

Spurring Innovation for the development of HIV/AIDS technologies

COMMISSIONED BY:

aids2031 Science and Technology Working Group

AUTHORED BY:

INTERNATIONAL AIDS VACCINE INITIATIVE

Disclaimer: The views expressed in this paper are those of the author(s) and do not necessarily reflect the official policy, position, or opinions of the wider aids2031 initiative or partner organizations

Spurring Innovation for the Development of HIV/AIDS Technologies

**International AIDS Vaccine Initiative
Submitted to the *aids2031* Science/Technology Working Group
November 2008**

Executive Summary

Given the long-term nature of the HIV/AIDS challenge, ensuring sufficient resources to promote research and development (R&D) of new HIV technologies will remain an urgent global health priority over the next generation. Despite significant successes over the past decades, the tools at our disposal are simply not enough. But as HIV/AIDS primarily affects people in low- and middle-income countries, private industry may lack financial incentives to make long-term investments in needed research and development of new HIV technologies, especially for HIV prevention. In addition to ensuring a high overall level of research attention to HIV/AIDS, funding streams and related policies must be carefully crafted to promote scientific innovation, the need for which is especially apparent in the AIDS vaccine field.

Several funding initiatives, including some with specific relevance to HIV/AIDS, have been established in recent years to encourage greater scientific innovation. Similarly, new institutional arrangements have been established to better organize/coordinate the conduct of R&D. As these initiatives are all relatively new, it is too early to ascertain their effectiveness in promoting innovation in HIV-related research. It will be important to monitor the evolution of these innovation-promoting mechanisms and to adjust them, as necessary, to maximize their success.

A number of other strategies have also either been tried or proposed to spur scientific innovation on HIV/AIDS and other global health issues. One especially intriguing approach, which has encouraged innovation in other scientific fields, is the establishment of prestigious, well-financed prizes for solutions to scientific challenges, or for the development of specific new health technologies. Although not a perfect solution, it may be an appropriate time to pursue this avenue.

Finally, funding is required to support innovation – and it must be flexible, sustainable, as well as sufficient in volume. Opportunities to diversify and grow the current funding base should be explored, including the possible expansion of existing mechanisms already providing HIV/AIDS treatments and other services. Of particular importance is the ability to marshal global funding to ensure that innovation can be supported beyond national boundaries.

During the 20th century, biomedical breakthroughs contributed greatly to increasing life expectancy and improving quality of life throughout the world. HIV control efforts have benefited from the fruits of biomedical research, as technological advances have dramatically strengthened the world's capacity to address HIV/AIDS. Therapeutic breakthroughs have effectively tripled life expectancy for a young male newly infected with HIV (Lohse, 2007), and technological innovations have strengthened efforts to prevent HIV infections, for example, by sharply reducing the risk of mother-to-child HIV transmission (Guay et al., 1999).

The comprehensive response to HIV/AIDS, encompassing efforts to deliver treatment and services today while developing new tools for the future, has had important successes, yet much more remains to be done. The tools at our disposal are simply not enough. Development of additional technologies to prevent and treat HIV infection will be needed to buttress global capacity to alleviate the pandemic's burden in the coming years. In addition to the need for simpler, more affordable therapeutic regimens, new prevention tools are urgently required to improve our ability to curb the expansion of HIV/AIDS (Global HIV Prevention Working Group, 2006).

However, it is unclear whether efforts to respond to HIV/AIDS over the next generation will benefit from a robust pipeline of new health tools to prevent and treat HIV infection. There are at least two reasons for concern.

First, as a disease that primarily affects low- and middle-income countries (LMICs), HIV/AIDS may not be perceived by private industry as an attractive target for future investments in research and development. In 2008, LMICs are estimated to account for more than 93% of prevalent HIV infections and for more than 96% of incident infections (UNAIDS, 2008). Although a sizable and profitable market for HIV therapeutics in the developed world continues to generate an impressive level of industry engagement, existing products remain inadequate. And in the case of HIV prevention technologies, particularly needed in LMICs where the ability to pay for such innovations is severely limited, private sector involvement is minimal.

Second, even where a commitment exists to support HIV-related R&D, such resources may fail to elicit the innovation needed to answer key scientific questions and to generate the new technologies needed to fight HIV/AIDS in the future. While peer review processes used by traditional research funders often do a good job of identifying “excellent” grant proposals, the approach is less successful in identifying “innovative” applications. In essence, critics of peer review argue that the approach promotes consensus, whereas innovation is often controversial because it goes against the grain of conventional thinking (Kaplan, 2007).¹ The need for innovative concepts is especially apparent in the AIDS vaccine field, where disappointing clinical trial results have underscored the need for new approaches (Johnston and Fauci, 2008).

Recognizing the centrality of scientific innovation to the future of HIV/AIDS, the Science/Technology Working Group of the collaborative *aids2031* project asked the International AIDS Vaccine Initiative (IAVI) to produce a brief analytical paper on strategies to spur innovation for the development of needed HIV/AIDS technologies. This report briefly

¹ The National Institutes of Health in 2007 began a formal review of its peer review system, seeking input from both external and internal stakeholders. In September 2008, preliminary implementation plans were announced in several areas, including engagement of the best reviewers, improving the quality and transparency of review, and ensuring balanced and fair reviews across scientific fields and career stages.

describes strategies that have either been tried or suggested to promote scientific innovation for HIV/AIDS and other “neglected” diseases.²

PUSH MECHANISMS TO SUPPORT INNOVATION

Incentives for R&D generally fall into two categories – “push” and “pull” mechanisms. Push mechanisms involve direct or indirect subsidies toward developing a desired product. Examples include grants to researchers, investments in product development programs, and R&D tax credits. Push mechanisms are relatively straightforward to implement and have proven to be politically feasible. They may also lead to research discoveries useful for products or diseases other than the one on which the incentive program specifically focuses.

However, they also have certain drawbacks. In general, push mechanisms rely on decision-making entities to “pick the winners” among competing product approaches – a methodology that may elevate conventional wisdom over innovative thinking. Moreover, the decision-making process may suffer from insufficient information, as potential recipients may have an incentive to exaggerate the promise of their own work. Even the most well-intentioned decision-making body may find it difficult to terminate funding for inefficient or unpromising research avenues (Kremer, 2001; Maurer, 2005). This risk is especially high for early-stage R&D and product development, leading some to advise that push mechanisms be reserved for basic research, where diffuse funding without pre-determined outputs can be a spur to innovation, or for late-stage clinical trials that involve standardized protocols (Maurer, 2005).

² HIV/AIDS arguably falls within a class of health conditions known as “neglected diseases.” References to the “10/90 gap” denote the fact that less than 10% of biomedical research spending is directed toward diseases reflecting 90% of the global health burden. Since the 10/90 gap was first documented almost two decades ago, a number of important developments have occurred: a significant increase in global spending on biomedical research, dramatic increases in rates of HIV/AIDS and other infectious diseases in developing countries, and growth of chronic diseases in both developed and developing countries. Although data are insufficient to generate up-to-date estimates on global research spending on diseases that primarily affect developing countries, it is apparent that the disparities identified in 1990 persist (Burke and Matlin, 2008).

Direct Funding

HIV/AIDS has generated extensive push funding – primarily in the form of government and foundation support for scientific research. In 2007 alone, the National Institutes of Health (NIH) provided almost US\$ 3 billion in funding for HIV-related activities, approximately 15% of all NIH grant funding. Roughly one-fifth of that amount – or US\$ 600 million – supported AIDS vaccine research.

However, grant funding, though substantial, may not necessarily be conducive to supporting innovative science. As most grants are short-term, researchers often lack the ability to secure long-term funding needed to support the years-long discovery process for new and innovative technologies.³ Moreover, current research funding streams are often inflexible, making it difficult for researchers to rapidly reallocate funds to new activities that merit their attention based on scientific developments. Lastly, most public funding for research is national in scope, with grants limited to individuals and institutions within geographic borders. This ignores the global nature of scientific efforts, and the need to reach far and wide in both the search for and development of innovations.

An approach to overcome some of these weaknesses of grant programs is to devise funding streams that specifically aim to fund scientific innovation. As a complement to conventional research funding that relies on peer review, new funding approaches have been proposed that explicitly target innovation – for example, by supporting unorthodox theories or applications, or by specifically soliciting ideas or proposals from researchers who do not work in a given field.

For any such funding initiative, a major challenge is crafting a review process that actually promotes innovation. Most grants, especially from public sector agencies that use taxpayer funds, have strict accountability procedures to avoid waste and real or perceived conflicts of interest. However, by limiting use of grant funds only to “proven” or “evidence-based” purposes, funders may inadvertently squelch innovation and encourage pursuit only of conventional research avenues. In response, innovation-promoting funding mechanisms now

³ Recent years have seen a trend toward longer duration of grants, with several NIH award programs now extending to five years. While a five-year grant is preferable to annual funding cycles, five years remains short in terms of scientific discovery.

underway have adopted novel strategies to address the tension between accountability and “outside-the-box” thinking regarding difficult scientific challenges.

National Institutes of Health. Although NIH is often regarded as the preeminent example of a traditional research funder, it has taken steps in recent years to supplement its conventional research grants with other mechanisms to spur innovation. Some of these programs include:

- **Pioneer Award Program.** Administered by the NIH Director’s office, these awards are designed to support individual scientists of exceptional creativity who propose pioneering or transformative approaches to major challenges in biomedical and behavioral research. The program aims to support research with the potential to produce an unusually greater public health impact and that reflects ideas substantially different from those already being pursued. These “awards” are actually research grants, and are not intended as a reward for prior achievements. Initiated in 2003, each Pioneer Award provides \$2.5 million over five years; sixteen awards were granted in 2008.
- **New Innovator Award.** This program seeks to stimulate highly innovative research and support promising new investigators. It is targeted to young investigators at early career stages who have not yet received a traditional NIH research grant. An unusual feature of the grant is the commitment of five years of funding from a single fiscal year budget, enhancing the long-term reliability of funding. The program began in 2007 and provides \$1.5 million over five years per grantee; thirty-one awards were made in 2008.
- **Transformative R01 Program (T-R01).** In response to concerns that the traditional NIH research grant program (R01) may discourage submission of bold and risky research proposals, NIH created T-R01 to expressly support exceptionally innovative, unconventional and high-risk projects with a potential for high impact. Launched in September 2008, the program will pilot novel approaches to peer review and program management. NIH expects to invest US\$ 250 million over the next five years, beginning with 60 awards anticipated in 2009.
- **Research Teams for the Future.** With the goal of encouraging scientists to test a variety of models for conducting research, NIH has awarded grants to transform the way researchers do their work. Grants to date have focused on interdisciplinary

research centers, innovative training programs, and development of methodologies to integrate different disciplines to tackle complex questions. The above-noted Pioneer Awards are a component of the Research Teams for the Future initiative.

Grand Challenges Explorations. In 2007, the Bill & Melinda Gates Foundation launched the Grand Challenges Explorations (GCE) program, expanding upon the Grand Challenges in Global Health initiative from several years earlier. GCE was established to support ideas that had never been tested before, and to involve people not typically working in the global health field. Looking specifically to generate creative, unorthodox thinking on the world's most important and difficult global health challenges, the initiative seeks to fund novel but unusually promising ideas, to engage new investigators in research on emerging health technologies, and to grow the field of global health science.

For each round of applications, Grand Challenges Explorations identifies priority research areas. Proposals are limited to two pages and are screened to assess their relevance to key global health needs. Four to six external experts, selected for their own innovative track records rather than their expertise in particular fields, review the applications and recommend selections. Each reviewer is allotted one "gold selection" that confers an automatic award to the applicant, as well as three "silver selections" that are funded depending on resource availability.

Round One of the program resulted in 4,000 applications from more than 100 countries, with 12% of applicants residing in developing countries. Applicants ranged from graduate students to Nobel Laureates. Roughly one-fifth, or about 800, of the applications related to HIV/AIDS. As awards have just been announced, it is too early to evaluate the program's success in promoting innovation. Out of every 100 novel concepts funded, GCE hopes that one or two ideas will transform the research field or dramatically alter the way we think about high-priority health interventions.

IAVI Innovation Fund. In 2007, the International AIDS Vaccine Initiative established an Innovation Fund to advance AIDS vaccine research by encouraging experimental or unconventional ideas in ways that other funding sources could not. Aimed at small- and medium-sized biotech firms and supported in part by an initial grant from the Bill & Melinda Gates Foundation, the Innovation Fund seeks to provide funding to companies and researchers that

work outside mainstream HIV research circles. It finances feasibility studies to demonstrate proof of concept, with the aim of identifying technologies for rapid advancement into clinical testing using IAVI's existing product development infrastructure and more traditional, long-term funding model. Using an expedited review process that includes input from a venture advisory committee, IAVI seeks decisions on proposals within six weeks of receipt. The Fund intends to reach into other areas of virology and immunology, promotes a cross-fertilization of ideas, and specifically targets technologies from beyond the AIDS vaccine field. To date, the Fund has supported six proposals, totaling US\$ 1.9 million.

Common Characteristics of Funding for Innovation

To investigate approaches to funding innovation, IAVI studied the design, structure and operations of 25 different mechanisms that specifically aim to fund innovative or unorthodox ideas. Most of these initiatives are less than five years old, and most grants are relatively small (under \$100K).

Examining experience in diverse health fields –cystic fibrosis, juvenile diabetes, lupus, inflammatory bowel disease and muscular dystrophy – IAVI identified a number of similarities in the approach, philosophy and process of existing innovation-promoting funding initiatives. First, these mechanisms sought to respond to the state of the science in each particular field, such as the lack of major therapeutic breakthroughs or the insularity of the research community focusing on a particular disease. Second, the initiatives targeted a particular funding niche, typically focusing on early-stage research or translational research to move candidates through the pipeline quickly. Third, the mechanisms relied on relatively rapid, fairly standardized evaluation processes, although there were some distinctive features: matching domestic proposals with international reviewers (and vice versa) to avoid political or competitive pressures, and including "lay volunteers", bringing in patients active in the advocacy organization to evaluate applications.

The output of these initiatives has been impressive, as measured in publications in peer-reviewed journals, subsequent funding, and licensing agreements ensuing from research projects. Two key lessons gleaned from these efforts were: 1) focus on novelty, but don't try to define it – don't require proof of principle or preliminary data, and don't try to define research priority areas a priori, since good ideas may come from out of the blue, and 2) be careful how you review – independent assessments are preferable to committees which may fund the least-criticized proposal rather than the most innovative one.

Tax credits

Tax subsidies for R&D in neglected diseases have been proposed as a way to increase the engagement of private industry in biomedical research to benefit low- and middle-income countries. The market-oriented attributes of R&D tax credits make them especially appealing to some, as decisions on the conduct of R&D would remain with the private sector (Hall and Van Reenen, 2000). However, the approach also has potential drawbacks. General R&D tax credits may not improve spending on neglected diseases, as prevailing market incentives will continue to encourage companies to develop products geared for more lucrative markets in high-income countries (Kremer, 2001). Firms with the most to contribute to early-stage R&D, such as small or start-up biotech companies, may not have sufficient (or any) taxable income to make an R&D tax credit meaningful as an economic incentive. Some consideration has been given to the concept of tradable or “sale-able” tax credits as a means of making them valuable to biotech companies and big pharma alike.

One tax-related incentive in place is the Orphan Drug Act (ODA) of 1983, which recognized that companies typically lack financial incentive to invest in costly R&D for technologies to treat or prevent rare, sometimes-complicated diseases. Cornerstones of the legislation include a 50% tax credit on clinical trials for products designed for illnesses that affect fewer than 200,000 patients in the U.S., as well as a guaranteed seven-year market exclusivity.

Although several companies sought to take advantage of ODA provisions for HIV-related research in the pandemic’s early years, the rapid expansion of HIV/AIDS in the U.S. quickly made such research ineligible for Orphan Drug protection. But the program’s success does suggest that such an incentive may have merit. While fewer than 10 health products for rare diseases were brought to market in the decade prior to the law’s enactment, more than 200 drugs and biological products for rare diseases reached the market during the Orphan Drug Act’s first two decades. As of December 2004, the US Food and Drug Administration (FDA) had granted orphan drug status to more than 1,400 pharmaceutical compounds (Grabowski, 2005).

In the UK, an R&D tax credit was introduced in 2000 for small and medium enterprises and later extended to large companies, with a goal of increasing R&D investment from 1.9% of GDP to 2.5% by 2014. By

2005 more than 17,000 claims had been made. A specific provision of the tax credit, the Vaccines Research Relief (VRR) program, targeted the development of vaccines and medicines for AIDS, TB and malaria in the developing world (HMT, 2005). During the 2003-2005 period, there were about 10 returns annually, with total R&D claims of approximately £6 million (HMRC).

PULL MECHANISMS TO ENCOURAGE INVESTMENT IN INNOVATION

While push mechanisms fund research inputs, pull mechanisms aim to reward specific outputs, thereby encouraging researchers to invest in targeted R&D. Examples of pull mechanisms include enhancements to intellectual property, advance commitments for purchase and/or price, tax credits on product sales, or prizes/rewards for successful efforts.

The ability of pull mechanisms to target specific research outcomes is one of their primary advantages. Because they maximize potential company profits, they also encourage companies to develop products that can actually be marketed (Kremer, 2001). Yet designing effective pull mechanisms confronts a number of challenges. These include the difficulty of identifying in advance the specific desired outcome of R&D efforts, ensuring that the pull mechanism is credible to developers, and overcoming the lack of resources by potential innovators to carry their ideas forward.

Prizes

In recent months the idea of offering prizes to major pharmaceutical companies or others to invest in neglected disease R&D has surfaced. Although the strategy has attracted high-level interest, it is not a new idea. Prizes were used as early as the 18th century to encourage scientists and inventors to tackle high-priority scientific challenges, such as determining one’s longitudinal position at sea. More recent examples have focused on the development of a reusable spacecraft, fuel-efficient cars, super-efficient refrigeration, and innovations that extend the lives of mice (Harford, 2008; Masters, 2008; Travis, 2008a).

Experience shows that prizes often generate total R&D investments that substantially exceed the amount of prize payout (Travis, 2008a), suggesting that a high-profile prize may function as much as an intellectual challenge to the field as a financial enticement to increased R&D. The number of entrants for prize competitions such as Netflix and the Ansari X Prize indicates a high level of interest

from the scientific community. The following table includes examples of prizes used to encourage scientific innovation

Use of Prizes to Answer Scientific Questions

Date prize established	Nature of challenge (sponsor)	Prize offered / 2008 USD value	Solved?	Of note
1714	How to determine longitude at sea (British government)	£20,000 / \$3.65 million	Yes	Multiple winners; over £100,000 awarded
1775	How to produce alkali soda (French government)	100,000 French francs / \$457,000	Yes	
1906	Proof of Fermat's last theorem (Paul Wolfskehl, mathematician)	100,000 marks / \$34,400	Yes	
1919	Solo flight from New York to Paris (Raymond Orteig, hotel magnate)	\$25,000 / \$316,000	Yes	Total investment by competitors about 16X the prize amount
1990	Develop (and sell) super-efficient refrigerator (consortium of 24 utility companies)	\$30 million / \$41 million	No	14 entrants; one achieved 25% reduction in energy, but failed to meet sales requirement to claim full prize
1994	Develop diagnostic test for sexually transmitted infections (Rockefeller Foundation)	\$1 million / \$1.3 million	No	
1995	Private space flight (X prize, funded by Amir and Anousheh Ansari, aerospace entrepreneurs)	\$10 million / \$12 million	Yes	Total investment of competitors \$100 million
2006	Improved movie recommendations (Netflix)	\$1 million / \$1.1 million	Yes, but only partial	\$50,000 interim award 2,500 teams and 27,000 competitors entered
2007	How to remove greenhouse gases from the atmosphere (Virgin Earth Challenge)	\$25 million / \$26 million	No	

In the public health field, the Rockefeller Foundation offered a US \$1 million prize in 1994 to develop simple point of care diagnostics for sexually-transmitted infections. Strict criteria were specified: tests had to be 99% accurate, use non-invasive samples, cost less than \$0.25 to manufacture, produce rapid results, require no equipment, and be stable at high temperatures (Mabey et al, 2001). The Rockefeller Prize was never claimed, and the offer was not renewed. Some have suggested that the specifications were too strict, the timeline too short, and the prize too small (Kremer, 1998; Masters, 2006).

More recently, there have been a number of proposals to use prizes to encourage research on improved tuberculosis diagnostic tools, new treatments for Chagas disease, medicines and vaccines for cancer, and other medical priorities. While the various proposals for prize-based strategies to drive innovation focus on different products and have unique characteristics, most revolve around the establishment of a government-financed prize fund

and propose the World Health Organization as the intermediary or organizer.

Critics have cited the zero-sum competitive nature of prizes as a potential weakness of the approach (Masters, 2008). In response, proponents of prizes for public health R&D have proposed the implementation of prizes that reward intermediate or incremental achievements, such as achieving pre-defined steps toward development of a technology. Another option is to award a range of prizes, such as a large prize for the first to develop a product that satisfies all specific technical requirements, complemented by smaller annual prizes for further technological strides, a shared percentage of the grand prize by those in the field whose work may have contributed, and discrete prizes for firms that solve specific steps that are relevant to achievement of the grand prize (Love, 2008).

A well-designed prize competition must include an achievable, yet difficult target, define clear measures of success, have a credible commitment to pay the

winner, and rely on an impartial process (such as a jury) to determine the winner (Masters, 2008). Prize competitions may work best for scientific challenges that call for a true technological breakthrough, as opposed to well-established fields where clearly-defined technological needs lend themselves to traditional funding mechanisms. However, a significant drawback to prizes may be that they provide no up-front resources to those interested in and potentially able to solve the problem. This may mean that promising innovative ideas cannot get off the ground, even with the prospect of a significant award at the end of the road.

Prize competitions typically complement rather than replace existing frameworks to promote innovation, such as grants or patents. An exception is a proposal by U.S. Senator Bernie Sanders, the *Medical Innovation Prize Act of 2007*. This legislation would eliminate patent exclusivity and instead award a prize to the winner, who may still market the product, although not exclusively. The bill would authorize a prize fund amounting to 0.6% of US GDP, an estimated \$80 billion in 2008, to be administered by the US Treasury Department. To be eligible for a prize, a firm would have to be the first to receive market clearance for a product or hold the patent for a manufacturing process. Prize payments would be based on the number of patients benefiting from the innovation, its incremental therapeutic benefit, and the degree to which the product or process addresses priority health care needs⁴. Sanders suggests minimum award amounts for innovations relating to neglected diseases (4% of prize fund), global infectious diseases (4%), and orphan drugs (10%).

Another novel approach is InnoCentive, based on the open source software community, and which broadcasts specified R&D problems to a community of “solvers” in exchange for cash prizes (Travis, 2008b). Individual companies post problems on InnoCentive’s website, with specifications for an acceptable solution, a timeline and the amount of the prize. A major review suggests that key elements of the InnoCentive approach – transparency, collaboration and the free sharing of intellectual

⁴ This is similar in approach to a recent proposal for a Health Impact Fund, financed by governments or foundations, to purchase new medicines. Rather than exercise patent rights, companies would register with the Fund, agree to sell their product at an administered price near the cost of production, and then receive ten years of payments from the Fund based on the proportional assessed global impact of the drug, on the basis of Quality-Adjusted Live Years saved. (Hollis and Pogge, 2008).

property – may be more efficient than traditional methods that rely on scientific publishing and patenting, which may reduce information flow and misalign incentives for innovation. According to the study, which examined 166 problems posted on InnoCentive’s website, the odds of a solution were proportional to the diversity of the community of problem solvers (Lakhani et al., 2007). Significantly, more than half of InnoCentive’s registered solvers are located in China, India and Russia. As importantly, after analyzing the characteristics of winning solvers, it was clear that the further a challenge was from a person’s specialty field, the higher the probability of finding a solution – suggesting that fresh eyes and a new perspective might be particularly critical to success (Travis, 2008b).

The Rockefeller Foundation has partnered with InnoCentive to focus on solving challenges faced by poor and vulnerable populations. By paying InnoCentive’s access, posting and service fees on behalf of non-profits, and by financing the awards paid to solvers, the Foundation is supporting the search for solutions to science and technology problems prevalent in low- and middle-income countries. The first challenge, expanding the functionality of a solar-powered light, was solved within a few months, leading to a \$20,000 award (Parmar, 2008).

The InnoCentive model has a number of advantages: as it already exists, it does not require new legislation or new infrastructure; the model is flexible and consistent with existing intellectual property provisions, as companies can require solvers to sign confidentiality agreements, anonymity is permitted, and solutions are not publicly posted. An important drawback, however, may be companies’ reluctance to publicize particular R&D challenges or alert competitors to the products on which they are working. In addition, while InnoCentive is ideal for scientific challenges that can be clearly defined or for discrete incremental steps in the R&D process, its potential applicability to large, more complex and abstract problems is unclear.

Contracts

Another pull mechanism is the execution of contracts for the purchase of a particular product once it is developed. The advantage is that this approach straightforwardly addresses a key reason for under-investment in new technologies for neglected diseases – the widespread belief that no buyer will be

willing or able to purchase a new product primarily for use in low- and middle-income countries.

However, use of contracting mechanisms to encourage R&D investment and innovation faces several challenges. The first is the need to ensure that the contract is sufficiently large to be meaningful to pharmaceutical companies in light of the enormous investment required to bring a new product to market. The second challenge is making the contract sufficiently credible. In the case of most public sector entities, which rely on year-to-year appropriations, advance commitments are typically dependent on the availability of funds, leaving potential developers wary of unfulfilled commitments downstream.

BioShield. In response to the anthrax attacks that killed five people in the U.S. in 2001, and concern among policy-makers about U.S. preparedness to respond to bioterrorism, the Project BioShield Act of 2004 was passed. This law aimed to encourage R&D for new vaccines by guaranteeing a U.S. government market for new biomedical countermeasures for bioterrorism. While the law authorized nearly \$5.6 billion over 10 years for the purchase of vaccines and drugs for storage in a strategic national stockpile, only eight contracts amounting to US\$ 1.5 billion were actually executed (Gottron, 2007).

The first BioShield contract was awarded to VaxGen in 2004 for US\$ 877.5 million for the delivery of 75 million doses of a new anthrax vaccine within three years. After the company's failure to meet a key contract milestone, the U.S. government terminated the VaxGen contract in 2006 (Gottron, 2007). A review by the Government Accountability Office (GAO) determined that the contract was awarded too early in the development process, before critical manufacturing issues had been resolved. The GAO also found that the U.S. government demanded – and VaxGen accepted – unrealistic deadlines and that the contract limited the company's options to secure additional funding when a budget shortfall became apparent (GAO, 2007).

In addition to the problems exposed by the failure of the VaxGen contract, other aspects of the original BioShield legislation limited its impact. Most of the big industry players declined to participate, primarily because the fund was not considered sufficiently large to make it credible. The market ostensibly guaranteed by the law extended only to purchases by the U.S. government, based solely on the anticipated need in case of a bioterrorism attack. Moreover, procurements made under BioShield were only for

products in later stages of development, requiring developers to assume substantial financial risks (Gronvall, 2008).

To ameliorate some of BioShield's shortcomings, the U.S. adopted the Pandemic and All-Hazards Preparedness Act. To better protect developers from financial risks, the new legislation authorized milestone payments of between 5-50% of the total amount of the contract during the development process. A new authority was created under the legislation to award prizes or other support for relevant activities undertaken after pre-clinical development but prior to government procurement. Responding to concerns about the limited size of the fund, the new legislation also authorized an additional US\$ 1 billion to fund product development.

The amended BioShield approach nevertheless has a number of important limitations, especially with regard to the development of technologies for HIV/AIDS. The legislation focuses on U.S. national security interests, potentially excluding products for infectious diseases generally, and categorically barring support for technologies to address health effects that do not occur on U.S. soil. Moreover, while the authorizations in the legislation are heartening, the existence of U.S. government support when and if it is warranted will depend on actual year-to-year appropriations. The additional monies called for in the new legislation for product development grants have been authorized but not yet funded. Thus, the ultimate aim of the legislation – to encourage R&D investments by increasing confidence in the existence of an ultimate market for health technologies – may be undermined by the uncertainties inherent in the U.S. government's funding cycles.

Advance Market Commitment (AMC). As questions regarding market viability impede robust private industry investments in R&D for neglected diseases, advance market commitments for the purchase of future vaccines have been suggested as a means to encourage companies to invest in relevant R&D. An advance market commitment is a binding commitment to purchase a product once it is developed, typically a minimum number of doses at a pre-determined price.

In 2007, Canada, Italy, Norway, Russia and the United Kingdom joined with the Bill & Melinda Gates Foundation to launch the first advance market commitment. This AMC, totaling US\$ 1.5 billion, aims to speed the development and deployment of

vaccines to prevent pneumococcal disease, a leading killer of children. While the first AMC seeks to accelerate new generations of pneumococcal vaccine, it is unclear whether the mechanism can promote early stage innovation. Its primary aim is to entice companies to invest in the clinical testing and future marketing of products that are already well advanced in the development process. Health advocates hope that the approach may eventually be extended to other products, such as vaccines for HIV/AIDS or malaria (IAVI, 2005).

It remains to be seen whether the global community will be willing or able to create advance market commitments for products that do not yet exist, or are at much earlier stages of the development process. Crafting an advance market commitment would be somewhat more complicated for a product with uncertain characteristics or pricing, although analysts believe the approach remains feasible (CGD, 2005; Kremer, 2000).

Intellectual property approaches

Creative use of intellectual property protections has also been proposed as a way to encourage innovation in high-priority scientific areas. For example, some have suggested allowing companies that invest in R&D for neglected diseases to extend patent protections on one or more of their other products. A legislative proposal to broaden BioShield provisions had included such a “wild card patent extension” although it was never passed. The rationale was that a patent extension applied to a blockbuster product could present a significant enough financial incentive for companies to sway investment decisions.

Reliance on patent extensions to promote innovation has several drawbacks. The approach is arguably inequitable, in that it places the burden of financing neglected disease R&D on consumers of the product for which the patent is extended. In addition, the incentives deriving from a patent extension are greatest for firms that have patents on commercially valuable products, but such entities may not be best placed to advance R&D on the high-priority health challenges that motivated lawmakers to enact the patent extension (Kremer, 2001); however, making the extension tradable could serve to encourage the desired R&D efforts, as innovators might find a willing market among companies with blockbuster products in their pipelines. Lastly, it is not clear that proposals to extend patent protections for pharmaceutical products would be politically viable. The pharmaceutical industry is deeply unpopular,

with its public standing compared by some to the tobacco industry. Lawmakers might well hesitate to support legislation to extend a company’s patent monopoly for an expensive medication that is not itself used to treat or prevent a neglected disease.

Regulatory approaches

In 2007, the US Congress amended the Food and Drug Administration Revitalization Act to establish a transferable voucher to encourage the development of drugs and vaccines for so-called “tropical diseases.” The provision allows the sponsor of a newly developed drug or vaccine to receive a priority regulatory review voucher that can be applied to another product. The developer may use this for a product in its own portfolio, or transfer it to another entity (including through sale). Priority review reduces the average FDA regulatory review time for a new product from an average of 18 months to a maximum of six months. With economic estimates valuing the worth of priority review for a new blockbuster drug at more than US\$ 300 million (Ridley et al., 2006), it is hoped that the provision will spur industry investments in R&D for neglected diseases. However, it is too soon to ascertain the law’s effect on industry investments in R&D for neglected diseases.

Because it is sometimes challenging to know in advance whether a particular product will achieve blockbuster status, it may be difficult for companies to place a value on the voucher, potentially reducing industry’s willingness to make the desired R&D investments. Even for blockbuster drugs, the value of priority review may be insufficient to coax major pharmaceutical companies to invest in costly R&D for neglected diseases, although such an incentive could be persuasive for a cash-starved biotech company. Moreover, it is uncertain whether companies with potential blockbuster drugs in the pipeline would also be those that would be best situated to contribute to the development of new technologies for HIV/AIDS. Again, the prospect of being able to sell such a voucher may provide significant incentive to those who could make important research contributions to the HIV or other neglected disease fields; issues regarding timing and the ability to “match-make” between buyers and sellers of vouchers will be critical. Lastly, the challenge remains of having the up-front resources needed to undertake the innovative scientific work, prior to being awarded a voucher for success.

OTHER APPROACHES TO ENCOURAGE INNOVATION

Organizational Models

As the above-noted innovations in policy and funding underscore, the desire to encourage innovation has prompted considerable reflection regarding the optimal way to organize research efforts.

Consortia or centers of excellence. In recent years a number of institutional arrangements have been established to bring together different scientific disciplines as a means of solving key problems. Examples include the NIH's Research Teams for the Future Initiative, and several consortia in the HIV vaccine field: the Collaboration for AIDS Vaccine Discovery, the Center for HIV-AIDS Vaccine Immunology, the Neutralizing Antibody Consortium and the Live-Attenuated Consortium. The common theme across these efforts is that the more traditional model of scientists working independently may not be adequate to solve vexing scientific challenges – rather, by bringing together the best minds from disparate domains, linking them to central facilities, they can easily share ideas, data, and results, speeding the path to solutions. However, these models are new enough that their value at making breakthroughs has not yet been proven.

The IAVI Model. An organization often-cited for its innovation in preventive HIV research is the International AIDS Vaccine Initiative. Since its inception in 1996, IAVI's strategy has been to identify and fill neglected niches and ensure complementarities to efforts by other global stakeholders. IAVI has built a comprehensive R&D infrastructure, patterned on best practices from industry, and complemented by policy, advocacy and communications initiatives to remove barriers impeding AIDS vaccine development. Along the way, it has introduced some unconventional approaches to vaccine development. These include: creation of scientific consortia (the Neutralizing Antibody Consortium, the Live Attenuated Consortium), pioneering new collaborative institutional arrangements which have since been widely adopted by the field to answer the most difficult scientific questions; product development teams, which have brought six candidates to trials; leading efforts to build partnerships with developing countries for AIDS vaccine research, including establishing a network of clinical research centers and laboratories in East and Southern Africa and India, operating at international standards; creating

the first industrial-style AIDS vaccine development laboratory outside of industry; and a global surveillance program to identify state of the art vaccine technologies and candidates, aimed at optimizing and diversifying the clinical pipeline. As the world's first "public-private product development partnership" (PDP), IAVI's multi-functional approach is seen as critical for the risk-taking and provocation needed for the field (AVAC, 2008).

Encouraging new researchers

In the wake of recent setbacks in the AIDS vaccine field, many have suggested that "new blood" is needed to reinvigorate the discipline, to question old assumptions and to contribute new ideas. Strategies to entice new researchers to the AIDS vaccine field were explored in sessions at the 2008 International AIDS Conference and the AIDS Vaccine 2008 meeting. Discussions suggest that funding streams for innovation may be critical to attracting new scientific talent to the AIDS vaccine field. Many feel that existing funding programs prioritize grants to large, established research consortia, and that the perceived hegemony of the "old guard" in the field reduces the prospects for scientific independence and professional credit for new ideas. Some of the efforts to target new and unproven ideas, and to explicitly fund those who haven't received more traditional support, may improve opportunities for younger researchers as well as those from other disciplines who may contribute fresh ideas.

HOW BEST TO SUPPORT INNOVATION IN THE DEVELOPMENT OF HIV/AIDS TECHNOLOGIES

The above discussion highlights not only the need for innovation in the development of HIV/AIDS technologies, but the many challenges in finding the best ways to support that innovation. There is, of course, no silver bullet that will miraculously allow us to perfectly identify, fund, organize and implement innovative ideas. Nonetheless, we must maximize the odds that risky but good ideas will come to fruition, while acknowledging that pursuit of those ideas will sometimes fail.

What are the critical next steps for the HIV/AIDS technology fields to take? We propose three specific actions:

Review results of new funding mechanisms and organizational arrangements for innovation

In the past few years, several new programs have been established with the explicit goal of identifying and supporting innovative research efforts – especially those which would not be funded through traditional research grants. This includes new NIH programs and an improved peer review process, the Gates Grand Challenges Explorations, IAVI's Innovation Fund, and similar initiatives in other fields. While it is still too early to judge the results of these undertakings, it will be critical to monitor them in the coming months and years, to identify successful elements and apply them more broadly, and to modify components that are not achieving the goal of spurring innovation. This may also require reaching some degree of consensus within the field as to what success looks like – e.g., if 50% of “innovation awards” prove concepts, are we taking enough risk? Can we agree on what a “transformational” finding is?

The same approach holds true for new organizational models underway, namely the scientific consortia or “centers of excellence” being tried. A similar critical eye must be applied to their progress in the near- and medium-term, with commitments to spread their benefits or correct any shortcomings to ensure speedy success.

Consider prize competitions to generate new ideas

Governments and private parties have sometimes sought to promote innovation by offering prizes for solving specific scientific or technological problems. Although this year's Nobel Prize for medicine was awarded for the discovery of HIV 25 years ago, inducement prizes would specify in advance both the size of an award and the detailed nature of the expected achievement. If done correctly, such a prize competition could drive progress toward a defined goal without specifying how that should be achieved. This could generate interest in and enthusiasm for the challenge, leading to efforts and investments that might outstrip the size of the actual prize itself.

Perhaps now is an appropriate time to design prizes for significant innovative achievements in new HIV/AIDS technologies. The challenge will be to specify appropriate solutions – particularly in the case of an AIDS vaccine, establishing interim milestones (short of a successful vaccine) that will sufficiently transform the field and pave the way forward. Recognizing that funding constraints may already limit the involvement of those with possible answers (whether in biotech or in academia), it will also be important to consider options that will not require self-funding as the only way to compete for such prizes.

Consider new sources of funding for innovation in HIV/AIDS technologies

While the questions of how to identify and fund innovative ideas for new HIV/AIDS technologies are tremendously important, a significant corollary relates to the actual source and volume of funding for such purposes. Investment in R&D for these technologies has grown dramatically over time; although there is no comprehensive figure for global spending on HIV/AIDS R&D, the NIH alone committed close \$3 billion for these efforts this year. However, there may be opportunities to diversify and grow the current funding base, especially in light of substantial resources being devoted to AIDS care, treatment and prevention efforts. For example, existing mechanisms such as the Global Fund, GAVI or IFFIm at the multilateral level, or the US PEPFAR program at the national level, channel significant monies into delivering goods and services. Extending their mandate to directly fund R&D, or possibly having them contribute to R&D for new products through a premium added to future purchases of drugs and vaccines, could expand the resource base for innovation. Other new funding mechanisms focused on private capital markets might also be considered to generate additional or alternative monies, although the current global economic crisis may not allow for this in the short-run.

References

- AIDS Vaccine Advocacy Coalition (AVAC). 2008. *The Search Must Continue*. AVAC Report 2008. New York.
- Burke, Mary Anne and Stephen A. Matlin, eds. 2008. *Monitoring Financial Flows for Health Research 2007: Behind the Global Numbers*. Global Forum for Health Report. Geneva: Global Forum for Health Research.
- Center for Global Development (CGD). 2005. *Making Markets for Vaccines: Ideas to Action*. Report of the Center for Global Development Advance Market Commitment Working Group. Washington DC.
- Global HIV Prevention Working Group. 2006. *New Approaches to HIV Prevention: Accelerating Research and Ensuring Future Access*. August 2006 Report.
- Gottron, Frank. 2007. *Project BioShield: Purposes and Authorities*. Congressional Research Service Report No. RS21507.
- Government Accountability Office. 2007. *Project BioShield: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine*. GAO Report No. 08-88.
- Grabowski, Henry. 2005. Encouraging the Development of New Vaccines. *Health Affairs* 24(3): 697-700.
- Gronvall, Gigi Kwik. 2008. Biodefense Countermeasures: The Impact of Title IV of the U.S. Pandemic and All-Hazards Preparedness Act. *Emerging Health Threats Journal* 1: e3.
- Guay, Laura, et al. 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 354: 795-802.
- Hall, Bronwyn, and John Van Reenen. 2000. How effective are fiscal incentives for R&D? A review of the evidence. *Research Policy* 29: 449-469.
- Harford, Tim. 2008. Cash For Answers. *Financial Times Magazine*, 26 January, 21-23.
- Her Majesty's Revenue and Customs (HMRC). *Corporate Tax: Research and Development Tax*: http://www.hmrc.gov.uk/stats/corporate_tax/randdtcmenu.htm. Accessed November 2008.
- Her Majesty's Treasury (HMT) and Her Majesty's Revenue and Customs. 2005. *Supporting growth in innovation: enhancing the R&D tax credit*.
- Hollis, Aidan and Thomas Pogge. 2008. *The Health Impact Fund: Making New Medicines Accessible for All*. A Report of Incentives for Global Health.
- International AIDS Vaccine Initiative (IAVI). 2005. *Advance Market Commitments: Helping to accelerate AIDS vaccine development*. Policy Research Working Paper No. 7.
- Johnston, Margaret I., and Anthony S. Fauci. 2008. An HIV Vaccine – Challenges and Prospects. *New England Journal of Medicine* 359: 888-890.
- Kaplan, David. 2007. POINT: Statistical analysis in NIH peer review—identifying innovation. *The FASEB Journal* 21:305-308. <http://www.fasebj.org/cgi/content/full/21/2/305>.
- Kremer, Michael. 1998. Patent Buy-Outs: A Mechanism for Encouraging Innovation. *Quarterly Journal of Economics* 113(4, November): 1137-1167.
- Kremer, Michael. 2000. *Creating markets for new vaccines. Part I: rationale*. National Bureau of Economic Research (NBER) Working Paper No. 7716.
- Kremer, Michael. 2001. *Public Policies to Stimulate the Development of Vaccines and Drugs for the Neglected Diseases*. Commission on Macroeconomics and Health Working Paper No. WG2:8.
- Lakhani, Karim R., Lars Bo Jeppesen, Peter A. Lohse and Jill A. Panetta. 2007. *The Value of Openness in Scientific Problem Solving*. Harvard Business School Working Paper No. 07-050.
- Lohse, Nicolai, et al. 2007. Survival of Persons with and without HIV Infection in Denmark. *Annals of Internal Medicine* 146: 87-95.
- Love, James. 2008. *The Role of Prizes in Developing Low-Cost, Point-of-Care Rapid Diagnostic Tests and Better Drugs for Tuberculosis*. Paper presented at the Médecins Sans Frontières expert meeting on Interagency Gender Working Group and R&D for tuberculosis. Geneva, 11 April.
- Mabey, David, Rosanna W. Peeling, and Mark D. Perkins. 2001. Rapid and simple point of care diagnostics for STIs. *Sexually Transmitted Infections* 77: 397-401.
- Masters, William A. 2006. *Prizes for Innovation in African Agriculture: A Framework Document*.
- Masters, William A. 2008. *Accelerating innovation with prize rewards: A history and typology of prize contests, with motivation for a new contest design*.
- Maurer, Stephen M. 2005. *The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research*. Paper presented at the CIPIH Workshop. UC Berkeley, 30 May.
- Parmar, Arundhati. 2008. InnoCentive project leads to a better flashlight. *Finance and Commerce*: <http://www.finance-commerce.com/article.cfm/2008/10/28/InnoCentive-project-creates-a-better-flashlight>. Accessed November 2008.
- Ridley, David B., Grabowski, Henry G., and Moe, Jeffrey L. 2006. Developing Drugs for Developing Countries. *Health Affairs* 25(2).
- Travis, John. 2008a. Prizes Eyed to Spur Medical Innovation. *Science* 319: 713.
- Travis, John. 2008b. Science by the Masses. *Science* 319: 1750-1752.
- UNAIDS. 2008. *Report on the global AIDS epidemic*. Geneva.