As a medical epidemiologist at the US Centers for Disease Control and Prevention (CDC) Umesh Parashar has spent the last 10 years of his career chasing an intestinal virus that, outside of medical circles, few people have ever heard of. Even so, rotavirus is a ubiquitous infection among infants and is the most common pathogen associated with the severe diarrheal disease known as acute gastroenteritis that is responsible for around 600,000 deaths and more than two million hospitalizations each year worldwide in children under five years of age.

The death toll in resource-poor countries and soaring medical costs in industrialized nations associated with such a pervasive infection spurred scientists into developing vaccines that could prevent the severe and all too often deadly dehydration caused by this disease, launching a 25 year quest that Parashar refers to as a “rollercoaster ride.” Despite early success, the rotavirus vaccine efforts faced a serious setback when the first licensed prod-

A fundamental biological process that was first discovered only eight years ago could revolutionize research and medicine, and may hold promise for HIV infection

By Andreas von Bubnoff

This year’s Nobel Prize for the discovery of RNA interference (RNAi) to Andrew Fire and Craig Mello is the preliminary end point of a rise to prominence that can only be described as meteoric. The award came just eight years after Fire and Mello found in the nematode worm *Caenorhabditis elegans* that pieces of double-stranded (ds) RNA are much more powerful than single-stranded RNA in specifically inhibiting expression of genes with the corresponding sequence (Nature 391, 806, 1998).

The dsRNA pieces Fire and Mello used were several hundred bases long, too long to specifically inhibit gene expression in mammalian cells. That’s because they would induce the interferon response, a non-specific general shutdown of gene expression. But only three years later, it became clear that very short dsRNA pieces—around 21 nucleotides, so-called short interfering RNAs (siRNAs)—can specifically inhibit genes in mammalian cells as well (Nature 411, 494, 2001).

It is now clear that these siRNAs inhibit gene expression through the same natural phenomenon that cells normally use to regulate their own genes. The cells do this by transcribing genes that encode micro RNAs (miRNAs), which are the functional equivalents of siRNAs. A ribonuclease protein called Dicer helps process these miRNAs into short dsRNAs that look just like siRNAs, and from there the cell treats both (siRNAs or miRNAs) the same, in that one strand is incorporated into an enzyme complex called the RNA-induced silencing complex (RISC; Figure 1). Once that strand binds a complementary target mRNA, the target mRNA is degraded or is not translated into protein. The complex acts catalytically, meaning it is recycled and can act again and again. That, combined with the exquisite specificity afforded by the nucleotide sequence matching, explains why RNAi has such potential, in research and possibly medicine too.

Gene knockout

For molecular biologists, RNAi has become a powerful and specific tool to study gene expression and function by making it much easier to knock out genes than ever before,

Vaccinologists battle an intestinal virus to prevent one of the leading causes of potentially deadly diarrheal disease in infants

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Cells can control expression of iAVI 23,76, 12 SEPTEMBER-OCTOBER 2006 J. Virol.

Soon they found a way to coax cells into expressing them constitutively, infecting (applications, including prevention and treatment of HIV. “HIV is an obvious target,” says Bryan Cullen of Duke University Medical Center in Durham, North Carolina. Cullen’s group was among the first to show that siRNAs can inhibit HIV replication in cultured human T cells, one of the main cell types that HIV infects (J. Virol. 76, 9225, 2002).

Initially, researchers transfected siRNAs transiently into cells, but soon they found a way to coax cells into expressing them constitutively. They infected cells with viruses engineered to insert genes for short hairpin RNAs (shRNA) into the host cell genome. The host cell processes them in a similar way to endogenous miRNAs to inhibit the expression of target genes.

These advances opened the door to a gene therapy approach by introducing cells that stably express shRNAs into HIV-infected patients. Several groups are planning to start Phase I clinical trials in the next two years.

Delivery obstacle

Almost immediately after the discovery that siRNAs can work as a therapeutic strategy, Judy Lieberman’s lab at Harvard Medical School is working on ways to deliver siRNAs directly to cells to treat or prevent HIV infection. One major obstacle, she says, as with all gene therapy approaches, is delivery.

“[siRNAs] don’t naturally get into cells,” Lieberman says. In a study three years ago she literally forced the siRNAs into the livers of mice. She used high volume injection into the bloodstream, temporarily damaging the cell membranes of liver cells so the siRNAs got in and protected the cells from hepatitis infection. The problem was that the volume was so large that the treatment also resulted in heart failure.

In more recent experiments, Lieberman has encapsulated siRNAs into liposomes to get mucosal surfaces to take them up, for example in the genital tract of mice. She has found that this approach can silence genes for more than a week, and has shown that siRNAs targeting herpes simplex virus type 2 (HSV-2) genes can protect mice from HIV-2 infection by silencing any viral genes that enter cells in a potential transmission event (Nature 439, 19, 2006). HSV-2 is the leading cofactor for HIV transmission in the world, increasing people’s susceptibility to HIV infection (see HIV prevention in a pill, LVVI Report 9, 4, 2005).

Prevention or treatment

Next Lieberman wants to use the approach to develop a microbicide women could use to prevent HIV transmission. “Because the silencing lasts for a while, you don’t have to remember to use it immediately before you have sex,” she says. It could also be cheap because it uses very small amounts of siRNA, according to Lieberman, one dose in humans could cost as little as US$8.

She is also developing a method that can direct siRNAs to HIV-infected cells inside the body. To this end she has made fusion proteins of protamine (a protein that binds and condenses the DNA in sperm) to bind the siRNA, and an antibody that recognizes proteins on target cells like the HIV Env protein. This approach can support HIV replication in cultured T cells. She says. In whole animals, an Env-specific antibody directed the fusion protein to tumor cells expressing Env in the flank of mice (Nat. Biotechnol. 23, 719, 2005). These experiments show that cell-specific delivery of siRNA is possible, but it will be a long way until clinical trials. Lieberman says. Depending on the antibody targets, the method could be used to prevent HIV infection in the first place or to treat infected patients.

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Figure 1. Gene control by RNA interference. Cells can control expression of their genes by interfering with the messenger RNA (mRNA) that is transcribed from any particular gene, thereby preventing that mRNA from being translated into proteins. The RNA interference (RNAi) machinery is triggered into action by small double-stranded RNA molecules with ragged ends. An enzyme called Dicer cleaves these short interfering RNAs (siRNAs) from longer double-stranded RNAs that are produced by self-copying genetic sequences (1) or viruses (2). Regulatory RNA sequences known as microRNA (miRNA) precursors (3) are also cleaved by Dicer into this short form. Researchers can also introduce artificial siRNAs into cells using liposomes (4). The siRNA or miRNA fragments separate into individual strands (bottom panel), which then combine with proteins to form the RNA-induced silencing complex (RISC). The RISC then captures the mRNA that complements the short RNA sequence. If the match is perfect, the captured mRNA is cleaved into small fragments (top row). Less than perfect matches cause a different outcome; for instance, the RISC may remain bound to the mRNA, blocking ribosomal translation (bottom row). The end result is the same—no protein is manufactured.
Still, some experts say that to treat a chronic disease like HIV, gene therapy is a better approach than delivering siRNAs directly, which only has a temporary effect.

“A constant supply of siRNAs is required to control a chronic virus infection,” says Ben Berkhout of the University of Amsterdam. “The best way to achieve that is with a gene-therapy approach in which the siRNAs are stably expressed.”

Berkhout and others are planning Phase 1 gene therapy trials. They will use an HIV-derived lentivirus to introduce HIV-suppressing shRNAs into the genome of CD4+ hematopoietic stem cells taken from HIV-infected individuals. CD4+ cells give rise to T cells and macrophages, two of the major cell types infected with HIV. These CD4+ cells will then be reintroduced into the patient’s blood. Berkhout says that the hope is that the protected stem cells will preferentially survive and reconstitute the patient’s immune system, as only the untreated, non-protected cells will be killed by HIV.

So far, animal studies suggest that the approach could be safe and efficient. In transgenic mice, siRNAs can be expressed without deleterious consequences for the host. What’s more, the lentivirus is derived from HIV itself, which does not seem to cause cancer in HIV-infected individuals. “There has never been a known case of a lentivirus causing cancer,” says Berkhout. However, he has also looked at about 130 lentivirus integration sites and found that it almost always integrates into introns, genomic regions that are inactive. “It’s relatively benign,” Berkhout says. The lentivirus vector, adding that he is now ready to go into patients since experiments in mice and monkeys have indicated that it is safe.

**Interference escape**

Still, even if gene therapy turns out to be safe, there are additional challenges that any RNAi approach needs to overcome. One major obstacle is the high mutation rate of HIV. Researchers have shown that siRNAs are required to escape from the virus. “If there is one point mutation, it doesn’t work anymore,” says Daniel Boden of the Aaron Diamond AIDS Research Center in New York. He found that in cultured T cells HIV can escape from siRNA targeting CCR5. “The reason this can happen is because the virus has a mutation in a viral protein,” Boden says.

Cullen agrees that an escape of the virus is not a question of if, but when. “Every possible mutant is there 1000 times every day,” he says. “This is because HIV is not a single species that varies greatly within an infected individual. "I don’t see this as something that can be done," Boden says.

Cullen says that the virus may make a mutation that is not likely to happen. “The reason we can’t do it now is because the virus is not likely to happen,” he says. “But we are far from RNAi as a therapeutic agent against HIV.”

**The reason that so many people are working on this approach is because we are optimistic that it can work. [But] we are far short of RNAi as a therapeutic agent against HIV.**

Kuan-Teh Jeang

Andrea von Bubnoff, PhD, is a freelance writer whose work has appeared in such publications as The Los Angeles Times, the Chicago Tribune, Nature, and Prevention.
The major immune response in rotavirus infection is against the VP7 (yellow) and VP4 (red) proteins on the outer surface of rotavirus. Researchers are using the human rotavirus variant of these proteins in a bone or seminal rotavirus background to construct the new vaccines. Rotavirus and Rotarix.

The virus targets the villi of the duodenal epithelium and directly infects the cells that form the lining between the inner cavity and tissues of the intestine. Rotavirus also encodes for a peptide (non-structural protein 4) that opens chloride channels on the surface of uninfected cells, allowing it to further wreak havoc in the gut. These two mechanisms of action trigger a range of symptoms, from mild intestinal discomfort to prolonged episodes of diarrhea and vomiting. That, together with the usual and severe dehydration that can result from rotavirus infection.

Oral fluid replacement is the easiest way to reverse these effects but, if necessary, fluids and electrolytes can be administered intravenously. Severe cases, however, often require hospitalization and providing treatment to the 600,000 children in the US that seek medical care for rotavirus infection costs an estimated $1 billion a year. Only between 20 and 60 children die annually from rotavirus-induced dehydration in the US. In developing countries where clean water is a risk, a rare commodity and prompt access to healthcare services is limited, failure to rehydrate rotavirus-infected infants and children results in a huge death toll, and around 1 in 200 children infected with rotavirus will die.

Even though rotavirus kills far more children in developing countries, the incidence is similar throughout the world. Alan Shul, a researcher at Vaxinnate who worked previously on vaccine development programs at Merck, points out that most prevalent rotavirus strain can vary widely, with several unusual strains occurring in developing countries.
Almost all children have been infected at least once by the time they reach five years of age, making a vaccine the only hope for control. Shortly after licensure in 1998 the Advisory Committee on Immunization Practices at the CDC recommended vaccination with Rotashield for all infants at the age of two months in the US, which turned up an unexpected number of cases of intussusception in infants that had received Rotashield. Intussusception is a potentially fatal bowel obstruction that happens when part of the small intestine folds over itself like a collapsing telescope. It occurs naturally in 1 of every 2000 infants and requires surgical treatment in approximately 10% of cases. If left untreated it can be fatal. There were enough hints of this rare but serious side effect in pre-licensure studies to warrant a warning in the packaging materials that accompanied the vaccine.

Close-up analysis of vaccine recipients showed an association between receipt of the vaccine and development of intussusception effective when tested in developing countries. The next generation of rotavirus vaccines took advantage of rotaviruses' segmented genome, which allows it to reassort during coinfection. These reassortant viruses can be selected to carry the VP4 and VP7 surface proteins of human rotavirus in a simian or cowpox vector, allowing the reassortant to stimulate antibody production without causing disease. Two of these reassortant vaccine candidates based on the bovine rotavirus were developed, one at the US National Institutes of Health (NIH) and the other at Children's Hospital of Philadelphia (CHOP). A third vaccine candidate, based on a rhesus macaque rotavirus, was also developed at NIH. This simian-based rotavirus strain, known as RV311, was a tetenalent strain carrying human VP7 from three different serotypes (G1, G2, and G4) and the G3 of the parent rhesus rotavirus. The vaccine was more effective at preventing 74% of any rotavirus-related intussusception cases, says Heaton. For his research he shared the $1 million Simons Foundation Prize for Innovation and Discovery.

Risk versus benefit

This ignited debate among scientists and bioethicists on the risk/benefit calculations that go into picking a vaccine. “We don’t really have a risk/benefit notion of safety in the US,” says Parashar. “The public notion of safety in the US,” says Paul Offit, “is that a vaccine is always safe. We have an ethicists’ concern that this vaccine may cause intussusception if given to older infants in the US, which secured the vaccine as an option for gastroenteritis. Shortly after two episodes it becomes unlikely that an infant will experience severe gastroenteritis. Efforts were then focused on developing a vaccine to mimic this effect,” says Parashar. The initial approaches to rotavirus vaccines followed the classic example of Edward Jenner’s smallpox strategy. Nearly all vertebrates are infected with rotaviruses and the species barrier is substantial enough that animal viruses are safe for testing in humans. This approach, using simian and bovine rotaviruses, seemed immunogenic in initial testing but protection against rotavirus was inconsistent in larger trials and the vaccine development process was effective when tested in developing countries.

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Enrolling teens in trials

Researchers consider the special circumstances of AIDS vaccine clinical trials among adolescents

By Kristen Jill Kresse

AIDS vaccine trials have the potential to offer a preventive strategy for adolescents who are at an increased risk of contracting HIV. However, enrolling such participants into clinical trials has been challenging due to concerns about safety, efficacy, and adherence. Here are some considerations for enrolling adolescents in AIDS vaccine trials:

1. **Safety and Efficacy:** Adolescents are a vulnerable population, and safety is a primary concern. Research has shown that the vaccine candidates are generally well-tolerated, with minimal side effects. Adolescents are expected to benefit from the vaccine's protection against HIV infection.

2. **Protocol Flexibility:** Clinical trials for adolescents may require modifications to the standard protocols. Adaptations may include dosage adjustments, additional monitoring, and tailored follow-up care to ensure participant safety and adherence.

3. **Participant Recruitment:** Adolescents may require special recruitment strategies, such as school-based programs or community outreach, to ensure adequate representation in the trials.

4. **Adherence and Engagement:** Adolescents may have unique challenges related to medication adherence and engagement in clinical trials. Strategies to enhance adherence, such as ongoing support and education, may be necessary.

5. **Ethical Considerations:** The ethical implications of enrolling adolescents in trials are complex. Researchers must ensure that adolescents are fully informed about the risks and benefits and provide informed consent.

6. **Collaboration:** Collaboration with healthcare providers, schools, and community organizations can help in the recruitment and support of adolescents in clinical trials.

7. **Supportive Environment:** Creating a supportive environment within the clinical trial setting can improve participant satisfaction and retention.

By addressing these considerations, researchers can better enroll and retain adolescents in AIDS vaccine clinical trials, thereby expanding the potential benefits of these trials to a vulnerable population.
Some people are more conservative and say not to test a vaccine in adolescents until you know it’s effective. But this doesn’t take into account the urgency,” he adds. The guidance document issued by the FDA in 2005 (Guidance for Industry—Prevention of HIV Infection in Young People) recommends that trial sponsors submit their plans to the agency for review and comment to ensure that this data will be applicable to adolescent approval within the US.

Other regulatory agencies are also involved, including in South Africa where researchers involved in adolescent trials due to the especially high prevalence of HIV infection in young people there. The South African AIDS Vaccine Initiative (SAAVI) is currently collaborating with the HTVN to prepare an adolescent trial protocol. The WHO and the AAPP also sponsored a meeting earlier this year in Gaborone, Botswana, to address some of the challenges related to including adolescent volunteers in AIDS vaccine trials. Flores is in the process of preparing a document on adolescent trials for the NIH which he hopes will inspire discussion among researchers on the critical issues.

And now Mercik is considering testing a new HPV vaccine in young people in South Africa as part of a Phase IIb trial that will start there soon in cooperation with the Western Cape government and the NHV and the HTVN.” The plans are very much in the discussion phase,” says Robertson. “We’ve discussed expanding the planned trial and amending the age cutoff to include ado-

...when you look at the epidemic in Africa, adolescents are the highest incidence group. And if you’re going to make headway in dealing with the epidemic you need to involve them.

Michael Robertson

Elizabeth Glaser Pediatric AIDS Foundation. The Phase III efficacy trials for Merck’s HPV vaccine involved thousands of adolescent and young adult volunteers (age 12-18) and pre-adolescent girls and young women with proven efficacy and well-tolerated safety and immunogenicity data for AIDS vaccine candidates should be collected in adults before adolescent trials begin. Flores favors that all HIV vaccine candidates be a single vaccine candidate into efficacy trials. Phase IIb or III, they should also be preparing for adoles-

Jorge Flores
The need to protect this vulnerable group from stigma and other social harms is still a substantial concern for researchers who are actively discussing the possibility of such trials in the near future.

Introducing the new VAX anthology

Deciphering AIDS Vaccines features articles originally published in VAX and IAVI Report, the only comprehensive publications on the AIDS vaccine field.

This anthology is intended to serve as a general introduction for non-scientists to AIDS vaccines, to educate and inform, to be used by trial sites, volunteers, educators, libraries and anyone else as a vaccine literacy tool.

The articles have been carefully selected to include information regarding all aspects of the AIDS vaccine field and to help the reader understand more about the science of AIDS vaccines and the clinical trials process, as well as alternate HIV prevention strategies and other vaccines that may provide lessons for the AIDS vaccine field. For more information, go to www.iavireport.org.

If you would like to receive one or more copies of the anthology, free of charge, please send your request to iavireport@iavi.org.

Nasal administration of AIDS vaccine candidate

A Phase I study of an HIV protein-based vaccine was initiated in the UK in September by researchers from St. George’s Vaccine Institute and the University of London in collaboration with Novartis Vaccines, Richmond Pharmacology Ltd., and the Commission of the European Union. The vaccine candidate is comprised of HIV gp140 protein with the V2 loop deleted, and is being delivered nasally along with LTtk, a heat-labile enterotoxin from Escherichia coli that has been shown to enhance immune responses at mucosal surfaces.

The trial will enroll 30 volunteers who will be randomized to receive either 5 nasal immunizations of the vaccine candidate and adjuvant, followed by 2 additional immunizations with the same protein vaccine administered intramuscularly, or placebo. The booster immunizations will be administered along with a liquid adjuvant known as M59.

All volunteers will be followed for 52 weeks during which time researchers will evaluate the safety of this dosing regimen and collect preliminary information on the immunogenicity of both the vaccine candidate and route of administration. Nasal administration generally induces stronger mucosal immune responses than intramuscular injection, which are widely considered to be a necessary response for a vaccine that could prevent sexual transmission of HIV. In the future, investigators will be measuring the serum IgG neutralizing antibody responses to gp120 at several intervals as well as the IgA responses in both nasal and vaginal tissues to determine the frequency and type of immune responses induced at these surfaces.

IAVI opens southern Africa regional office

IAVI recently launched a new program in Johannesburg, South Africa, to support expanding AIDS vaccine research, development, and advocacy efforts for southern Africa. The global public-private partnership already operates several regional offices worldwide in Nairobi, Kenya; New Delhi, India; Amsterdam, the Netherlands; and New York City where the global headquarters is located. The Johannesburg offices will provide an opportunity for IAVI to work closely with existing partners and programs in southern Africa, including the South African AIDS Vaccine Initiative (SAAVI), the Medical Research Council (MRC), the Desmond Tutu HIV Foundation in Cape Town, the Medical University of South Africa, the Zambian-HIV Research Project, the University of Limpopo, and the Perinatal HIV Research Unit at the University of Witwatersrand.

Seth Berkley, Chief Executive Officer of IAVI, said that the new regional office will serve as a focal point for expanding AIDS vaccine programs and activities in southern Africa and will lead the organization’s efforts to build capacity to conduct clinical trials in the region to the highest scientific and ethical standards. In an editorial published in South Africa’s Business Day, Berkley also said the southern Africa program will take advantage of the region’s “growing biomedical capabilities, strong regulatory systems and manufacturing base.”

South Africa is collaborating with India and Brazil, two other countries severely affected by HIV/AIDS, to harness the power of their growing biotechnology sectors for the discovery of new vaccines.

South Africa is already hosting several HIV prevention studies, including a large Phase III microbicide trial and multiple AIDS vaccine trials. IAVI initiated a Phase II AIDS vaccine trial last year in South Africa with several partner organizations to evaluate the safety and immunogenicity of an adeno-associated virus vaccine candidate known as tGAA09 that encodes clade C HIV genes, which is the primary subtype of the virus circulating in the region (see http://www.iavireport.org/trialsdb/ for more information). The Vaccine Research Center at the US National Institutes of Health, in collaboration with the HIV Vaccine Trials Network (HVTN), is also conducting a Phase II trial in South Africa with their DNA and adenovirus serotype-5 vaccine candidates Merck and the HVTN will begin a Phase Ib AIDS vaccine trial there later this year with their lead adenovirus-based AIDS vaccine candidate.

For more information, go to www.iavireport.org.

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Phase I AIDS vaccine trial in infants begins in Uganda

Researchers at Makerere University in Kampala, Uganda and Johns Hopkins University in the US recently initiated the first Phase I trial of an AIDS vaccine aimed at preventing the transmission of HIV from mother-to-child during breastfeeding. According to the World Health Organization, breastfeeding remains one of the major routes of HIV transmission to infants in developing countries; it is estimated that as many as a half of all HIV-infected infants acquire the virus not during delivery but through HIV-contaminated breast milk. Alternatives to breastfeeding, such as liquid formula or powdered milk, could easily prevent these infections, but in many settings these options are either prohibitively expensive or impractical because they require access to clean water. Also, HIV-infected women who do not breastfeed their babies are subjected to stigma in many cultures where it is common practice.

Another option for preventing HIV transmission from breastfeeding is administering antiretrovirals (ARVs) to the mother. Several studies have shown that treating HIV-infected women with ARVs throughout late pregnancy, labor, and during the period they are breastfeeding is a highly effective way to prevent HIV transmission to infants (see New strides in protecting infants from HIV, IAVI Report 9, 2, 2005). However, not all women have access to these drugs so a vaccine that could effectively protect babies during the period they are breast fed would be a major advance. To date only one vaccine trial has been conducted in infants.

This new randomized, placebo-controlled trial is being conducted through the HIV Prevention Trials Network (HPTN) and will enroll 50 infants born to HIV-infected mothers at Mulago Hospital in Kampala to evaluate the safety of a live-attenuated, recombinant canarypox virus vaccine candidate encoding HIV Env proteins from clades B and E. Forty of the infants will receive four doses of the vaccine candidate over three months and will be followed by researchers for two and a half years. The vaccine candidate, known as ALVAC-HIV, was developed by Sanofi Pasteur and was previously evaluated in a safety trial in Uganda involving adult volunteers and in another study involving infants in the US. No serious safety issues were reported in either of these completed trials.

ALVAC vCP1521 is also now being tested in a Phase III efficacy trial in Thailand to see if it can protect adults against HIV infection. The Thai trial recently completed enrolling volunteers but final efficacy data will not be available for a few years. For more information on these and other ongoing AIDS vaccine trials, visit the IAVI Report vaccine trials database at www.iavireport.org/trialsdb.

New global vaccine conference to accompany annual Grand Challenges for Global Health meeting

Grant recipients through the Grand Challenges in Global Health Initiative, a US$436.6 million program funded by the Bill & Melinda Gates Foundation to increase research on diseases that primarily affect developing countries, recently convened their annual meeting in Washington, DC to highlight progress on the 48 ongoing projects. Grantees include scientists from 33 countries who are working to tackle either scientific or technological challenges that could enhance global public health (see www.gcgh.org for more information). Plans for this innovative funding mechanism were initially announced at the World Economic Forum in 2003 and the first round of grants were awarded last year in collaboration with the US National Institutes of Health (NIH).

The Gates Foundation also recently awarded the Keystone Symposia on Molecular and Cellular Biology, a US non-profit organization that hosts many high-profile scientific conferences, a three-year grant of $2.6 million to further expand their offerings of meetings that focus on global health. Keystone already sponsors several conferences concerning infectious diseases, including the annual symposia on HIV Pathogenesis and HIV Vaccines that are held in conjunction each spring (see www.keystonesymposia.org). IAVI Report Travel Awards will be provided to scientists from developing countries to attend this meeting in 2007.

With the new funding from the Gates Foundation, Keystone will sponsor an additional meeting on vaccines, called “Challenges of Global Vaccine Development,” which will be held either immediately before or after the next Grand Challenges in Global Health Meeting. The first annual conference will take place from October 8-13, 2007 in Cape Town, South Africa and will involve 300 scientists, many of whom are investigators on one of the Grand Challenges projects. The Keystone Symposia will also use part of this grant to provide scholarships and travel awards to researchers from developing countries, and specifically to graduate students and post-doctoral fellows who are completing their studies in Africa.