this finding.

However, the mean total T-score in the femur was significantly lower in the HIV-positive participants than in the controls (-0.2 standard deviation [SD] vs +0.05 SD, p = 0.018).

Osteoporosis was present in 11% of the patients and 4% of controls. Osteopenia was detected in 57% of individuals with HIV infection and in 51% of the uninfected controls.

Normal bone mineral density was present in only a third of the HIV-positive participants, which was significantly lower than the prevalence in the controls (45%, p = 0.019).

"Increasing numbers of children and adults are affected by low BMD [bone mineral density], probably because secondary forms are becoming more common as a result of lifestyle, diet, chronic illness and medication,” note the investigators.

Analysis of the results according to gender showed that osteoporosis was more common in HIV-positive men compared to control men (12 vs 6%, p = 0.033), as was osteopenia (57 vs 46%, p = 0.014).

Mean total femoral T-score was -0.3 SD in HIV-infected men compared to +0.1 SD in the control men (p = 0.03).

Bone mineral density, T-score and the prevalence of osteopenia and osteoporosis were similar between the HIV-positive and HIV-negative women.

A low nadir CD4 cell count and therapy with a protease inhibitor were associated with lower peak bone mass in the lumbar spine and total femur (p = 0.022 and p = 0.005, respectively).

The authors suggest the “negative effect of low nadir CD4 T-cell count on BMD could be explained by the high levels of immune activation and inflammation usually associated with severe immunodeficiency”.

However, total lean mass and total fat mass were associated with increased bone density at all sites. “Since lean mass is strongly related to physical activity, it is clear that exercise is an important component in the prevention of bone loss,” the researchers comment and they suggest exercise should be “strongly recommended in HIV-infected patients from the very early stages of the infection.”

They conclude: “Considering that this young population will be living with HIV infection for many years, risk factors for osteoporosis should be modified, if possible.”

Reference
October 28, 2013

Sangamo BioSciences Presents Clinical Data From HIV Study
Demonstrating Sustained Control Of Viremia
Reduction of Viral Load at or Below Limit of Detection Ongoing at 14 Weeks
Additional Presentations of Preclinical Data at Annual Meeting of European Society of Gene and Cell Therapy (ESGCT)

RICHMOND, Calif., Oct. 28, 2013 /PRNewswire/ -- Sangamo BioSciences, Inc. (Nasdaq: SGMO) announced today the presentation of new data demonstrating sustained control of HIV viral load (VL) at or below the limit of detection for 14 weeks (at last measurement) in an SB-728-T- treated HIV-infected subject who was not on antiretroviral therapy (ART). The CCR5 delta-32 heterozygote subject is enrolled in Sangamo’s clinical trial (SB-728-902 Cohort 5) and, as part of the clinical trial protocol, is undergoing an ART treatment interruption (TI), which is ongoing.

Data were presented at the Annual Meeting of the European Society of Gene and Cell Therapy (ESGCT and SETGyC Collaborative Congress) which is being held in Madrid from October 25-28, 2013.

"These data demonstrate that sustained functional control of HIV in the absence of ART is possible with a single SB-728-T treatment," stated Geoff Nichol, M.B., Ch.B., Sangamo’s executive vice president of research and development. "Our aim is to provide a population of immune memory cells that are protected from HIV infection and are capable of generating an effective immune response against the virus throughout the body. These data represent a further step toward demonstrating the efficacy and durability of this therapeutic approach."

Dr. Nichol added, "We continue to follow these Cohort 5 subjects and look forward to presenting a complete data set from this study, and a second ongoing trial (SB-728-1101), designed to maximize the engraftment of SB-728-T in subjects who are not CCR5 delta-32 heterozygotes, later this year."

Data from Sangamo’s Phase 1 and 2 studies demonstrate that VL became undetectable during a TI from ART in three of seven evaluable CCR5 delta-32 heterozygote HIV-infected subjects, including two of six subjects that had completed TI in the ongoing SB-728-902 Cohort 5 study and an additional CCR5 delta-32 heterozygote subject from an earlier Phase 1 clinical trial of SB-728-T. In one SB-728-902 Cohort 5 subject, VL has remained undetectable (at or below the limits of quantification of the current ultra-sensitive assays for HIV) for 14 weeks (to last measurement taken) and the TI is ongoing. Reduction in VL from peak during TI showed a statistically significant correlation (p=0.015) with estimated numbers of engrafted ZFN modified cells (SB-728-T) in which both copies of the CCR5 gene had been disrupted (biallelic modification), in line with previously presented data from this program.

Collectively, data from these studies demonstrate that in all trial subjects, SB-728-T treatment results in a durable increase in total CD4 T-cells. In addition, seven of nine subjects enrolled in Sangamo's Phase 1 study (SB-728-902 Cohort1-3) experienced a longer term reduction in the viral reservoir as measured by HIV DNA in peripheral blood mononuclear cells, a source of chronic HIV infection not addressed by current ART.

Sangamo scientists and collaborators also presented data from preclinical and research programs in hemophilia and lysosomal storage disorders, hemoglobinopathies, cancer, cystic fibrosis, immunodeficiencies and the application of ZFN-mediated CCR5 modification in stem cells for HIV.

"The presentations at the ESGCT meeting demonstrate the diversity and breadth of potential therapeutic applications of Sangamo’s ZFP technology,” said Edward Lanphier, Sangamo’s president and CEO. "We look forward to continuing to update on our progress in the coming months at a translational medicine meeting organized by The Lancet entitled, 'What Will it Take to Achieve an AIDS-free World?' in San Francisco, from November 3-5, as well as at the Sixth International Workshop on HIV Persistence, Reservoirs & Eradication Strategies in Miami in early December. In addition, we will present data from Sangamo’s preclinical programs at the Annual Meetings of the Society for Neuroscience in November and the American Society of Hematology (ASH) in early December."

Summary of Clinical Trial Design
About SB-728-902 Cohort 5
Ten HIV-infected subjects heterozygous for the CCR5 delta-32 mutation (i.e. with one CCR5 gene that is naturally modified) who are currently on ART have been enrolled and have received a single intravenous infusion of SB-728-T (5 to 30 billion modified cells). Two months after SB-728-T treatment, subjects undergo a 16 week TI during which time their ART is discontinued. ART is re instituted in subjects whose CD4 T-cell counts drop to < 350 cells/mm^3 and/or whose HIV-RNA increases to > 100,000/mL for three consecutive weekly measurements. At the end of the TI, subjects with a sustained detectable HIV viral
load are reinstituted on ART. Subjects with an undetectable viral load can remain off ART until HIV RNA levels are detectable or their CD4 T-cell count drops below 350 cell/mm\(^3\) for three consecutive weekly measurements.

A total of ten subjects have been treated in this cohort.

Of the six evaluable subjects, we observed two subjects in which their VL became undetectable during TI from ART:
- In one subject, VL suppression at, or below, the limit of quantification (LOQ) of virus was sustained from week 11 — 25 of TI and the TI is ongoing.
- In the second subject there was a transient suppression of VL at or below LOQ.
- A third subject completed the TI with 1-log decrease in VL from peak.

In three subjects, there was no reduction in VL during the TI, one completed the TI and in two the TI was terminated early due to their viral loads exceeding the upper limit allowed in the protocol. A seventh subject has not completed TI and is still being evaluated.

**About SB-728-902 Cohorts 1-3**

The study is an open-label Phase 1 clinical trial to evaluate the safety and tolerability of single infusions of an escalating dose of an autologous (a patient’s own) CD4+ T-cell product genetically modified at the CCR5 gene by CCR5-specific ZFNs (SB-728-T). The trial enrolled nine HIV-infected subjects (three cohorts of three subjects each) who have sub-optimal T-cell levels and no detectable viral load on long-term ART. Subjects remained on their existing antiviral therapy while receiving treatment with SB-728-T.

**About SB-728-T**

Sangamo's drug, SB-728-T, is generated by ZFN-mediated modification of the gene encoding the CCR5 receptor in a patient’s own T-cells. ZFN modification disrupts the expression of this key co-receptor for HIV entry and renders cells resistant to HIV infection. The approach is based on the observation that a naturally occurring mutation in the CCR5 gene, CCR5 delta-32, provides protection from HIV infection. Individuals in whom both copies of the CCR5 gene carry the delta-32 mutation are generally not susceptible to the most common strain of HIV.

**Human immune system shapes skin microbiome**

October 29, 2013 – Our skin plays host to millions of beneficial and potentially disease-causing microorganisms; however, whether our immune system influences these microbial communities to prevent disease is unknown. In a study published online in *Genome Research*, researchers have explored the microbes living on the skin of patients with primary immunodeficiencies with eczema-like skin conditions.

The human body contains many microbes, some of which are necessary for healthy bodily functions including digestion. Others, such as some microbes living on our skin, may be pathogenic.

Previous studies investigated how these microbes educate and shape the human immune system. There is little known, however, if the immune system influences the types of microbes that live on the skin and thus potentially prevents disease. "In addition to questions about how microbes affect the human host, there is an interest in understanding how the human host affects the microbes that make our skin their home," said Heidi Kong of the National Cancer Institute (NCI) and co-senior author of the study.

To study this, the authors enlisted patients with reduced immune function as a result of rare genetic defects. Despite the diversity in disease-causing mutations in the patients, all patients shared an eczema-like skin condition. The scientists identified the patients’ skin microbes by sequencing microbial DNA from skin swabs. The immunodeficient patients had types of bacteria and fungi on their skin not found on healthy individuals, suggesting the patients’ skin was more permissive to microbe growth. "Our findings suggest that the human body, including our immune systems, constrains and potentially selects which bacteria and fungi can inhabit skin," said Kong.

Interestingly, the skin sites specifically prone to disease showed significant differences in microbial diversity, or the number of different types of microbes present, in immunodeficient patients. The skin at the elbow crease, for instance, had fewer types of microbes than found on healthy individuals, while skin behind the ear had more types of microbes. The authors suggest that an imbalance in microbial diversity at a given site may contribute to disease. In addition, "the communities of bacteria and fungi on the skin
of primary immunodeficiency patients are more likely to change over time,” said co-senior author Julie Segre, of the National Human Genome Research Institute (NHGRI).

Immunodeficient patients overall had much more similar microbial communities across their entire bodies, which are usually distinct in healthy individuals. The authors suggest correcting the diversity of microbes on the skin, not just targeting pathogenic ones, may aid in the treatment of disease. Although the individuals in this study have rare genetic disorders, this research may have implications for patients with temporary impairments in immune function, such as cancer patients and transplant recipients, and may inform the use of preventative antibiotics that are routinely given to these patients.

**HIV—Geneticists map human resistance to AIDS**

Do our genes hold the key to future AIDS therapies? Using a supercomputer, scientists analyzed the genomes of thousands of strains of the HIV virus and have produced the first map of human AIDS resistance

The key to future HIV treatment could be hidden right in our own genes. Everyone who becomes infected deploys defense strategies, and some even manage to hold the virus at bay without any therapy at all. This immune system struggle leaves its mark within the pathogen itself – genetic mutations that indicate how the virus reacted to its host's attacks. Scientists from EPFL and the Vaud university hospital center (UNIL-CHUV) retraced the entire chain of events in these battles, from the genome of the virus to the genome of the victim. They have created the first map of human HIV resistance. The goal of their research, which has been published in the journal *eLife* on the 29th of October, is to find new therapeutic targets and to enable individualized treatment strategies.

The human immune system is constantly developing strategies to fight HIV. Unfortunately, “the genome of the virus also changes rapidly, at a rate of millions of mutations a day,” explains Jacques Fellay, co-author and EPFL researcher. In the majority of cases, the pathogen finds an effective strategy via this natural selection.

Sometimes the virus is faced with a tougher opponent. It resists, but its ability to replicate is compromised. "The virus survives but replicates more slowly, and thus its capacity for destruction is in some sense neutralized," says the scientist.

By studying strains of HIV that have been living in human hosts, the researchers can identify specific genetic mutations. These are like scars that each bear witness to a very specific attack launched by the immune system. What are the human genes involved in these defense strategies? And which, among all our genetic variations, predispose us to increased HIV resistance or, on the contrary, increased vulnerability? The scientists developed a method that allowed them to find answers to these questions.

**A supercomputer, 1,071 patients and millions of combinations**

To draw up the first map of human HIV resistance, the researchers had to analyze an enormous amount of data. They studied various strains of HIV from 1,071 seropositive individuals. They crossed more than 3,000 potential mutations in the viral genome with more than 6 million variations in the patients' genomes. Using supercomputers, they studied all these possible combinations and identified correspondence between patients.

"We had to study the virus before the patient had undergone treatment, which is far from easy," says Fellay. This meant they had to search in data banks established in the 1980s, before effective therapies were made available.

This novel, indirect method made it possible to obtain the most complete global overview to date of human genes and their implications in terms of HIV resistance. It allows us to not only better understand how we defend ourselves from attack but also how the virus adapts itself to our defense mechanisms. "We now have a true database that tells us which human genetic variation will induce which kind of mutation in the virus", explains Amalio Telenti, co-author and UNIL-CHUV researcher.

**Therapies inspired by our own natural defense**

This research has two major implications. New therapies could be developed based on studying humans' natural defenses, particularly those that result in a reduced replication of the virus. In addition, the scientists hope that by profiling the genome of HIV-infected individuals, it will be possible to develop individually targeted treatments that take into account the patients' genetic strengths and weaknesses.
Model Virus Structure Shows Why There’s No Cure for Common Cold

Oct. 28, 2013 — In a pair of landmark studies that exploit the genetic sequencing of the “missing link” cold virus, rhinovirus C, scientists at the University of Wisconsin-Madison have constructed a three-dimensional model of the pathogen that shows why there is no cure yet for the common cold.

Writing today (Oct. 28, 2013) in the journal Virology, a team led by UW-Madison biochemistry Professor Ann Palmenberg provides a meticulous topographical model of the capsid or protein shell of a cold virus that until 2006 was unknown to science.

Rhinovirus C is believed to be responsible for up to half of all childhood colds, and is a seriouscomplicating factor for respiratory conditions such as asthma. Together with rhinoviruses A and B, the recently discovered virus is responsible for millions of illnesses yearly at an estimated annual cost of more than $40 billion in the United States alone.

The work is important because it sculpts a highly detailed structural model of the virus, showing that the protein shell of the virus is distinct from those of other strains of cold viruses.

“The question we sought to answer was how is it different and what can we do about it? We found it is indeed quite different,” says Palmenberg, noting that the new structure “explains most of the previous failures of drug trials against rhinovirus.”

The A and B families of cold virus, including their three-dimensional structures, have long been known to science as they can easily be grown and studied in the lab. Rhinovirus C, on the other hand, resists culturing and escaped notice entirely until 2006 when “gene chips” and advanced gene sequencing revealed the virus had long been lurking in human cells alongside the more observable A and B virus strains.

The new cold virus model was built “in silico,” drawing on advanced bioinformatics and the genetic sequences of 500 rhinovirus C genomes, which provided the three-dimensional coordinates of the viral capsid.

“It’s a very high-resolution model,” notes Palmenberg, whose group along with a team from the University of Maryland was the first to map the genomes for all known common cold virus strains in 2009. “We can see that it fits the data.”

With a structure in hand, the likelihood that drugs can be designed to effectively thwart colds may be in the offing. Drugs that work well against the A and B strains of cold virus have been developed and advanced to clinical trials. However, their efficacy was blunted because they were built to take advantage of the surface features of the better known strains, whose structures were resolved years ago through X-ray crystallography, a well-established technique for obtaining the structures of critical molecules.

Because all three cold virus strains all contribute to the common cold, drug candidates failed as the surface features that permit rhinovirus C to dock with host cells and evade the immune system were unknown and different from those of rhinovirus A and B.

Based on the new structure, “we predict you’ll have to make a C-specific drug,” explains Holly A. Basta, the lead author of the study and a graduate student working with Palmenberg in the UW-Madison Institute for Molecular Virology. “All the [existing] drugs we tested did not work.”

Antiviral drugs work by attaching to and modifying surface features of the virus. To be effective, a drug, like the right piece of a jigsaw puzzle, must fit and lock into the virus. The lack of a three-dimensional structure for rhinovirus C meant that the pharmaceutical companies designing cold-thwarting drugs were flying blind.

“It has a different receptor and a different receptor-binding platform,” Palmenberg explains. “Because it’s different, we have to go after it in a different way.”
New Drug to Help Common Bowel Disease
Oct. 29, 2013 — An international team led by University of Adelaide researchers has identified the mechanism of pain relief of a new drug for treating Irritable Bowel Syndrome with Constipation (IBS-C), based on nonclinical studies, and quantified its effectiveness in pain relief in human trials.

Published in the journal Gastroenterology, the study describes the pain mechanism of action for Linaclotide, a recently approved drug for the treatment of chronic abdominal pain and constipation in adult IBS-C patients.

"This is a significant finding and very good news for IBS-C sufferers," says study leader Dr Stuart Brierley, NHMRC RD Wright Biomedical Fellow in the University's Nerve-Gut Research Laboratory. "IBS affects many people, particularly women, on a daily basis and has a significant impact on their quality of life. Abdominal pain is often the most troubling symptom to IBS patients and has been the most difficult symptom to treat."

"The drug is effective in relieving abdominal pain associated with IBS-C and is already available and registered for use by IBS-C patients in the USA and Europe. It is yet to go through the regulatory process in Australia."

The research is a collaboration between the Nerve-Gut Research Laboratory, (University of Adelaide) and Ironwood Pharmaceuticals Inc, the developers of Linaclotide. Linaclotide is a new class of medicine and is the only treatment for IBS-C currently registered with the European Medicines Agency; it is also the first prescription treatment available in over six years for adults with IBS-C in the US.

Linaclotide binds the receptor domain of guanylate cyclase-C on the inner lining of the intestines. It is marketed by Ironwood and Forest Laboratories Inc as Linzess® in the US and by Ironwood and Almirall SA as Constella® in Europe. Ironwood has partnerships through which it is conducting clinical trials of Linaclotide in China and Japan. Ironwood is exploring partnership opportunities for advancing Linaclotide in unpartnered territories, including Australia and New Zealand.

Dr Brierley, in the Nerve-Gut Research Laboratory, collaborated with Ironwood to further investigate how Linaclotide acts within the gastrointestinal tract to reduce abdominal pain. It had been shown to increase the secretion of fluids into the intestine and improve transit through the gastrointestinal tract. However, initial trials had shown that it also reduced abdominal pain associated with IBS-C, independently of its action on improving constipation.

Pre-clinical studies by the Nerve-Gut Research Laboratory showed that Linaclotide inhibits pain nerve endings in the intestine through a novel physiological pathway localised to the gastrointestinal tract. "The study also showed the analgesic effect translated into clinical findings in humans," says Dr Brierley. "IBS-C patients given the drug orally showed significant improvement in abdominal pain over those given placebo during a 26-week trial."

Journal Reference:

Placebo’s Double Whammy
Sham treatments can both reduce pain and increase pleasure, and do so affecting similar circuitry in the brain.
By Kerry Grens | October 14, 2013
Expectations give placebos their power, allowing them to dramatically alter our experience of a stimulus. Researchers demonstrate in Proceedings of the National Academy of Sciences today (October 14) that not only can placebos tamp down feelings of pain, they can also ramp up pleasurable sensations. It all depends on where a person starts. If she is expecting an improvement in pain, her sensory processing
decreases. If, on the other hand, she anticipates a heightened sense of pleasure, then the sensory processing is magnified.

The researchers, led by Dan-Mikael Ellingsen at Gothenburg University in Sweden, offered a nasal spray placebo (supposedly containing oxytocin) or nothing at all to 30 study participants. On one day, the participants received gentle strokes on the left arm; on another day, a painful heat stimulus. In the pain scenario, the nasal spray was tied to a decrease in pain sensation, and in the pleasure scenario, it was associated with an increase in pleasure, compared to the times when the person was given no spray.

Using functional MRI, the researchers found increases in activity in the posterior insula and primary and secondary somatosensory areas—regions involved in sensory processing—during the pleasurable arm stroke placebo treatments. They also found decreases in these areas during the painful heat placebo sessions. These results suggest that a placebo can enhance good feelings by increasing sensory processing and squelch pain by decreasing sensory processing.

Interestingly, they also found that parts of the brain involved in reward and emotion, a network they called “emotion appraisal circuitry,” were activated in both the painful and pleasant situations. The researchers interpret this activation in both scenarios as having opposing regulatory effects on sensory processing. “Overall, our results suggest that emotion appraisal circuitry is recruited by expectations of a benefit, whether it is pain relief or enhanced pleasantness of a positive stimulus, and modulates sensory processing accordingly to meet these predictions.”

The research team says that focusing on both the pain-reducing abilities of placebos and the pleasure-enhancing abilities are important in clinical studies.

**Mouth Microbes Influenced by Ethnicity**

**Researchers identify oral microbiome signatures that correlate with a person’s cultural background.**

By Tracy Vence | October 24, 2013

Oral infections have previously been found to correlate with ethnicity, and now researchers from The Ohio State University found that this correlation may be partly rooted in causation: ethnicity appears to actually determine colonization of the mouth microbiome. The team reported its findings in *PLOS ONE* this week (October 23).

Purnima Kumar and her colleagues sequenced dental plaque and saliva samples from 192 people in the U.S. representing four major ethnicities—non-Hispanic blacks, non-Hispanic whites, Chinese, and Latinos—finding apparent ethnicity-specific clustering of microbial communities in biofilms isolated from the samples. The researchers also found that a machine-learning classifier was able to reliably identify a person’s ethnicity based on their subgingival microbes.

“People’s background—in terms of foods they ate and other lifestyle trends—didn’t seem to have any correlation with the bacterial communities in their mouths,” reported *Surprising Science*. “But their ethnicity and thus their similar genetics matched their microbiome more often than chance.”

“This is the first time it has been shown that ethnicity is a huge component in determining what you carry in your mouth. We know that our food and oral hygiene habits determine what bacteria can survive and thrive in our mouths, which is why your dentist stresses brushing and flossing,” Kumar said in a statement. “Can your genetic makeup play a similar role? The answer seems to be yes, it can.”

She added that ethnicity-specific oral microbiome signatures could have implications for a person’s risk for future disease. According to *The Indian Express*, “[t]he research also confirms that one type of dental treatment is not appropriate for all, and could contribute to a more personalized approach to care of the mouth.”

**Trouble in the Heartland**

**A new tick-borne disease has emerged in the US Midwest—and the culprit is not a bacterium.**

By Jef Akst | October 1, 2013

In June 2009, two male patients were independently admitted to the Heartland Regional Medical Center in northwestern Missouri with fever, headache, muscle pain, nausea, and diarrhea—all classic signs of ehrlichiosis, a common tick-borne disease in the region. Although both men reported having recently been bitten by ticks, blood and serum samples sent to microbiologist William Nicholson, chief of Pathogen Biology and Disease Ecology at the Centers for Disease Control and Prevention (CDC), came back negative for *Ehrlichia chaffeensis*, the disease-causing bacterium.
Nevertheless, Nicholson says, when the researchers plated the samples over a culture of canine tumor cells, they started to see signs of a pathogen. First, they noticed increased vacuole formation in the cells.

“When we see that, within a day or two we usually see Ehrlichia,” Nicholson explains. But in this case, no Ehrlichia appeared, and the cells eventually began to fall apart. Then, the single layer of cells that lined the bottom of the flask started to detach earlier than normal—within 6–7 days, instead of 2 weeks.

Nicholson and his colleagues continued to transfer the cells to fresh media, “and then it’d do it again,” he says. “That was an indication that we have something in there, we just can’t see it.”

After finding none of the various pathogen culprits familiar to the researchers, Nicholson’s group turned to their colleagues in the CDC’s electron microscopy (EM) department for help. When they got the transmission EM images back, “you could clearly see the cell just loaded with virus,” he says. “That was a nice bit of detective work,” says Sam Telford, an epidemiologist at Tufts University.

Based on the virus’s shape and size, the researchers suspected it belonged to the family Bunyaviridae. To get a more precise identification, Nicholson turned to Laura McMullan in the CDC’s viral special pathogens group, which had recently purchased a 454 sequencer. Its sequence revealed the virus to be a novel Bunyaviridae species belonging to the genus Phlebovirus, and the researchers named it the Heartland virus (HRTV) following the convention of naming viruses after their region of origin, which was coincidentally the name of the hospital where it was discovered (N Engl J Med, 367:834-41, 2012).

The next step was to determine the virus’s vector. Interestingly, the closest known relative of HRTV was the severe fever thrombocytopenia syndrome virus (SFTSV), a tick-borne Phlebovirus identified in 2011 after causing several cases of severe fever in China. Indeed, with both Missouri patients having reported tick bites, the researchers suspected that HRTV might also be carried by the arachnids.

In April, June, and August 2012, Nicholson and his colleagues collected more than 56,000 ticks of various species and life stages from several sites in northwestern Missouri, including the farms of both HRTV patients. They froze them in vials and sent them off to the CDC center at Fort Collins, Colorado, for molecular analysis. Sure enough, some of the ticks—specifically nymphs of the lone star tick Amblyomma americanum—carried HRTV, including those found at the farm of one of the patients (Am J Trop Med Hyg, doi:10.4269/ajtmh.13-0200, 2013). All told, however, the virus was relatively rare, Nicholson says, estimated to be present in about 1 in every 500 ticks. For comparison, Ehrlichia is found in some 10 percent of ticks. This rarity could explain why no virus was found in the ticks at the second farm, where the researchers were not able to collect nearly as many animals.

The researchers suspect that the ticks are becoming infected from the blood meal they ingest as larvae, after which they fall to the ground and burrow into the soil, where they will develop and molt into the nymphal stage. Then, when the nymphs emerge in the spring looking for their next meal, they can pass the infection on to people. Of course, “this is speculation based on the fact that we’re getting these hot ticks in the spring,” Nicholson says.

“It just goes to show that the diversity of potential pathogens carried by ticks is fairly large.—Sam Telford, Tufts University

To get more answers, the team has been out in the field again this year, and is expanding its search for the virus from just ticks to the vertebrates that A. americanum generally feeds on, such as wild turkey, deer, raccoons, and gray squirrels.

As for the virus’s origin, “none of us believe that this is a new introduction,” says Telford. More likely, “it’s been under our noses all along. It just goes to show that the diversity of potential pathogens carried by ticks is fairly large.”

One possible explanation for the virus’s recent emergence as a disease-causing pathogen, then, is the country’s changing demographic. “The American population as a whole is aging,” Telford notes. “Previously, maybe something like this was infecting perfectly healthy younger farmers in Missouri, and they just sort of shrugged it off.” Indeed, the two case patients were 57 and 67 years old. “It’s a pattern that we’ve seen in infectious biology all along—that as people age they become immune-compromised and far more susceptible to severe disease,” says Telford, who in 1997 discovered a flavivirus carried by deer ticks—which also transmit Lyme disease—that has shown up on the radars of epidemiologists only in the last 5 years.

“It’s much more than just a story of pathogen discovery and a new threat from ticks,” he adds. “I think the more interesting stuff is how these [pathogen] communities evolved, where they come from, and what are the things that lead us to recognize them as potential causes of disease.”
Scientists identify molecular signals that rouse dormant HIV infection

Perhaps the single greatest barrier to curbing the spread of HIV/AIDS is the dormant, or "latent," reservoir of virus, which is out of reach of even the most potent medications. But now, scientists at the Gladstone Institutes have uncovered new clues that may help researchers awaken HIV from its slumber—laying the foundation for purging all trace of the virus, and for one day finding a cure for the more than 34 million people worldwide living with HIV/AIDS.

In a paper being published today in PLOS One, researchers in the laboratory of Gladstone Investigator Warner C. Greene, MD, PhD, have uncovered the molecular signals that guide the activation of latent HIV. Specifically, they showed how molecular crosstalk between calcium and an enzyme called calcineurin, along with a molecule called prostratin, switch on members of the NF-κB family of proteins—thereby activating latent HIV. These findings point to a new strategy of artificially activating HIV—a process that experts believe is key to flushing out all evidence of infection and developing a cure for HIV/AIDS.

During the initial stages of HIV infection, often within hours, the virus infects a type of white blood cell called CD4 T cells. In the majority of cases, HIV then hijacks the cell’s DNA to produce, or "transcribe," new virus, infecting more cells. But every so often something different happens: the viral DNA inserts itself into the host cell's DNA, but then stops, maintaining a holding pattern that can persist for decades. This latent HIV is virtually undetectable and therefore cannot be targeted by medication.

"Current treatments, which involve a complex cocktail of antiretroviral (ARV) medications, are fine-tuned to target and destroy active, replicating HIV—but they can't touch the latent virus," explained Dr. Greene, director of virology and immunology research at Gladstone and professor of medicine at the University of California, San Francisco, with which Gladstone is affiliated. "But most troublingly is that within weeks of stopping ARV treatment, the latent virus wakes up, and the cycle of replication and infection begins all over again."

What this means for patients is a lifetime of treatment with expensive ARVs. This is an unsustainable strategy in today’s world, where more than two-thirds of those infected live in the developing world and have limited access to ARVs. And for every 10 people who do receive ARVs, 16 become newly infected.

Recently, researchers have championed the "shock-and-kill" strategy for combating HIV latency. This approach would activate the latent virus, and then bombard this newly active virus with ARVs. Precisely how to do so has been fraught with difficulty. But in this study, Dr. Greene and his team have identified a potential strategy.

In laboratory experiments using latent HIV introduced into CD4 cells from donors or cell culture, the research team tested a series of proteins believed to regulate activation and transcription of the virus. One such family of proteins, called NFAT, was previously shown to induce HIV transcription during the initial stages of infection. So the researchers tested whether it would also function in activating latent HIV.

"Surprisingly, NFAT didn't appear to play a central role so we went back to the drawing board, exploring other protein families we thought might be involved," said Gladstone Postdoctoral Fellow Jonathan Chan, PhD, the paper’s lead author. "Interestingly, we observed that members of the NF-κB protein family appeared to act as a molecular alarm clock, rousing latent HIV and spurring viral replication."

Even more interesting was what they observed when they added prostratin to the mix. Prostratin, a naturally occurring compound that is extracted from the Samoan mamala tree, helps to activate latent HIV. But prostratin is difficult to procure and, as of right now, impossible to synthesize on an industrial scale. Now, the experiments performed by Drs. Greene and Chan suggest a potential workaround.

"When we stimulated the calcium/calcineurin pathway in the presence of low levels of prostratin, we in turn boosted prostratin's effectiveness," explained Dr. Chan. "These findings, while preliminary, hold promise that we could develop a way to purge the latent HIV reservoir with even suboptimal levels of prostratin."

"Our results give us much-needed insight how the shock-and-kill approach to eliminate the virus might work," said Dr. Greene. "Slowly but surely we are finding new components of a cure cocktail that might be able—at long last—to realize a broadly applicable and scaleable cure for HIV/AIDS."