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What gives me hope is the incredible progress in the scientific tools at our disposal and our understanding of what we are after

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Founded in 1996 to coordinate and promote HIV vaccine development, IAVI has had a major impact across HIV vaccine development efforts, capacity building in low- and middle-income countries, advocacy work, and access initiatives. While there have been several high-profile late-stage failures in HIV vaccine candidate trials, IAVI scientists like Johan Vekemans have not given up hope. In conversation with PharmaBoardroom, Vekemans outlines how the germline targeting approach to HIV vaccines could generate broadly neutralising antibodies in humans, thus potentially paving the way to the effective HIV vaccine that has eluded science for over 40 years.

Could you give us a brief history of your work in the HIV field?

I am a paediatrician and epidemiologist by training. Over 20 years ago, I got my PhD doing immunological research at the Medical Research Council Unit The Gambia / London School of Hygiene & Tropical Medicine, where I also did clinical work. I then worked on the development of a malaria vaccine at GSK for ten years, from early Phase II trials all the way up to late Phase III and submission to the European regulatory authorities.

Following that, I spent five years at the World Health Organization (WHO) where I worked on vaccine R&D across several disease areas. Then, during the COVID-19 pandemic I took on the role of Global Clinical Head at AstraZeneca with responsibility for the COVID vaccine developed in

collaboration with Oxford University and the Serum Institute of India.

I have now spent two years with IAVI coordinating HIV vaccine efforts with a particular focus on the germline targeting strategy.

I have always been driven and motivated by making a difference for vulnerable populations and have maintained my interest in paediatrics and global health issues throughout my work on vaccine development.

IAVI was founded 20 years ago, what were its original aims?

IAVI was founded in 1996 with the objective of coordinating and promoting HIV vaccine development. At that point, it was clear that the classical approaches to support vaccine development, in terms of business model and collaborative partnership, were not going to do the job. There was a need for a dedicated institution to coordinate the efforts.

Why were the classical approaches to vaccine development not suitable for HIV? What is it about this disease that necessitates an alternative approach?

A lot of it has to do with scientific complexity, which has knock-on effects on funding strategies. The last 30 years have been marked by continuous learning about how complicated an undertaking a HIV vaccine is and, unfortunately, we have still not been able to bring a vaccine all the way to patients. We *have* learned a lot in the process and there have been a lot of lateral benefits in terms of just scientific progress, and how we do vaccine R&D beyond HIV. But, having worked in other areas, I can say the scientific complexity of HIV is huge and beats them all.

HIV has shown itself to be an incredible champion in terms of its ability to harbour mechanisms that resist immunity. Over the last four years there has been a lot of talk about the viral diversity of COVID-19 and how mutations can lead to new waves of infections, but the viral diversity of HIV is far higher and thus the disease is more complex to target.

The HIV envelope protein, which is the target of many of the vaccine approaches, is covered by a ‘glycan shield,’ sugars hanging around the protein that hide it from the immune system. There *are* immunogenic areas of the protein that are displayed and accessible to the immune system, but the responses targeting these areas of the protein are not protective. Additionally, the HIV virus can rapidly hide within cells. Moreover, its DNA can integrate with human DNA, become latent and then

reactivate later.

What are some of the most promising current approaches to HIV vaccine R&D that might finally lead to a breakthrough?

Unfortunately, many of the late-stage evaluations undertaken in the last few years led to negative results, finding that there was no significant protection. There was one approach that provided some breakthroughs and some signals of protection, but not sufficient to warrant its continuation.

Today, there is a broad consensus in the field now on the need to generate ‘broadly neutralising antibodies.’ Most vaccines against viruses work by inducing neutralising antibodies, but in the context of a hugely virally diverse disease like HIV, these neutralising antibodies need to be *broadly* protective. Broadly neutralising antibodies have been shown to develop, in a small minority of people living with HIV after long chronic infections.

IAVI scientists, along with researchers at other institutions, have played an important role in characterising the biological mechanisms that lead to the expression of these broadly neutralising antibodies in people living with chronic HIV infections. It is really a story of an infection that generates a certain immune response and then a continuous back and forth of immune control and viral escape. This drives the differentiation of a specific type of antibody response which leads to the expression of these broadly neutralising antibodies.

The approach involves starting by initiating a relatively narrow antibody response, and then through waves of immune escape and re-stimulation of this same antibody response, the antibody response mechanisms evolve in a way that drives breadth. Because these mechanisms have now been characterised in detail, we are now trying to reproduce that through vaccination. This is being explored via complex, cutting edge and novel techniques built on learnings from genomics, structural biology, and big data analysis. With these techniques, we are looking to come up with immunogen design aimed to activate the right type of immune response; i.e., that engages the right type of immune cells and then drives them towards a differentiation pathway that will lead to production of broadly neutralizing antibodies.

There has been a move away from empirical immune strategies where the immune system is shown something of the virus in the hope that it is going to generate a protective response. Now we are looking towards intelligent design vaccine strategy, building on structural biology knowledge and the knowledge of the conformation and sequence of the proteins to generate these

complex responses. The good thing is that all along the way, we can follow the response and see whether vaccination with those specific immunogens is doing what we expect it to do.

Another positive is that there are very good animal models – primarily mice and non-human primates – have been developed for this assessment and can be used to test various approaches.

It is important to note that we think we are going to need to target several epitopes on the HIV envelope viral protein and generate several classes of broadly neutralising antibodies to cover the spectrum of viral diversity. We are trying to generate complex immune schedules that will deliver several different immunogens in sequence, combined to target several target epitopes on the HIV protein.

This approach, known as germline targeting, is one of the mainstream and priority approaches that the field is contemplating but there are others that also aim to generate broadly neutralising antibodies. Additionally, there are a few other approaches that aim to induce other types of protective immune responses, including T-cell vaccines and live attenuated viral constructs.

How far along the R&D pathway are these new approaches to HIV vaccines?

Most of the approaches are now in the translational medicine space, with early human investigations targeting some sort of biological proof of concept. We know what we are after, those strategies are aimed at inducing broadly neutralising antibodies. Once we get there, if there is an immunization regimen worthy of late-stage testing, that has the potential to eventually be implemented, it will then be appropriate to move to classical Phase II and III clinical trials. We are currently in the discovery medicine trials stage which involves back-and-forth evaluation between small-scale exploratory investigations in humans and iterative testing in animals.

Why do we still need a HIV vaccine, given the epidemic control that existing treatments could potentially achieve and the long history of HIV vaccine R&D failures?

We need to acknowledge that important progress has been made, which is good news.

However, the facts are that in 2022 there were 630,000 HIV-related deaths and 1.3 million new HIV infections. Even though the global trend is towards a diminution of HIV-related deaths and new infections, this is not the case in all world regions. There is still a very high disease burden in Sub-Saharan Africa, where adolescent girls and young women account for a disproportionate number of

new infections. HIV remains, together with TB, the leading cause of disease burden due to infectious diseases. We are not at all at a place where we can be complacent and think that the job is done.

The new interventions have the potential to have an important impact on the epidemic and reduce the number of new infections, but unfortunately, it is unlikely that these products really fit the needs of all world regions. Some of these interventions may be more adapted to specific populations. For instance, preventive treatment-based therapies like PrEP, even the long-acting PrEP which is hopefully going to become available soon, may not fit the product characteristics needed for all epidemiological settings.

Long-acting, neutralising monoclonal antibodies could also play a role in controlling the epidemic, but are also unlikely to fit the needs of all populations. Therefore, there is broad consensus that only a vaccine would really bring us to the goal of eliminating HIV as a global health problem. The other strategies need continued investments and continued health-seeking, and that is just not a very sustainable model.

Developing a HIV vaccine is one thing, but if and when we eventually get a product, manufacturing it, distributing it, and implementing it is quite another. How much do downstream questions of eventual implementation, access and affordability play into your work at IAVI?

It is clear that vaccine development requires at least some degree of an end-to-end perspective. From the offset, we need to have a vision of where the research will eventually lead and none of these questions are trivial. Concepts such as community engagement, understanding demand, public health need, user preference, product characteristics, implementability, are vital to consider.

However, these concepts should not prevent us from undertaking the basic science research that’s going to drive innovation. Naturally, some of these questions around access and product characteristics become more relevant once the science of a vaccine candidate has been established, but no fixed vision should prevent us from doing the science that is going to help us get there.

These considerations are part of what drives the critical need for partnerships. Most of IAVI’s vaccine development efforts are being conducted within multi-institutional partnerships with support from public funders, philanthropic organisations, and private sector actors, leveraging the

know-how, expertise and resources of all partners.

Partnerships are ultimately necessary for successful product development. And in that context, IAVI has worked really hard on building collaborative partnerships that enable vaccine R&D efforts. One of them is a recent collaborative multi-institutional partnership aimed at delivering a germline targeting HIV vaccine, bringing together IAVI, the Bill and Melinda Gates Foundation, the NIH Division of AIDS, the HIV Vaccine Trial Network, USAID, Scripps Research, and Moderna. This complex vaccine R&D project necessitates iterative testing of multiple immunogens and the mRNA technology that this project uses holds significant promise in this aspect as it is quite amenable to flexible access to immunogens which can help speed up the process. All of that being said, these initiatives always take some time to come to fruition.

Many pharma companies have divested or wound down their HIV R&D projects in recent years. Given your experiences within and outside the industry, as well as some of the unique characteristics, of HIV as a disease and as a market, what role do you hope that pharma can play in developing a HIV vaccine? What are they bringing to the table in terms of these partnerships?

They bring a lot to the table, including their manufacturing platforms, a lot of expertise, and sometimes also resources. This means that part of these efforts relies on being able to engage the industry and come up with models that support their involvement. We must ensure that there is a common vision about where the program is headed and align on priorities and strategies. With that, there is a better chance of progress and potentially ultimately coming up with a product.

There are also a lot of opportunities for pharma to learn a lot about the science and impact global health, which is tied to the notion that complying with corporate social responsibility has value. That was certainly the case in my own experience. I worked on a malaria vaccine development effort that was instrumental in progressing the discovery of novel adjuvants. It went all the way for the malaria vaccine to be successfully now recommended and implemented. I also worked on the AstraZeneca/University of Oxford COVID-19 vaccine effort, which brought a new live attenuated vaccine platform onto the map.

On a personal level, is it challenging to stay positive while working in the vaccine development field, given the daunting timelines and multiple failures involved?

I had the privilege of having worked on one vaccine that made it to being implemented after more than 30 years of development and another that took about one year. Vaccine R&D requires an understanding that there can be failures, but resilience is crucial as it is ultimately worth the effort.

There is a sense of urgency, and we would all like things to progress more quickly, but diseases like malaria and TB have been with humanity for thousands of years. We can be frustrated that we have not made more progress in the HIV vaccine field, but HIV is about 40 years old – a long time in an individual's lifespan but a speck on the timeline of humanity. We should be resilient and understand that we need to put the building blocks for these efforts. It could take some time, but we are making progress, both in terms of scientific concepts and developing tools and platforms that have the potential to get us there.

How many years are we from having a HIV vaccine and, if we are still some way away from it, what gives you the most cause for optimism in your work?

It is very difficult to say how many years we are from a HIV vaccine. The most important thing is the setup of successful partnerships with an alignment in strategy and vision, ongoing support for them without complacency or discouragement, and continued investment in them. We hope that – for the new generation of broadly neutralising antibody-generating HIV vaccines coming through – we could have a biological proof of concept in animal models this year or next year. A human proof of concept would then follow in the next few years, and then a demonstration of the prevention of HIV infection a few years after that. We still have a way to go, but we clearly know what to do.

What gives me hope is the incredible progress in the scientific tools at our disposal and our understanding of what we are after. There has been tremendous progress in our ability to understand protection and that drives our vaccine R&D strategies. Additionally, what gives me a lot of resilience and courage is the understanding of what our work could mean for those living under threat of these terrible diseases, such as the disproportionate number of adolescent girls and young women who account for new infections.

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