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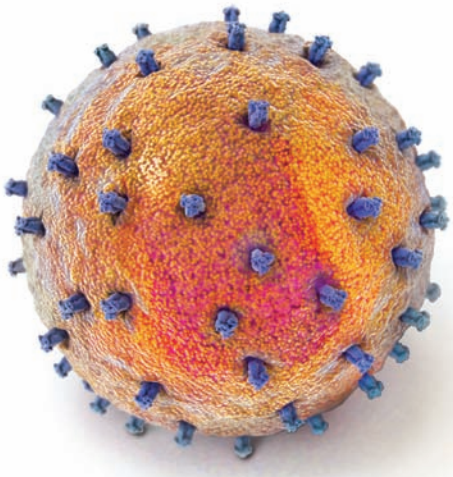
The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

Not Sure? Ask Everyone

Crowdsourcing is becoming an increasingly common tool to solve scientific challenges both big and small. It is even being put to the test in AIDS vaccine research ***By Kristen Jill Kresge***

Science is all about discovery. And new discoveries can come about in many different ways. In biomedical research, several companies and organizations are now exploring different approaches to encourage new discoveries or stimulate innovation, some of which rely on collective wisdom.

Crowdsourcing is one of these approaches. This principle, dubbed by Jeff Howe, a contributing editor at Wired, a popular technology magazine, describes a phenomenon by which an undefined, generally large group of people or crowd takes on tasks in response to an open call. The open call is often issued via the Internet. This approach is used to solve all kinds of simple tasks, such as digitizing books and periodicals published before the Internet, as well as for more complicated scientific problems. Crowdsourcing is now even being used to address some of the challenges confronting AIDS vaccine researchers.

Reaching the crowd

There are several different ways to get the public or crowd involved in solving scientific challenges. One way is to use online games. Last year, researchers at the University of Washington introduced the online game Foldit, which aims to find the lowest possible energy structure of different proteins. Foldit players use their computer mouse to move around parts of proteins, which are displayed on the screen. They score points by getting the protein in a conformation closer to its lowest energy state.

Recently, Foldit announced a new component of the game that allows players to manipulate HIV's Envelope protein (Env), which covers the exterior of the virus, to expose areas of that protein that would be potentially vulnerable to neutralizing antibodies (Y-shaped proteins that bind to viruses and disable them).

Originally, a team led by David Baker, a University of Washington professor of biochemistry, developed a program called rosetta@home. This program, which could be downloaded by anyone, used the downtime of multiple computers to sort through protein structures. The results of the calculations were then displayed as a screensaver. Foldit was created because users of rosetta@home wanted to participate, not just watch, Baker says. "They thought they could do better," he adds. And it seems that they can. People see which particular options to try in a more efficient way than computers would, says Zoran Popović, a computer scientist at the University of Washington who developed Foldit with Baker and others. "They can find solutions that the computers have not found," Popović says.

New companies have also sprung up to facilitate crowdsourcing of scientific or engineering challenges. InnoCentive and NineSigma are two of these companies. They run websites, where, for a fee, organizations (referred to as seekers) can post specific challenges they want solved. Anyone can view the challenge or have it sent to them by email and then propose a solution. The seeker can then review the submitted solutions and determine if any of them meet their requirements.

At InnoCentive, some challenges only require a written proposal of ideas about how to solve the problem, while others require additional evidence showing that the solution actually works, such as original

ALSO IN THIS ISSUE

data from experiments or even a physical sample. The seeker then pays a cash award to the solver who provides the solution that they find suitable.

NineSigma was founded in 2000 by Mehran Mehregany, a professor of electrical engineering and computer science at Case Western Reserve University. Mehregany says he founded the company once he realized that the elaborate system the government uses to issue open calls to academic researchers wasn't available to industry. "Industry does not have a similar systematic infrastructure to broadcast its science and technology needs," he says.

The solutions to challenges posted on InnoCentive or NineSigma can come from anyone, anywhere, and they often do—the success rate for the challenges posted through these sites is surprisingly high. InnoCentive says that about a third of its challenges get solved. Karim Lakhani, an assistant professor in the technology and operations management unit at Harvard Business School, says it's hard to know how this compares with the in-house success rate of companies, since most don't keep track of that or share it publicly. But, he says, in his conversations with research and development chiefs at various organizations, they seem "very surprised" by the high success rate of InnoCentive, especially considering that the challenges that get posted on InnoCentive's website are likely there because the companies couldn't solve them in-house.

Ed Melcarek, a 60-year-old Canadian engineer and scientist, says he has made over US$115,000 for solving seven challenges on InnoCentive since 2003. InnoCentive declared him one of the most successful solvers of 2007.

On average, it takes two weeks, or 80 hours, for solvers to come up with a solution to an InnoCentive challenge, according to a study of 166 challenges solved through the company's website between 2001 and 2004. The study also found that the further removed the background of the solver was from the area the challenge pertained to, the more likely it was that the problem got solved, says Lakhani, who helped conduct the study. "In our analysis the problem solvers said that the problem that they tried to create a solution to was typically outside their own field of expertise," he says.

For example, John Davis solved a challenge to help with oil spill recovery. The challenge, from the non-profit Oil Spill Recovery Institute, was to find a way to liquefy the oil/water slush collected on barges from arctic waters in the case of an oil spill so that it could be pumped from the barges to larger storage tanks on land. Davis says he remembered that construction workers used a vibrating device to keep the concrete from solidifying at construction sites. He thought the same approach might work on the oil/water slush. After a day of work, and a call to the company asking if they could modify the vibrating device for this purpose, he filed the solution. A few months later, he received $20,000.

InnoCentive most often has companies as clients but it also tries to attract non-profits to post challenges, says Dwayne Spradlin, president and CEO of InnoCentive. "We try to make it very appealing for non-profits because we think [they] have not had access to the same innovation channels that commercial interests have," Spradlin says.

From 2006 until 2008, the Rockefeller Foundation collaborated with InnoCentive to encourage non-profits to participate. The foundation would typically pay the fee required to post a challenge as well as half of the award money on behalf of the non-profit, according to Amanda Sevareid, a research associate at the Rockefeller Foundation. Once a problem was solved, the foundation paid the rest of the award money if there was evidence that the solution was successfully implemented. Six non-profits have taken part in the program, and most of their challenges have been solved. In late 2008, the TB Alliance announced two awards of $20,000 each for improving the synthesis of a tuberculosis drug candidate.

In 2008, IAVI posted a challenge on the InnoCentive website as part of the Rockefeller Foundation program. The challenge issued was to create a stable version of HIV Env. In its natural state, the Env protein is unstable and breaks down easily when entering the body, according to Kalpana Gupta, director for new alliances and initiatives at IAVI, who was involved in developing the challenge. As a result, it has been difficult to trigger antibody responses against this protein. Having a stable form of HIV Env—the primary target for neutralizing antibodies—which researchers could experiment with in the laboratory, could help in the development of AIDS vaccine candidates. ■

This article was adapted from an article written by Andreas von Bubnoff in the May-June 2009 issue of IAVI Report.

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– Dwayne Spradlin

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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 24 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

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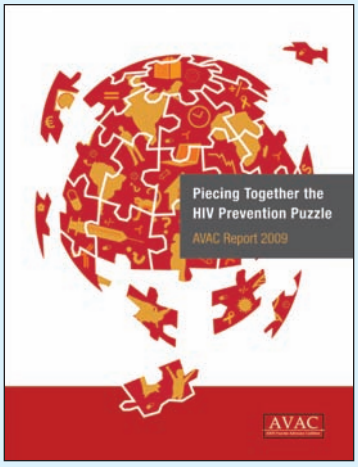
AVAC Reports on the HIV Prevention Puzzle

In its 13th annual report, "Piecing Together the HIV Prevention Puzzle," the AIDS Vaccine Advocacy Coalition (AVAC) says there is an "energized focus on discovery, innovation and basic science" in the field of AIDS vaccines, but noted that successful HIV prevention will likely depend on a combination of approaches and strategies.

Casting comprehensive HIV prevention as a puzzle still missing vital pieces, AVAC lists eight recommendations in its report. The recommendations include development of better communication tools to explain upcoming vaccine trials to a lay audience, as well as to communicate the result of the soon-to-be-completed Phase III prime-boost trial in Thailand. Another focus of the report is the role of the Global HIV Vaccine Enterprise, an international alliance of researchers, funders, and advocates committed to accelerating the development of an AIDS vaccine. Based on interviews with various stakeholders, AVAC concluded that the "added value" of the Enterprise is "not yet completely convincing." The AVAC Report recommends that the Enterprise should demonstrate greater leadership, particularly through publication of an updated scientific plan in 2010.



To access a copy of AVAC's report, go to www.avac.org

AVAC also highlighted advances in the field—more initiatives aimed at bringing young investigators into HIV prevention research was a notable area of progress. And with the initial results from the now infamous STEP trial nearly two years old, AVAC noted that the failure of Merck's vaccine candidate has helped propel new and exciting directions in research.

AVAC, which was formed in 1995, uses public education and policy analysis to advocate for the development of an AIDS vaccine. The organization has also taken a central role in advocating for other HIV prevention strategies, primarily pre-exposure prophylaxis (PrEP)—the delivery of antiretrovirals to uninfected individuals to prevent HIV infection. The report, written by AVAC staff, urged the HIV prevention field to prepare for the potential efficacy of prevention strategies such as PrEP, and said governments in the countries hardest hit by HIV needed to "add specificity" around financial, infrastructure, and other implications regarding the possible use of this modality in the future.

AVAC dedicated its report to AIDS activists Martin Delaney, who helped found the San Francisco-based AIDS service organization Project Inform, and Lynde Francis, one of the first HIV-infected individuals to disclose her status in Zimbabwe and the founder of The Centre for AIDS Services in that country. Both died this year.

New South Africa Institute to Tackle HIV and TB

The University of KwaZulu-Natal (UKZN) in South Africa, which claims the highest AIDS prevalence in the world, has teamed up with the Howard Hughes Medical Institute (HHMI) in Maryland to develop a research center focused on the twin scourges of tuberculosis (TB) and HIV. When HIV and TB infections coexist, it often comes with dire consequences—TB is the leading killer of people with HIV/AIDS, according to Joint United Nations Programme on HIV/AIDS (UNAIDS).

The KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH) will receive US$60 million over 10 years from HHMI—$20 million to establish K-RITH and $4 million a year for 10 years to support research projects. The UKZN is committing about $11 million for infrastructure costs. The new institute will be housed within the Nelson Mandela School of Medicine in Durban. K-RITH will also be adjoined to the Doris Duke Medical Research Institute, which houses several AIDS research groups, including the Human Pathogenesis Programme headed by Bruce Walker, an HHMI investigator, and the Center for the AIDS Programme of Research in South Africa, led by Salim Abdool Karim.

K-RITH will initially focus on four research areas: the development of rapid and more effective diagnostic tests for TB; characterizing drug-resistant strains of TB; analyzing immune responses to TB, particularly those seen in people also infected with HIV; and the study of recurrent TB infections in HIV-infected individuals. K-RITH will also be involved in testing candidate vaccines, both for TB and HIV, and researchers hope the new institute will become a magnet for young African scientists who want to base their laboratory work there but are hindered by the lack of research facilities and funding.

[PRIMER]

Understanding Data Collection in AIDS Vaccine Clinical Trials

What are the methods used to ensure that data from AIDS vaccine trials are of high quality? *By Regina McEnery*

AIDS vaccine clinical trials depend upon a number of factors to be successful. The candidates undergoing testing must first submit to extensive pre-clinical evaluation—initially in the laboratory and later in animal models—so researchers and regulators, who approve the clinical studies, can obtain essential information about whether the vaccine candidates are safe, and whether they demonstrate efficacy in animals. This can help predict how well they might work in people (see *VAX* October 2006 *Primer* on *Understanding AIDS Vaccine Pre-Clinical Development*).

AIDS vaccine trials must also follow Good Clinical Practice (GCP) guidelines, which are an international quality standard for conduct of clinical trials. Ethical and regulatory review committees from the countries and institutions that are involved in the clinical trial must provide approval for the trial before it can begin, and also provide guidelines for the trial staff (see *VAX* June 2005 *Primer* on *Understanding Informed Consent*).

In addition, external committees known as Data and Safety Monitoring Boards (DSMBs) or Safety Review Boards (SRBs), monitor the trial once it is underway (see *VAX* June 2007 *Primer* on *Understanding Data Safety Monitoring Boards*). The DSMB or SRB for a clinical trial evaluates the data regarding safety and efficacy that emerges from the trial while it is in process.

Collecting quality data is central to the mission and purpose of a clinical trial. Without consistent and unambiguous methods of data collection, researchers run the risk of conducting a trial that is unable to draw any firm conclusions about side effects, adverse events, or even whether the vaccine candidate is effective or not. Therefore, clinical trial sites continually work to make sure the process of data collection is as accurate as possible. Also, since many clinical trials are conducted at multiple centers, often in different countries and regions of the world, it is necessary for all data to be recorded consistently, so that they are comparable.

Data entry

Collecting high-quality data starts with training the staff to properly collect and record information, both by hand and electronically. Usually, nurses, physicians, and counselors working on a clinical trial collect data from volunteers. During the screening process for a trial, nurses will conduct physical exams, HIV tests, and other baseline medical criteria from potential volunteers so there is a record of their general health before they are enrolled in the trial. Then, throughout the course of the trial, nurses, physicians, and counselors will collect additional data from all of the volunteers such as measuring and recording a volunteer's vital signs—generally their temperature, blood pressure, pulse, and respiratory rate.

Once volunteers in the trial have received vaccinations with either the vaccine candidate or placebo, nurses or physicians also examine volunteers for any potential adverse events, including fever, rash, or headaches. Periodic testing for HIV is also performed and all volunteers receive counseling about how to reduce their risk of HIV infection. The frequency at which data are collected is defined in the trial protocol, which describes the objectives, design, methodology, and statistical considerations for the study. It is essential that all clinical research centers participating in a trial record data in consistent intervals of time.

These observations are all carefully recorded on what is known as a source document—a paper record kept for each volunteer with the observations made by the nurse, physician, or counselor.

Along with the source documents, staff at the vaccine research centers record data on electronic case report forms, which are transmitted to a data coordinating center for analysis by statisticians. It is important to use a common case report form so that all data is collected in exactly the same manner for each volunteer, and to ensure that the same standards are used to evaluate any possible adverse event. For instance, if clinical trial centers have different guidelines for what constitutes moderate or severe redness on the arm following inoculation, it may be difficult to conclude how to characterize the severity of this reaction at the conclusion of the trial. Although such observations are still subject to some level of human interpretation, clinical trial specialists try to control this as much as possible by creating standardized tools.

They also have built a series of checks and balances into the case report forms, which can help identify erroneous entries—such as an unusually high blood pressure of a trial volunteer—and alert researchers to take a closer look. Additionally, the sponsors of a trial have monitors who compare the data on the source document with information on the case report forms to make sure the information is consistent.

Standardized case report forms become particularly important in large, Phase III trials where there are several thousand volunteers and hence drastically more data to analyze and compare. Since these large trials are also the final step of clinical evaluation prior to the candidate being considered for regulatory approval, it is essential that data regarding any adverse events or the efficacy of the candidate is recorded accurately and consistently since this information will influence regulatory considerations regarding licensure of the vaccine candidate for public use. ■