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Unleashing Europe's Biopharmaceutical Innovation Potential

Europe's significant scientific capacity could prove pivotal in the quest for an AIDS vaccine. However, key challenges, including a translational research gap, must be addressed to best harness Europe's expertise.

What can be done to accelerate AIDS vaccine research and development?

AIDS is one of the greatest public health crises of our time. While worldwide mobilisation appears at last to be slowing the spread of the human immunodeficiency virus (HIV) that causes AIDS, the pandemic still kills some two million people every year and newly infects nearly three million more. The best hope for reversing this toll is investment in promising prevention technologies and, most critically, the development of an AIDS vaccine.

Unfortunately, attempts thus far to come up with an immunological shield against HIV have faltered. The scientific obstacles to success appear far more daunting than once thought. Surmounting them will require fierce resolve from public and private stakeholders everywhere. In Europe, many researchers remain dedicated to the search for an AIDS vaccine, but their passion has not been matched by all the funds needed to take up their work.

This policy brief is part of an exploration launched by the International AIDS Vaccine Initiative (IAVI) to identify opportunities to stimulate AIDS vaccine research and development (R&D) in both developing countries (including Brazil and India) and industrialised nations. This brief summarises a study of AIDS vaccine R&D across Europe, undertaken in collaboration with the George Institute for International Health. It is based on consultations with more than 50 government and biopharmaceutical sector representatives about how best to encourage such research.

Europe could prove pivotal in the quest for an AIDS vaccine. Home to renowned universities, three of the world's four largest vaccine manufacturers, and a multitude of biotechs, Europe has much to offer to any scientific endeavour. IAVI's study examined how Europe's world-class biomedical expertise might best be leveraged to facilitate innovative AIDS vaccine work.

iavi International AIDS Vaccine Initiative

A new focus for AIDS vaccine research: The search for innovative ideas

In recent years, the focus of AIDS vaccine inquiry has shifted from later-stage product development towards investigation of novel vaccine concepts. Spurred by the failure of several vaccine candidates in clinical trials, this "course correction" has led to renewed pursuit of basic and translational research.

Basic research generally occurs in the labs of public institutions and usually spurs **non-product discoveries** that solve key scientific questions. In the search for an AIDS vaccine, basic research might enable a better understanding of the immunopathology of the disease or development of more useful animal models. Basic research may also lead to **breakthrough innovation** – for instance, to wholly new approaches to vaccine development.

Translational research, on the other hand, contributes to incremental innovation. Often conducted by biotechs, such research might entail taking the most promising innovations from public sector labs and developing them into product prototypes.

Biotechs also contribute to **enabling innovation** – essentially making development processes more efficient through shrewd design and testing.

Product candidates advanced by biotechs are often transferred to multinational biopharmaceutical companies equipped to bring products to market. These firms conduct elaborate clinical trials, devise manufacturing protocols, and secure regulatory approval. While such companies also undertake translational research activities, recent trends show increased reliance on public sector and biotech researchers to generate innovation leads.

Figure 1 provides a simplified overview of the biomedical innovation system and the roles of public institutions, biotechs, and multinational biopharmaceutical companies in the vaccine R&D process.

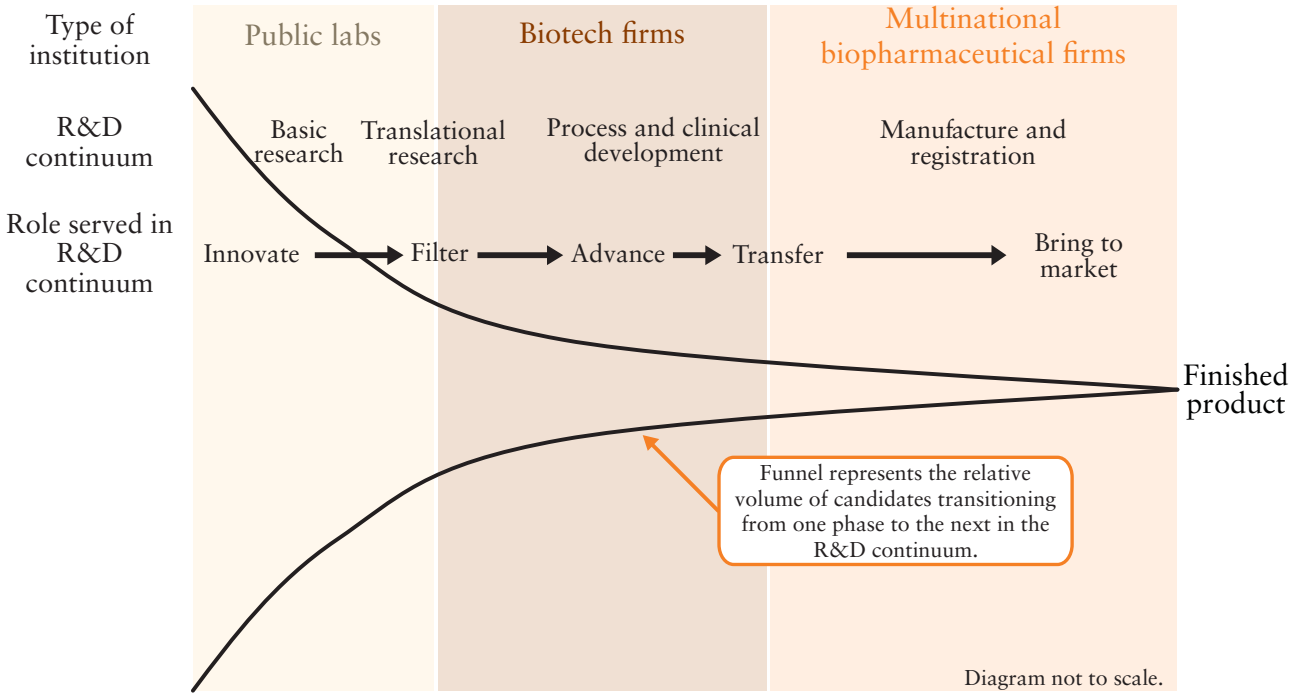
Despite a seemingly well-defined biomedical innovation system, research funding practices sometimes impede optimal engagement of the various stakeholders in Europe.

How is biomedical R&D funded in Europe? What are the challenges?

For the most part, basic research is funded by

FIGURE 1

A simplified depiction of Europe's biomedical innovation flow



public-sector investment, while venture capital firms commonly underwrite translational research by biotechs. Money for later-stage product development by multinational corporations comes almost entirely from capital markets and reinvested product-sale revenues. While the US biomedical innovation system is by no means perfect and has its own structural issues, research funding in Europe presents unique challenges which are exacerbated in the context of AIDS vaccine R&D.

Budgets for public researchers are too small, decentralised and fragmented

Public-sector support for biomedical research in Europe lags behind that of other regions of the world, particularly the United States. In 2003, EU-15 governments spent a combined €4.9 billion on health research. That same year, US spending on such investigation amounted to €24.2 billion – five times the European outlay (and more than six times as much per capita) (Enzing et al, 2004). And even though they receive such limited government support, Europe's public labs still draw a greater share of their backing from public sector sources than do US universities. Why? American researchers can rely on a diverse funding base that includes government, foundations, corporations, tuition revenues, and alumni donations. Some private US universities also enjoy large endowments.

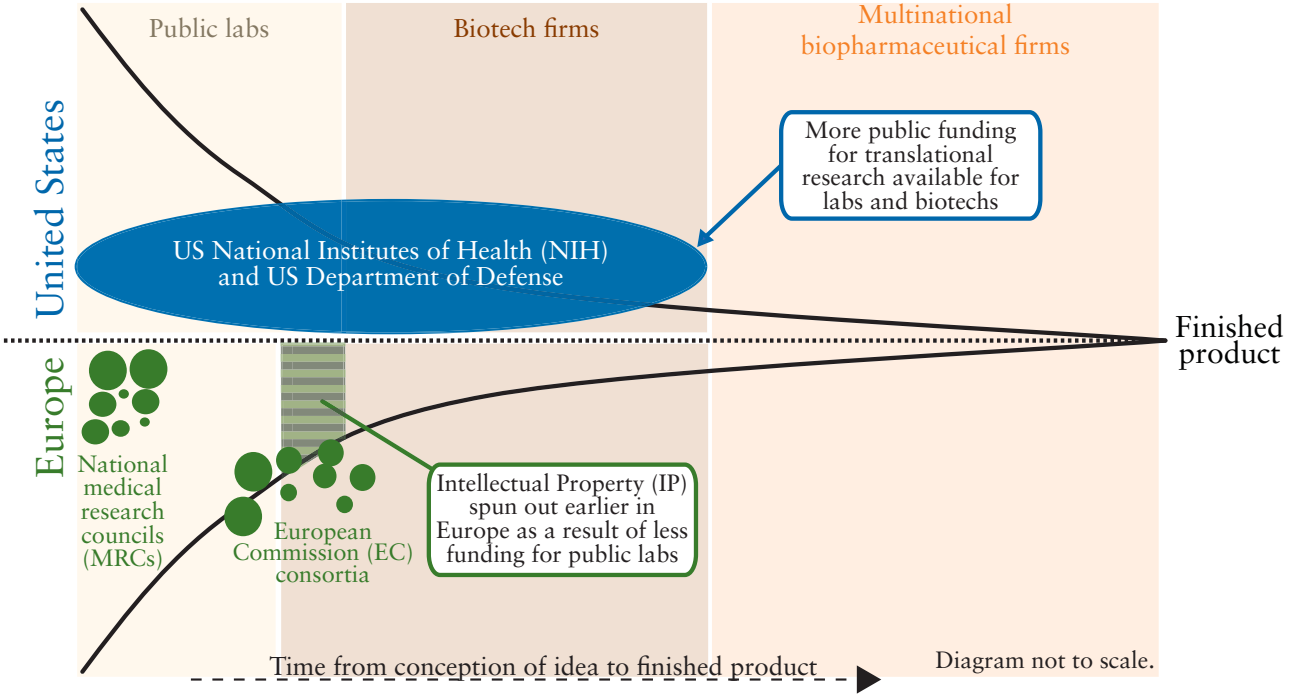
The funding disparities between Europe and the United States are even more striking when considering spending on AIDS vaccine R&D. Europe invested significantly in 2006, totalling US$82 million, reflecting 11% of global public sector investments. But US public sector contributions to AIDS vaccine R&D that year were US$654 million, 84% of the global total (HIV Vaccines and Microbicides Resource Tracking Working Group, 2007).

Part, but not all, of this disparity can be explained by differences in accounting methodology—e.g., in the US grants routinely include significant overhead costs, which are not included in European accounting. European scientists interested in AIDS vaccine research therefore have far fewer public funding opportunities than their US counterparts.

This imbalance is compounded by the fact that research funding in Europe is

FIGURE 2

Comparative funding dynamics in Europe versus the United States



fragmented and decentralised (Gillespie et al, 2007). Spending decisions are made independently by each of Europe's member nations, often through public bodies such as the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS) in France, the Medical Research Council (MRC) in the UK, and the Swiss Institute for Vaccine Research (SIVR), which largely, but not exclusively, fund AIDS vaccine projects within their borders. And most funding agencies must contend with budget constraints and wavering public will – factors that mean most research ventures get too little money to thrive (Owen-Smith et al, 2002).

Centralised research funding across the EU is provided through the multi-year Framework Programme for Research and Technological Development, which has tried to remedy the fragmentation problem by making bigger grants to transnational research projects. In 2006, for instance, the sixth Framework Programme (FP6) spent €15.5 million on 12 transnational vaccine research projects involving 132 institutions from 22 countries (European Commission, 2006a; IAVI, 2006). But these cross-border collaborations are viewed by many European researchers as bureaucratic, rule-bound, uncoordinated, and inefficient. Requirements of a minimum of three partners from three countries have meant that 'small' consortia involve five to six partners, with 'large' groups having up to 30 partners. The result is a high degree of administrative burden combined with a small share of grant funds flowing to each research partner (Owen-Smith et al, 2002).

Public funding disappears too early in the R&D continuum

Since its research budget is limited, so are Europe's funding choices. Its grants tend to go to inexpensive, simpler, earlier-stage vaccine work. And because more complex and costly ventures can't readily attract scarce public money, little such investigation can properly be pursued at public organisations. The few new techno-
logies that *do* emerge from public labs are sometimes spun out earlier than is ideal – leaving biotechs to shoulder costs and risks they may not be prepared to handle.

This may lead to promising innovations being overlooked because they haven't been sufficiently developed to demonstrate their potential to investors. Europe may therefore be suffering from a case of 'premature delivery' into the biotech field. The implications are most troubling for AIDS vaccine research: passed on too soon, the life-saving promise of a vaccine innovation may never be taken up by the private sector.

Pressure on universities to manage intellectual property as a revenue source limits interest in translational research for AIDS vaccines

Europe's funding constraints oblige universities to seek alternative funding. One option involves capturing returns on university generated innovations – either through licensing or spinning out companies. Another entails arranging contractual research with industry.

These days, reaping the financial benefits of research is the job of university technology transfer offices (TTOs), though only a few do it well – and many onlookers question whether TTOs present the right "public face" for academic institutions (Heller et al, 1998). Many European TTOs have faced challenges in promoting university ideas, often lacking the resources and entrepreneurial acumen of successful US institutions such as the Massachusetts Institute of Technology or Stanford University. The latter benefit from more generous public sector research funding in the US, allowing for innovations to be developed further before being out-licensed or sold. And since European TTOs tend to focus on ideas with the greatest sales potential, European innovators have little incentive to explore AIDS applications with uncertain market opportunities (IAVI, 2007).

Budgets for biotechs and translational research are scarce

Funding constraints in Europe aren't a problem for just public sector researchers. Grant scarcity also hobbles biotechs eager to pursue AIDS vaccine research. Nor can biotechs count on backing from venture capital firms – the traditional source of translational research funding. Compared to the United States, there is far less venture-capital money available in Europe (Table 1) (IAVI, 2006).

Concern over high failure rates associated with poorly developed innovations has led venture capital investors to retreat to later stages of R&D. While this is also true in the United States, the venture capital sector in Europe is more nascent and as such, European venture capital investors tend to be more risk-averse (George et al, 2007).

Public funding for European biotechs interested in AIDS vaccine R&D is scarce. At the European Union regional level, only a little funding for AIDS vaccine R&D is available – and

the amount that reaches biotechs is tiny. In recent years, only 1 in 8 recipients of Europe's transnational research grants were biotechs. Indeed, even the European Commission has acknowledged that its FP6 arrangements lacked adequate incentives for industry participation.

Moreover, since EU grants are based on a co-financing principle, this has acted as a large barrier to biotechs engaging in AIDS vaccine research. This is because the perceived high risks and uncertain market potential mean that biotechs and their venture capital financiers demand close to full-cost coverage to engage in AIDS vaccine R&D, something that cannot be achieved through co-financing.

In the United States, higher levels of public commitment to AIDS vaccine R&D– in 2005, US federal funding of biotechnology was €20.1 billion (US$ 23.2 billion), almost six times as much as the public budget for biotech research in the EU-15 plus Norway, Iceland, and Switzerland, which amounted to €3.4 billion – and greater access to research funds for biotechs have enabled many firms to use public grants for AIDS vaccine research. For instance, one small company, VaxGen, Inc. received a US$2 million grant from the NIH for AIDS vaccine R&D in 2003. This type of public funding for private firms is particularly important for AIDS and other neglected disease technologies for which scientific risks are high and market opportunities uncertain.

Table 1

Total venture-capital investments in biotechnology, 2001 to 2003 (OECD, 2006)

Country	Investments (Millions of US Dollars)	Percentage
United States	9526	74.4%
Germany	769	6.0%
Canada	721	5.6%
United Kingdom	502	3.9%
Sweden	323	2.5%
France	302	2.4%
Denmark	159	1.2%
Netherlands	127	1.0%
Belgium	124	1.0%
Switzerland	98	0.8%
Norway	74	0.6%
Finland	29	0.2%
Italy	23	0.2%
Spain	14	0.1%
Austria	6	0.0%
Ireland	3	0.0%
Iceland	2	0.0%
Portugal	1	0.0%
Czech Republic	1	0.0%
Poland	1	0.0%
TOTAL	12805	100.0%

What does all of this mean for biomedical R&D in Europe? Many factors are to blame for the lack of public and private sector backing for translational research – a "translational gap":

- Budgets for public researchers are too small, decentralised and fragmented – and disappear too early in the R&D continuum.
- Pressure on universities to manage intellectual property as a revenue source limits researchers' interest in translational research activities.
- Public and private funding for biotechs and translational research is scarce.

While this translational gap may hamstring biomedical R&D in general (Figure 3), the gap is widest for AIDS vaccine research. Investigators dedicated to the AIDS vaccine field must contend not only with significant scientific obstacles, but also with the possibility that they will spend their careers working on a series of non-product discoveries. Even the prospect of developing a promising AIDS vaccine carries risks – since the market potential for such a vaccine is still considered uncertain.

What can be done to improve the situation for European biotechs?

Many of the traditional push-and-pull incentives designed to encourage biotech and large biopharmaceutical firm research (such as tax credits or market commitments) likely won't work to bridge the translational gap or stimulate private sector AIDS vaccine R&D. These mechanisms may make AIDS vaccine R&D a slightly more attractive investment proposition and therefore have some positive effect, but only at the margins.

Given the scientific challenges AIDS poses and the consequent need for radical new research concepts in investigating AIDS, standard approaches

simply don't apply. To extend new research opportunities to European biotechs, steps must be taken to tackle the troubles public researchers now face. The core challenge, after all, is that Europe's system for stimulating biomedical innovation is both underfunded and undermanaged. These challenges could be addressed through a number of strategies that fall into two areas:

1. Improving funding flows

- ***Larger budgets and longer-term grants for public labs***: Centralising and sustaining funding for health R&D could help public sector researchers develop their ideas to maturity – and *then* refer them to the private sector.

- ***Funding public-private partnerships***: Encouraging collaborative translational research partnerships could create a critical mass of expertise and skills. Bringing together innovators and entrepreneurs could offer an alternative to relying on inexperienced and under-funded TTOs that often labour in vain to propel ideas from the academy to the market. Examples of funding mechanisms that emphasise university-biotech collaboration already exist in Europe (e.g., the Danish National Advanced Technology Foundation). Governments and funders should examine these models and extend them to AIDS vaccine work.

- ***Public funding for biotechs***: More public funding for biotechs, specifically to promote later stage research for AIDS vaccines, could help alleviate Europe's translational gap.

2. Strengthening dedicated R&D infrastructure for AIDS vaccine translational research in Europe

Public institutions that already excel in vaccine and infectious disease research should receive more funding to create a critical mass of resources. That move will ensure public research efforts can be pursued until they are ready for out-licensing to the private sector.

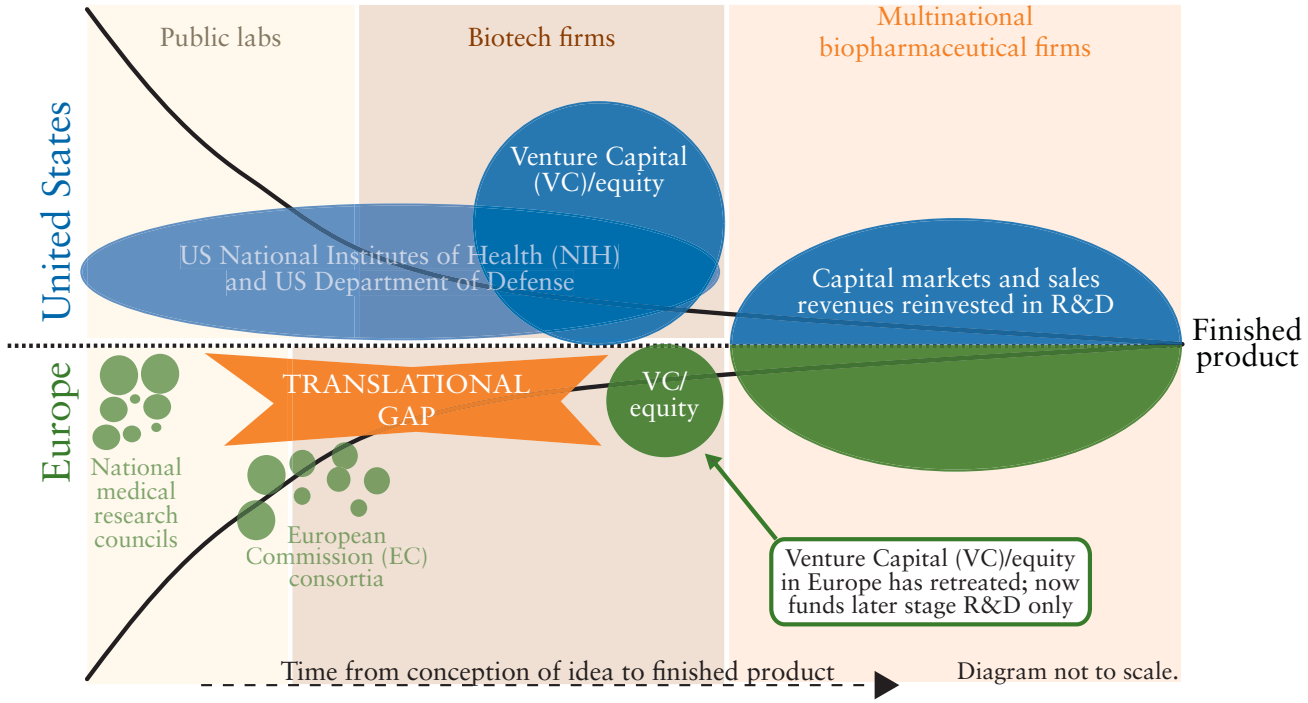
These proposals offer the first steps toward jump-starting innovation flow in Europe. But they also raise some critical questions that demand thought and conversation. For example:

- What is the appropriate scale of these suggested solutions? How much research funding is really required?

- How should these monies be invested? Which institutions should receive the additional funds?

Figure 3

The funding gap for translational research in Europe



- What is the optimum balance of resources that should be dedicated to AIDS vaccine R&D relative to other research priorities?

Answering these questions and implementing solutions will require a careful assessment of local institutions, their performance capacity, and the environment in which they operate. Identifying appropriate stakeholders and decision makers will be as challenging as it is essential.

Readying Europe's scientists to face the greatest public-health challenge of our age will entail tackling many tough questions. It will also oblige all players to assume responsibility for ensuring wise use of resources and wise coordination of research efforts across Europe and throughout the rest of the world. Groups such as the Global HIV Vaccine Enterprise are already working to rationalise scientific plans and keep watch over the vast AIDS vaccine field. They may be well placed to assist Europe as it begins to accelerate the region's research engine, in collaboration with national medical research councils, the European Commission, and other funding agencies.

Europe as part of the global effort: Reasons for hope

Despite the funding inefficiencies with which they struggle, European researchers have managed to pursue their work by tapping a number of international funding streams. These include the Center for HIV-AIDS Vaccine Immunology (CHAVI) and the Collaboration for AIDS Vaccine Discovery (CAVD). CHAVI is a worldwide consortium of 39 universities and medical-research centres, seven of which are European. The CAVD is an international network of discovery consortia, central laboratories, and data analysis facilities that includes organisations from 10 European countries (CAVD, 2008). In addition, five of the 16 primary investigators in the CAVD are Europeans.

CHAVI, the CAVD, and other groups deserve credit for starting a new surge of basic and applied research across the globe – all funded by public-sector money. The groups are willing and welcome grant sources for Europe's researchers. However, few biotechnology firms have taken part in these initiatives, with only one European biotech company and a handful of contract research organisations taking part in the CAVD consortia.

That means international funding for biotechs and for purely translational research endeavours may remain scarce. Even so, there is hope that these AIDS research networks may help generate necessary non-product discoveries, answering fundamental questions now impeding AIDS vaccine development. Over the long term, these massive enterprises could open many avenues for biotechs.

The European Union remains committed to AIDS vaccine research as well, having committed €6.5 billion in health-related R&D between 2007 and 2013 through its newest Framework Programme (FP7). This funding includes a focus on biotechnology, targeting high-throughput technologies that might facilitate AIDS vaccine R&D. Importantly, FP7 responds to earlier criticism that required co-financing discouraged biotech involvement in AIDS vaccine R&D by improving grant terms with lower levels of co-funding (European Commission, 2006b). Additionally, FP7 focuses specifically on translational research in infectious diseases, which should ease the translational gap in Europe. However, given the continued requirement of at least three partners from three countries, it remains to be seen how effective FP7 funds can be in supporting AIDS vaccine research.

Other initiatives also look hopeful. A relatively new class of organisation – the product-development partnership (PDP) – could help Europe in the search for an AIDS vaccine. Neither public nor corporate in identity, PDPs are R&D partnerships designed solely to develop much-needed products , and can act as funding intermediaries to channel funds from donors to researchers. IAVI essentially plays this role for AIDS vaccine research and disburses about US$ 5 million a year to research ventures in Europe.

But even as worldwide networks and hybrid partnerships appear to speed up the race for an AIDS vaccine, Europe's researchers may not be able to engage in the global effort at an optimal level. Despite an EU health budget promising new R&D money, AIDS vaccine investigators remain stymied by the translational gap. Scientific and political stakeholders alike must seek to overcome this gap, strengthening the ability of public sector researchers to transfer innovations to private developers, and encouraging collaboration among innovators of all kinds. Given the level of scientific expertise, the capacity, and political will in the region, promising opportunities exist across Europe to achieve these goals, and to maximise the region's contributions to the global search for an AIDS vaccine.

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IAVI's policy brief series outlines key public policy issues in the research, development, and eventual distribution of AIDS vaccines.

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