nature medicine

Roadblocks in HIV research: five questions

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What are the most important questions that the HIV field needs to answer to make progress? *Nature Medicine* asked this question to a group of HIV researchers to identify some of the key roadblocks in HIV research.

We asked a group of HIV experts to tell us what they believe are the most pressing questions for the field. Twenty-five experts told us what they thought and their answers revealed some of the most important scientific questions that need to be answered, including elucidating how to elicit protective antibody responses against HIV, solving how to flush out HIV from reservoirs of infection with the goal of eradicating the virus, and establishing why some HIV-1–infected people and natural nonhuman primate hosts for SIV infection do not develop disease (**Box 1**). But their responses also revealed other roadblocks to progress, such as a need to develop better nonhuman primate models for vaccine research and to better filter the vaccine and microbicide pipeline, a need to find ways to encourage scientists from related disciplines to engage with and bring new perspectives to the HIV field and a need for more flexible approaches to how HIV research is funded. From all of the feedback we received, we identified five nonscientific questions, which we then posed to a broader pool of researchers, soliciting their ideas about how to overcome these obstacles. Their responses were diverse, but we try below to present a synthesis of their views.

HOW SHOULD WE DECIDE WHAT TO TRANSLATE?

To say that efficacy trials of HIV vaccines and microbicides have, to date, been disappointing is something of an understatement. Several microbicides have been tested in phase 3 trials. At best, one of the candidates, the polyanion PRO-2000, has been shown to reduce HIV-1 acquisition by 30%. Unfortunately, this result was not statistically significant. At worst, some microbicides have increased HIV-1 infection in recipients. Although microbicide candidates further down the pipeline—such as those incorporating reverse transcriptase inhibitors—seem more promising, resources are being wasted through the redundancy of efforts between rival organizations[1].

> "When we have something really promising in the vaccine arena, I don't think we are going to need some big complex analysis to figure it out. It will be obvious." —Ronald Desrosiers, New England Primate Research Center

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In the vaccine arena, the field had shifted away from vaccines designed to induce a sterilizing antibody response toward vaccines that induce a protective T cell response and might either protect from infection or decrease viral load in infected people. Dozens of vaccine candidates entered the clinical trials pipeline. The most promising of them was an adenovirus type 5–based candidate developed by Merck. But, in 2007, a phase 2 clinical trial of the vaccine was halted; it failed to protect from infection, and, more worryingly, it seemingly increased susceptibility to infection in individuals with preexisting immune responses to the adenovirus vector[2].

> "The best candidates are always in the eye of the beholder." —Michael Betts, University of Pennsylvania

It now seems likely that an effective vaccine for HIV will not be found within the next 10–15 years, and it's clear that a back-to-basics approach is needed to learn more about the biology of HIV infection. It's crucial to place the failures in context and to remember that developing vaccines for some other viruses, such as polio virus, took decades. But given the current situation—the many vaccine candidates that differ only slightly from each other, the lack of understanding about how to generate a protective antibody response to HIV, the need to understand what else correlates with protection from infection and the competing organizations keen to show that their microbicide candidate is the best—it seems that, when thinking about vaccines and microbicides, it is more appropriate to ask 'how should we decide what to translate?' than 'what are the obstacles to translation?'

The answers that our respondents gave to this question were quite varied. A few scientists felt that product testing for vaccines should be halted until we better understand the biology of virus infection and the biological correlates of virus control. But most vaccine researchers felt that continuing to test a range of strategies in early-phase human trials is essential, even without fully understanding the correlates of protection. They felt that even failures in the clinic can provide important information. The translation of approaches from the bench to the clinic should, however, be based either on solid data that the concept works in a stringent nonhuman primate model (as discussed in more detail below) or on good evidence that the approach is novel, mechanistically plausible and considerably different from other candidates. Overeagerness to translate should not eclipse the basic research needed to address fundamental scientific questions (**Box 1**).

"Solve the science, and the translation will look after itself." —John Moore, Cornell University

Phase 1 trials can provide valuable information if they are designed to incorporate scientific end points, such as an immunological readout, instead of just evaluating safety. Because it's not yet certain which measurements will ultimately correlate with protection, a systems biology approach should be taken to make sure that all possible information is collected from any trial-derived samples. Crucially, a tough filter should be imposed before deciding to move candidates to larger-scale efficacy trials to avoid testing multiple products that differ only incrementally from one other.

Who should decide what goes forward? On the one hand, it is essential to ensure that decision makers have the expertise needed to evaluate the weight of scientific evidence supporting each candidate. On the other hand, it is difficult to avoid bias when some of these people may have their own candidates in the pipeline. Is it possible to put together an expert review panel that is truly unbiased? It may be difficult, but great effort is needed to eliminate redundancy and duplication of similar concepts. The Global HIV Vaccine Enterprise, created in 2004 in response to a call for a coordinated international effort to develop a vaccine[3], has made strides in facilitating communication and collaboration between vaccine researchers. More could be done to eliminate duplication in other areas of HIV research, such as microbicide research.

ARE MACAQUE MODELS HELPFUL?

Macaques infected with simian immunodeficiency virus (SIV) recapitulate many of the immunological, virological and pathological mechanisms of HIV infection in humans. To date, they are the best animal model available to study AIDS pathogenesis and to investigate protection strategies. But how useful is this model, considering that adenovirus type 5–based vaccines showed protection in macaques, but Merck's candidate failed in humans?

The overwhelming majority of the scientists we polled felt that macaque models are fundamental to the future of HIV research and that more emphasis should be placed on using them to inform the selection of vaccine and microbicide candidates, something that has been done in a haphazard way (or not at all) over the past few years. But some macaque models are better than others. Unfortunately, a 'wimpy' model (as one expert put it), using the chimeric simian-human immunodeficiency virus SHIV89.6P, was used to provide most of the evidence that T cell–based vaccines could reduce viral load after infection. This was not reproduced in humans during the Merck trial, but neither was it reproduced using the more stringent models of SIV infection. Thus, with the benefit of hindsight, it could be said that the SIV model predicted the lack of efficacy seen in that trial. It is impossible to validate the macaque model as a tool to predict vaccine efficacy in humans until a successful vaccine is shown to protect humans. But for evaluating T cell vaccines, it seems that the SIV model with a heterologous virus challenge is a good bet[4].

Should macaques be the gatekeepers for deciding which vaccine candidates to take to clinical trials? Some of our respondents believed so: a strategy that works in macaques may not work in humans, but why perform expensive human trials of therapeutics or vaccines that have shown no efficacy in macaques? Other experts (including some who have devoted their careers to studies in nonhuman primates) felt that these models need to be used to provide evidence of the plausibility of new concepts and new strategies for protection—they should complement human trials but should not be used as absolute gatekeepers for specific products. There are several fundamental differences between macaques and humans; for example, macaques have many more major histocompatibility molecules than humans and generally have higher viral loads after SIV infection than humans infected with HIV-1. Such differences may mean that a particular product that works in monkeys will not work in humans. We already know that rhesus macaques make very strong protective anti-Gag $CD8^+$ T cell responses, whereas humans make much more moderate responses to HIV Gag. But, as the overall biology of SIV infection in macaques is so similar to HIV infection in humans, it is very likely that concepts and mechanisms of protection in macaques will be translatable to humans. Once a clear mechanism is defined in macaque models, it will be easier to look for that 'signal' in phase 1 trials of vaccine candidates.

A priority should be to standardize some of these monkey models so that investigators can more reliably compare their approaches. There is an enormous number of variables, such as the various routes of infection, the use of low-dose versus high-dose challenge models, the multiple macaque species and the various virus strains used for the challenge. Macaques are expensive and scarce, and there are many ethical concerns about their use. It would therefore be advisable to reach consensus about which models are the most meaningful.

More work is also needed to generate additional viruses that can be used in macaque models. There are only a few available SIV strains, and these cannot be used to assess neutralizing antibodies. The currently available chimeric SHIV viruses do not recapitulate HIV pathogenesis very well and are too easy to protect against. We need more SIV strains and superior chimeric viruses that mimic the biology of HIV transmission in humans and better recapitulate HIV pathogenesis.

For pathogenesis studies, natural nonhuman primate hosts that do not develop AIDS after SIV infection, such as sooty mangabeys and African green monkeys, are very useful models. Comparing the biology of infection in natural primate hosts versus macaques will allow us to tease apart the factors that drive or protect from pathogenesis. Natural hosts can even offer clues for vaccine design[5].

"There is only one way to validate the macaque animal model for vaccine effectiveness, and that is to do human trials and see if the animal model predicts the result." —John Mascola, US National Institutes of Health

HOW CAN WE ENCOURAGE INTERDISCIPLINARY RESEARCH?

The HIV community is highly motivated and engaged, but some scientists felt it is also somewhat insular. Many of our respondents felt that the field needs to harness the expertise of scientists from other disciplines, such as basic immunology, autoimmunity, cancer, biochemistry and engineering. The Collaboration for AIDS Vaccine Discovery (CAVD; an initiative of the Gates Foundation and of the Global HIV Vaccine Enterprise) and the International AIDS Vaccine Initiative are good examples of initiatives that are bringing together small groups of scientists with differing areas of expertise to solve problems relating to vaccine development. But more could be done to promote cross-talk across different fields to help solve some of the basic scientific questions that relate to AIDS pathogenesis and protection from HIV infection.

A frequent comment from our respondents was that the most fruitful collaborations will arise naturally and gradually and will not be centrally directed. In other words, recruiting an engineer or a chemist just because a call for applications stipulates that such a person is needed will not be a good way forward. So what can be done to promote cross-fertilization

BOX 1 SCIENTIFIC ROADBLOCKS

How can we make HAART more accessible and sustainable?

Highly active antiretroviral therapy (HAART) has transformed an invariably fatal illness into one that can be managed with one pill once a day. These drugs can also prevent mother-to-child transmission of HIV, and several ongoing trials are exploring whether antiretrovirals can be used for preexposure prophylaxis[10]. HAART has enabled HIV-1–infected individuals to hope for a normal lifespan, but there are still several key roadblocks to be addressed. How can we make more affordable HAART regimens so that all infected individuals—particularly those in developing countries—have access to it? How can we identify and treat everyone who is infected to reduce transmission? (This concern applies equally to developed and developing countries; in the UK, up to one third of infected individuals are undiagnosed.) What are the toxicities and risks associated with long-term use of antiretrovirals? How can we develop drug regimens that avoid these toxicities?

Is eradication feasible?

Current drugs used in HAART regimens block various steps of virus replication. But even the most effective drug regimens succeed only in suppressing the virus, not clearing the infection. This is because the virus maintains a latent infection in certain cells, and there may be anatomical reservoirs of virus persisting because of inefficient penetration of drugs to these tissues. The cumulative toxicity of decades of treatment with HAART remains to be fully understood; a lifetime of treatment is expensive and difficult to maintain in developing countries, and the specter of drug resistance is ever present, despite the availability of a broad drug armamentarium. Key research priorities are identifying the nature of the anatomical and cellular reservoirs and establishing strategies to flush the virus out of these sites, such that HIV-1 infection need not equate to a lifetime on medication.

How do we elicit protective antibodies to HIV?

We know that broadly neutralizing antibodies can protect macaques from infection. Unfortunately, we do not know how to elicit these antibodies by immunization. Many HIV envelope constructs possess the conserved epitopes to which rare broadly neutralizing antibodies bind, but they do not readily induce these antibodies after immunization. Elucidating how to generate broadly neutralizing antibodies by immunization remains a major goal for vaccine research, as does understanding how to generate long-lasting protective antibodies at mucosal surfaces. An underinvestigated area is the protective role of binding, non-neutralizing antibodies. Are broadly neutralizing antibodies an absolute necessity? Are protective antibodies necessarily 'neutralizing antibodies' as defined by *in vitro* neutralization assays, or could they be antibodies that impede the movement of virus across mucosal barriers?

What are the correlates of protection from HIV infection and transmission?

Apart from broadly neutralizing antibodies, we understand relatively little about the immune responses that will be required for protection from infection. There is considerable evidence that $CD8^+$ T cells contribute to controlling HIV replication, but we need to understand how to generate robust antivirus $CD8^+$ T cell responses at mucosal sites, with the breadth to cope with the diversity of HIV. The basic biology of humoral and cellular immune responses at various mucosal sites needs to be better understood in humans. Nonhuman primates may be indispensible for this effort. Other key research priorities include the following questions: what is the role of innate immune responses in protecting from HIV infection and shaping the adaptive response to HIV? How can we counteract deleterious innate responses and capitalize on protective responses? Does innate 'memory' exist in humans, and, if so, can a vaccine induce memory responses in this fast-acting innate compartment? What are the key features that determine whether HIV virions successfully transmit across a mucosal surface? Are individuals that are exposed and uninfected protected from HIV-1 infection by genetic traits or by immune mechanisms?

How does HIV cause AIDS?

We still do not fully understand the mechanisms that contribute to the progressive decline of $CD4^+$ T cells in HIV-1–infected individuals. Recently, the focus has shifted from understanding how the virus directly kills $CD4^+$ T cells to understanding the role of the aberrant state of immune activation that accompanies infection. There are several key questions in this area. What are the respective roles of the virus, immune activation and a lack of cellular regeneration in contributing to disease pathogenesis? What is the role of the virus versus other microbial products in contributing to immune activation? Why don't natural African nonhuman primate hosts develop disease after infection, despite high viral loads? What is the basis for resistance to disease progression in some HIV-1–infected individuals?

between different fields and enable scientists from other disciplines to form productive collaborations with HIV researchers?

One option is to create funding opportunities specifically directed at researchers from outside the HIV field. The Ragon Institute in the US, established in February this year with $100 million from the Ragon Foundation, is doing just this. The institute is soliciting proposals from Massachusetts Institute of Technology-, Massachusetts General Hospital- and Harvard-based scientists who have not previously worked on HIV but could apply their expertise to help understand the mechanisms underlying the immune responses to and the biology of virus infection. Crucially, they must collaborate with an HIV researcher within the Ragon Institute, who would provide guidance and advice as the project evolves.

Others felt that more can be done to create interdisciplinary research environments. Traditional departmental structures in academia tend to group together individuals with similar expertise. Interdisciplinary collaborations are more likely to arise if scientists have more exposure to researchers with other backgrounds. Similarly, departments housing both clinical and basic research scientists are more likely to facilitate successful translational research.

Our respondents also felt that it is essential to increase the representation of scientists from developing countries, particularly at the top levels

"If we want to look forward to the time when the next generation of scientists is carrying the torch, we should be focusing more effort on training scientific leaders in developing countries." —Julie Overbaugh, Fred Hutchinson Cancer Center

of science. These voices will be crucial to ensuring diversity of thought and ensuring that those living and working in affected areas have the opportunity to help define the intellectual priorities for the field. This will require a long-term investment in building up infrastructure, training and career opportunities within developing countries. It is not sufficient to increase the number of opportunities for training these scientists in foreign labs; it will also be crucial to enable them to apply their skills and develop their careers in their countries of origin. Integration of these scientists into projects where funding is also provided for the development of infrastructure in their countries (for example, clinical trials funded by the European and Developing Countries Clinical Trials Partnership) could be one mechanism.

HOW CAN ACADEMIA AND JOURNALS SUPPORT MULTI-INVESTIGATOR COLLABORATIONS?

There are several major questions about HIV immunology and pathogenesis that can best be answered by teams of collaborative researchers. A good example is the analysis of affected populations. For example, investigating the factors that determine why certain groups of HIV–infected people progress to AIDS whereas others do not requires the creation of a large enough cohort of individuals to obtain meaningful results. Separate small groups of researchers investigating various aspects of the immune response in their own small cohorts are unlikely to be as successful as they would be if they combined their efforts and addressed each question in an integrated way. But this often creates a problem—how do those investigators ensure that they receive appropriate credit for their contributions so that they can secure grant money or obtain tenure? This problem applies to any area of translational research where teams of basic scientists and clinical researchers work together. The current focus on the first and last author may be impeding translational research.

"There is no doubt that many important studies now depend on more than just two people, but it remains the case that there are only two really important positions on a paper." —David Goldstein, Duke University

Our respondents felt that journals should allow as many joint first or last authors as the authors feel appropriate and should adopt a consistent policy for the order in which these joint names appear (for example, in alphabetical order). For large collaborative efforts, it should be possible to attribute the work to a consortium without designating a first or a senior author. And, crucially, academic departments should not focus simply on the number of first- or last-author publications to make decisions about promotion or tenure. Instead, evaluation committees should take the time to thoughtfully consider the value of each contribution, regardless of whether the research was collaborative or independent.

ARE CURRENT FUNDING MECHANISMS ADEQUATE?

There is plenty of money for HIV research, both in Europe and in the US. In the US, a large proportion of the National Institute of Allergy and Infectious Diseases budget is designated for HIV research. Large amounts of funding are also available from organizations such as the Bill and Melinda Gates Foundation. But many of our respondents in the US voiced concerns about the way the funding is distributed. The most common view of those involved with HIV vaccine research was that funding is skewed too heavily toward large consortia. Many people noted that it has been far too difficult to generate sustained and adequate funding for investigator-initiated projects. They felt that this has contributed to the current lack of innovation in the field. Breakthroughs often happen serendipitously and are not planned[6].

"The barriers are not a lack of questions, nor a lack of measurements, nor a lack of an engaged community willing to participate in higher-risk studies." —Steven Deeks, University of California–San Francisco

The creation of large consortia such as the Center for HIV-AIDS Vaccine Immunology (CHAVI; funded by the US National Institutes of Health (NIH)) was based on the recognition of the enormity of the challenge to develop an AIDS vaccine and on the idea that an international collaborative effort might decrease duplication of effort, promote information exchange and allow standardization of assays and a better comparison of different vaccine candidates[7]—a sound rationale, but one that has also apportioned huge sums of money to the hands of few.

There is an essential role for collaborative research in the HIV field, and CHAVI has already made some important contributions to determining the characteristics of transmitted viruses[8] and defining the role of the earliest immune responses to the virus[9]. As mentioned above, initiatives such as CAVD are also enabling more collaborative research. But key breakthroughs are likely to come from a greater diversity of thought. It's also clear that more innovation is needed, as well as a longer-term view of how long it will take to make progress. So is it time to explore additional funding mechanisms? Several of our respondents thought so and proposed the following ideas.

Some scientists suggested creating opportunities for longer-term funding for investigators with a proven track record—this would mean a commitment to funding an individual, or a small self-assembling group of researchers, for a sustained period of time, giving them the flexibility and freedom to pursue innovative, 'risky' science. In other words, funding 'people' and not 'projects'. Most of the current funding for investigator-initiated research is project based and relatively short term. Investigators have to spend much of their time writing grants, and then rewriting them, with inevitable delays before funding is secured and with huge pressures to obtain short-term results to ensure that funding is renewed. This process discourages innovation. In the US, the American Recovery and Reinvestment Act of 2009 has provided some temporary relief for independent investigators, but our respondents felt that this has only deferred the problem of a lack of adequate and sustained funding for investigator-initiated research.

Some scientists also felt that better and more sustained funding mechanisms are needed to maintain long-term cohort studies and other collaborative investigations; the systems in place are not ideally suited to doing this, as any gap in funding can shut down the cohort.

Many people noted the need to fund high-risk and creative, investigator-initiated projects. Steps have already been made in this direction: the Highly Innovative Tactics to Interrupt Transmission of HIV (HIT-IT) RO1 mechanism from the NIH encourages "innovative, risky but rational approaches that could provide long-term protection from acquiring HIV infection" and "out-of-the-box" approaches. The program is also open to researchers who do not have a track record in the area of HIV prevention. But the total allocation for this program—$4.5 million—seems a small amount compared what is being spent on the large consortia. The Gates Explorations mechanism will also fund high-risk innovative ideas, although the initial grant of $100,000 million is also small.

Finally, many scientists felt more investment in young investigators is needed. Talented young scientists may be discouraged from pursuing a career in the HIV field for several reasons, including a perception that the problem is too difficult and the field too competitive. A separate award process should be created for early-career investigators who are in the first five years of a faculty position, so that they do not have to compete with more senior, established investigators who have greater expertise in writing grants. Additional mechanisms to draw in young investigators to the field might include prestigious postdoctoral fellowship programs, where talented young scientists could obtain their own funding to cover their salary and some research money so that they could join an HIV lab of their choice.

CONCLUSIONS

A key roadblock to translational research in the HIV field is that there is insufficient understanding of the basic mechanisms of several areas of HIV pathogenesis, from elucidating the nature of the cellular and anatomical reservoirs of virus infection to understanding the earliest events in the establishment of HIV and SIV infection. Basic research is yielding strong glimmers of hope, as articles elsewhere in this issue show. Nonhuman primate models will be crucial for some of these investigations, but these models have limitations and vary considerably. It will be important to better understand the limitations of the various models and to reach some consensus about which models are most meaningful, particularly for vaccine research.

Solving the challenges that HIV presents will require the right balance between enabling researchers to work collaboratively and maintaining diversity of thought. The NIH has been bold in its support of collaborative research in its funding of CHAVI, but perhaps the balance of funding has been weighted too far in the direction of very large consortia. Some of our respondents felt that attention should also be given to enabling smaller, self-assembling groups to work together to address basic questions relating to HIV pathogenesis and virus control, to solve the problem of how to enable innovative research from independent investigators, to increase the participation of scientists from developing countries and to safeguard the future of the field by giving sufficient support to younger investigators.

ACKNOWLEDGEMENTS

We thank the following individuals for sharing their views with us: M. Altfeld, D. Barouch, B. Berkhout, M. Betts, J. Brenchley, M. Carrington, S. Deeks, R. Desrosiers, D. Douek, M. Feinberg, G. Franchini, D. Goldstein, W. Greene, A. Haase, B. Hahn, B. Haynes, D. Kabat, M. Lederman, M. Malim, M. Martin, J. Mascola, J. McElrath, C. Miller, L. Mofenson, D. Montefiori, J. Moore, D. Mosier, G. Nabel, D. Nixon, J. Overbaugh, G. Pantaleo, L. Picker, E. Poeschla, D. Richman, M. Robbiani, H. Robinson, S. Rowland-Jones, Q. Sattentau, O. Schwartz, R. Seder, R.-P. Sekaly, R. Siliciano, G. Silvestri, M. Stevenson, B. Walker, M. Wainberg and D. Weiner.

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