

Parasite genome similarities offer hope for new drugs and vaccines

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News

It took nearly 250 scientists from 47 institutions on 6 continents over 6 years to resolve the genetic makeup of 3 deadly parasites that are responsible for causing hundreds of thousands of cases of disease each year. The information, published in 3 papers in the July 15 issue of *Science*, provides new opportunities for developing new therapies (1–3). “The most immediate benefit will be a change in the way research in these fields is conducted,” said Matthew Berriman, lead author on one of the papers. “With a genome sequence, there’s a framework for generating new ideas and rapidly testing them. The ultimate aim of these projects is to accelerate development of vaccines, new drugs, and diagnostics.” African sleeping sickness, leishmaniasis, and Chagas disease are insect-borne diseases caused by the parasites *Trypanosoma brucei*, *T. cruzi*, and *Leishmania major*, respectively. Although incidences of these diseases are virtually unheard of in the US, they are endemic in sub-Saharan Africa, Central and South America, Brazil, India, and several other countries. Despite their prevalence, treatment options for these often-lethal diseases are suboptimal and expensive, and vaccines against the parasites have not been developed. African sleeping sickness, transmitted by the tsetse fly, causes people to sleep for long periods during the day and leads to personality changes and seizures, which become progressively worse. Although 40,000 new [...]

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New HIV vaccine center has Haynes at its helm

The new Center for HIV/AIDS Vaccine Immunology (CHAVI), set up by the NIH's National Institute of Allergy and Infectious Diseases (NIAID), is a consortium of researchers at various universities who will collaborate with the goal of creating an effective HIV vaccine that can be used worldwide. Barton Haynes, a Duke University immunologist and director of the Duke Human Vaccine Institute, is CHAVI's new director.

Haynes will work with foremost investigators Norman Letvin, Joseph Sodroski, George Shaw, and Andrew McMichael. Together they competed with and defeated 3 other potential teams to form the scientific leadership group for CHAVI, responsible for the overall work the consortium conducts. The *JCI* spoke to Haynes about his new position, the future of AIDS vaccines, and how this



Barton Haynes, new CHAVI director. Photo courtesy of Duke University Medical Center.

multimillion dollar endeavor might change the course of the AIDS epidemic.

JCI: How was your team selected for this position?

Haynes: We were selected through a peer review process of an NIH-funded grant.

JCI: How will CHAVI be different from other groups that carry out AIDS vaccine research?

Haynes: CHAVI will be more highly coordinated and will synergize with other groups in open and transparent ways. We will be an integral part of the overall effort of the Division of AIDS at NIAID and the Global HIV AIDS Vaccine Enterprise.

JCI: What do you think are the biggest challenges that AIDS researchers face today?

Haynes: Understanding correlates of protective immunity, overcoming HIV diversity, and [achieving] induction of broadly neutralizing antibodies.

JCI: What do you anticipate will be your biggest challenge in this new endeavor?

Haynes: The first challenge will be to establish the infrastructure for a functional, virtual organization. This will need to include a communications system of phone, video conferencing, and face-to-face meetings to develop and orchestrate functional research teams. Second, the initial focus of research for the CHAVI teams will be an extensive analysis of both the host and the virus during the very earliest stages of acute HIV infection. We will work to enroll a large cohort of acute HIV-infected patients for these studies. Third will be the analysis of those subjects repeatedly exposed to HIV who still appear to be uninfected. We will need to determine if they are truly uninfected, and if so, define the immunologic or genetic factors that contribute to protection. Next will

be the challenge to define correlates of protection in nonhuman primates to a virus challenge that is relevant to transmission of HIV in human infection. And finally will be the challenge to translate our discovery efforts to the development of novel vaccine candidates for iterative testing in human trials.

JCI: How do you foresee your typical day?

Haynes: Lots of conference calls, visits to collaborators and advisors, lots of data analysis. Initially, we will spend time setting up administrative infrastructure, and then after the first 4–6 months, will spend more time on technology development and scientific project administration. We have already assembled a crack administrative team that knows how to run such a large and diverse organization.

JCI: What are your 3 top initial goals for CHAVI?

Haynes: Establishing a functional CHAVI organization infrastructure, elucidating the correlates of protective immunity in the context of acute HIV infection and primate infection models, and bringing HIV vaccine candidates to phase I clinical trials in man that, in preclinical studies, induce immune responses at systemic and mucosal sites, and that we believe will be predictive of clinically relevant protective anti-HIV immune responses in man.

JCI: What in your life are you most proud of?

Haynes: My family. And coaching my children's sports teams.

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African sleeping sickness, transmitted by the tsetse fly, causes people to sleep for long periods during the day and leads to personality changes and seizures, which become progressively worse. Although 40,000 new cases are reported to the World Health Organization each year, the actual number of cases is probably much higher, since most cases are not reported at all.

Leishmaniasis, transmitted by the sand fly, can cause fever, swollen spleen, severe weight loss, and skin ulcers. The number of new cases of leishmaniasis each year in the world is about 2 million. Triatomine bugs spread Chagas disease, which is characterized by rash, diarrhea, cardiac problems, and enlargement of the esophagus or large bowel. According to the Centers for Disease Control (CDC), an estimated 50,000 of the 16 to 18 million people infected with Chagas disease will die each year.

"Thanks to these studies, scientists are much closer than they were 5 years ago to developing effective drugs against these terrible diseases," said Najib El-Sayed, one of the principal investigators and a lead author on all 3 papers.

The critical finding was that each of the 3 pathogens shared the same 6,200 core genes, which exist in a similar order



A triatomine bug (left), a vector for Chagas disease; and a sand fly (right), which transmits leishmaniasis. The parasites they transmit have much more in common than was previously thought. Images courtesy of the CDC.

and represent 70% of the genes present, explained coauthor Peter Myler.

"This is surprising, considering the substantial differences the parasites display," El-Sayed told the *JCI*. Each organism is transmitted by a different insect, infects a different set of tissues, has unique life cycle features, and causes very different symptoms and diseases.

"They also employ different immune evasion strategies," El-Sayed explained. "*L. major* hides within the very same cells of the immune response and alters the function of the macrophages it infects, *T. cruzi* expresses a complex variety of surface antigens from within the cells it infects, while *T. brucei* remains extracellular but circumvents the host immune response by the periodic switching of its major surface protein."

Nevertheless, the gene order and organization — called the synteny — along the parasite chromosomes is conserved. "This suggests that whole batches of genes are transcribed together and that regulating the activity of genes is very simple," Berriman said. "If we can find an exploitable weakness amongst those common genes, we may be able to devise an intervention strategy that works on all 3 parasites."

The genetic similarities uncovered among the parasites prevail over the differences, providing scientists with the opportunity to develop drugs to target all 3. On the other hand, detailed analysis of their variations could lead to targeted therapy against each parasite in particular.

A long-term goal for El-Sayed is to revitalize efforts to develop drugs against these neglected diseases. He is also sequencing the genome of *Schistosoma mansoni*, the causative agent of schistosomiasis, a disease caused by parasitic worms affecting 200 million worldwide.

"Genome sequences do not in themselves cure people," El-Sayed said. "However, they do bring the prospect of safe and effective drugs, vaccines, and diagnostics nearer to fruition."

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All eyes on the Nobel Prize

Some people associate the month of September with the end of summer or the start of a new academic year. But September is also the time of year when the process of selecting a winner of the Nobel Prize in Physiology or Medicine begins.

It is during this month that the Nobel Assembly, composed of 50 elected members (all professors at the Karolinska Institute

in Stockholm, Sweden), sends out nearly 3,000 invitations to nominate potential winners to a select group of individuals. The prizewinner is announced in October of the following year, and although the people involved and the events that transpire during these 13 months are not shrouded in secrecy, most of us are unfamiliar with exactly what goes on during this time.

The prize, according to the will of Alfred Nobel, is awarded for a discovery that has changed the scientific paradigm in an important area of life science, explained Goran Hansson, chairman of the Nobel Committee and a professor at Karolinska Institute.

"It is important to keep in mind that discovery is the paramount criterion," Hansson told the *JCI*. "We make great efforts to identify