

RECAP with the RBDCOV Community Advisory Panel | Why not HIV? A comparison between mRNA vaccine research for COVID and HIV

ReCAP is a series of interviews with the members of the RBDCOV Community Advisory Panel that will explore the world of community engagement in EU projects and the importance of including people living with immunocompromising conditions in clinical trials. Our guests for this second interview are Beatriz Mothe Pujadas, Infectious Diseases Physician and Research Scientist at IrsiCaixa acting as Principal Investigator of the HH-4 clinical trial in people with immunosuppressive conditions and Deniz Uyanık, EATG member and member of the Community Advisory Panel for the RBDCOV project.

Let's read this interesting conversation about mRNA vaccine research for COVID and HIV, its differences and similarities with our two guests. Thanks to Beatriz and Deniz for having accepted this interview invitation and for sharing their expertise and knowledge with us. Let's get started!

DENIZ

Hi Bea, it is great to be here with you. Allow me to ask the first question. The mRNA vaccine technology has demonstrated success in COVID-19 prevention. **What primary approaches are being explored in HIV vaccine research, and how do they compare to the strategies employed in COVID-19 vaccine development?**

BEATRIZ

Let's start by saying that the HIV and the SARS-CoV-2 viruses are two completely different viruses. We knew a lot about the immunology of SARS-CoV-2 from other coronavirus disease like MERS and SARS. In that sense, it was easier to develop vaccines for COVID because we already knew that antibodies against one of the proteins of the surface of the virus could protect from infection and disease. And there were existing vaccine candidates aimed at triggering immune responses against that spike protein, supported by pre-clinical data (data from animal studies). When SARS-CoV-2 and COVID appeared, scientists incorporated the genetic information of the spike protein into a vector platform to start vaccine production, which proved successful. And this is totally the opposite for HIV. The antibodies against the envelope proteins (proteins in the surface of the HIV virions) are not protective. Only very, very few antibodies, which are called broadly neutralising antibodies (bNAbs), help to protect against HIV infection. Another variable is the structural difference of SARS-CoV-2 and HIV as viruses.

However, mRNA technology is not new and has been used before especially in cancer research. Many immunotherapies for cancer have been utilising mRNA technology during the early clinical trial phases. It was the perfect situation because we already had the technology that could be used for that purpose. The mRNA technology is very flexible because it is easy to produce. Once you

have the gene information, you can use that gene code to generate mRNA, which in turn produces a specific protein. Production of big quantities of mRNA is relatively easy and this is also what helped to develop the vaccine for COVID-19 so fast.

mRNA technology is now being used in HIV vaccine development. The HIV vaccine field is investigating an approach called “*germline-targeting*”, where we want to stimulate our B cells, which are part of the immune system responsible for producing antibodies, through sequential vaccinations, and train or mature them so they could be able to produce the body’s broadly neutralising antibodies. This means that, unlike COVID-19, HIV vaccine development requires sequential vaccination to mature B cells and also, because HIV is highly changeable. When you consider a vaccine strategy that needs numerous vaccinations, mRNA technology could be very useful due to its flexibility in design and rapid development capability.

The germline-targeting strategy is already being tested through the International AIDS Vaccine Initiative (IAVI). They are already conducting Phase I clinical trials, focusing on safety and immunogenicity of the vaccine. We will see. Recently, there was a commentary in a scientific journal, followed by a [press release from IAVI](#) about the first results on safety and they apparently are quite immunogenic. There were some local reactions (reactions that occur at the area of injection, e.g. the upper arm), nothing severe, but there were reactions. If you remember, this was also the case for some of the first COVID-19 vaccines. Probably, it is an issue of the dosing level of the mRNA. Once you produce it, you need to stabilise it in a solution and sometimes, those products used can cause different local reactions when injected. It requires a bit of adjustment of the doses.

I think mRNA technology is going to be useful also for HIV vaccine development. But we should not forget that the mRNA technology is just the vector, the vehicle that we are using for putting the immunogen in our body. And, for HIV, the challenging part is the immunogen, not the vector. It is about how we stimulate our body to produce those antibodies that are going to be protective against HIV acquisition. So, it is going to help, but it is not going to be the solution for the HIV vaccine.

DENIZ

Thanks a lot, Bea. I am not a scientist, but from what I understand, I think the issue with HIV is that there are a lot of variants of the HIV virus, right? **Is there a limit for mRNA vaccines? I mean, how many versions of viruses can you encode in this mRNA?**

BEATRIZ

We will need to combine probably at least two or three different compounds. Now, in the clinical trials that are ongoing, they are only using one compound, because first, we need to demonstrate that, with this sequential vaccination approach, we are able to induce the production of at least one broadly neutralising antibody. For HIV, we are not working with live or full viruses. Instead, we are using an insert that targets the induction of broadly neutralising antibodies. Although these antibodies are termed “broad,” they are not as broad as we would like.

What science is telling us so far is that probably, like with antiretroviral treatment, we will need a combination from two or three antiretroviral drugs from different families. For an HIV vaccine to be protective and potentially cover the many strains and subtypes of HIV, it is likely that we will need antibodies targeting at least two or three different epitopes, which are like little “flags” on the surface of the HIV virus that the immune system can recognise in order to know to start the defence process. If we succeed in demonstrating that it works for one epitope, then we could replicate it for different epitopes and eventually combine them. Once we establish a strategy, we can mature the B cells capable of producing these broadly neutralizing antibodies and repeat this process for a second and third epitope. Eventually, when we have the various combinations, we might need one “cocktail” for a specific region and another for another region to address the diverse variants globally.

DENIZ

Thank you for your answer. May I also ask you **what is needed to develop a therapeutic HIV vaccine and what is needed for a COVID-19 vaccine?**

BEATRIZ

HIV vaccines are different from COVID-19 vaccines. For prevention, HIV vaccines focus lies more on antibodies to block acquisition. These antibodies target the virus, blocking and limiting its ability to infect new cells. On the other hand, for therapeutic HIV vaccines, we are dealing with cells that are already infected. For a therapeutic vaccine, or for a cure strategy, what we need is to try either to significantly reduce the amount of those infected cells, which would mean reducing the *viral reservoir*, or boosting our immune system to be able to control the virus once the antiretroviral treatment is suspended.

We usually talk about a **humoral response**, which is the response of antibodies, and an **adaptive response**, which is the response of T cells. T cells are white blood cells that go through our system and detect when a cell is infected and try to eliminate it. And the immune boosting I was referring to mostly relies on the T cell response rather than on the response of antibodies. Therapeutic vaccines are designed to boost our immune response, aiding in the more effective elimination of infected cells. Initially, T cells are active during acute infection (where the infection of cells occurs rapidly), but their efficiency diminishes over time as the virus evolves to escape the immune system. For a therapeutic vaccine, we would need something that enhances the T cell function to detect and eliminate infected cells that have evolved to escape the immune response. We need to reverse the immune damage caused by HIV.

In the therapeutic vaccine field, insights from oncology are being very valuable. Immunotherapies in oncology focus on reversing the immune exhaustion that impairs the immune system’s ability to eliminate tumour cells. These approaches could also benefit the HIV therapeutic field by rejuvenating T cells to efficiently target infected cells. Additionally, therapeutic vaccines may need to be combined with agents that activate the virus from its more latent and dormant viral reservoir. Reactivating dormant infected cells alerts the immune system, enabling it to recognise and eliminate them. This is another big challenge for cure research because we need to

understand from biology how to reactivate those infected cells. And we need to learn from the immunology and cancer fields how we reinvigorate our immune system.

However, I must say, progress for a therapeutic vaccine has been more significant than for an HIV preventive vaccine. Some T-cell vaccine candidates have shown not only safety but also high immunogenicity, generating good T-cell responses capable of partially controlling the virus without treatment. Combining these vaccines with strategies to address the viral reservoir could bring us closer to achieving a functional cure or inducing durable, treatment-free remission for people living with HIV. This would represent a significant step forward in HIV treatment.

DENIZ

So, do you have hope?

BEATRIZ

I do have hope. This is my area of expertise, and I am sure that before I retire, there will be something for my patients. I am completely hopeful.

DENIZ

And is there any indication about the timing of when this could happen?

BEATRIZ

That is a difficult question that I hear all the time... Science progresses step by step; it is not as if we have a brilliant idea now that we know will work, and we can make an estimated timeline for development, production, and marketing. No, we are still at the initial stages, waiting to see if the first step proves successful before moving onto the next. That is the challenge. We cannot predict when we will have something that works. If what we are trying now works, perhaps we will have something in 5 to 10 years. But if not, we may need to all start over.

What I am certain of is that mRNA technology will be integral to the various candidates we are testing. It is proven safe through COVID vaccine development, we understood how it works and we are reassured about its safety and efficacy. This will streamline the iterative process of vaccine development, which is a positive sign. Whether we will have a vaccine in five years depends on the effectiveness of sequential vaccination in inducing the desired immune responses. We will have to wait and see.

DENIZ

During the early stages of the COVID-19 pandemic, the work of researchers was crucial. **What challenges do researchers face when addressing COVID-19, and how do these challenges differ from those when addressing HIV? What are the similarities?**

BEATRIZ

Medically, dealing with COVID was incredibly challenging because it progressed so rapidly. After infection, some patients were dying within 10 days. That was truly devastating, especially given the lack of effective treatments. It is so different from HIV, where although diagnosing someone without treatment options was tough in the early years, patients typically lived longer with the virus. Facing the prospect of a patient dying within a week without family support was incredibly difficult. Therefore, medically, COVID presented a unique set of challenges. I think that what happened with COVID is that it evolved so quickly, all over the world at the same time and this also helped a lot to put a lot of resources, which is unfair if we compare it to HIV, right?

In terms of resources, the investment in COVID compared to HIV has been unprecedented. I think we have never seen such an investment for any other disease. Rich countries mobilised significant resources globally due to the immediate threat COVID posed. We were able to perform high-quality research very fast and deliver results. In very few months, we already had antivirals, corticosteroids. We knew how to treat COVID in very few months. The mortality in March 2020 compared to the mortality in October 2020 was already different. It was a six-month gap. That same gap in improvement took years in the HIV field. It is true that the HIV epidemic began in the '80s and the '90s, and nowadays we have much more resources. Probably all the investigation, all the research and knowledge that we have generated for HIV has been very useful for COVID. For example, infrastructures and research, like the HIV Vaccine Trials Network (HVTN), were repurposed for COVID research, and thanks to that, we have been able to go so fast with COVID research.

There are a lot of similarities, but it is also true that SARS-CoV-2 research, compared to HIV, is much easier, to be honest. I do not want you to get the feeling that this is just because it affected rich countries, as they invested a lot. No, HIV is much more difficult as a virus. It is a much bigger scientific challenge than the coronavirus by itself. I mean, if you see the variability, it has nothing to do with each other. But it is true that, well, I think that the COVID pandemic was also fortunate to happen *after* all that we had achieved for HIV. That we had all this knowledge and all these infrastructures in place that could be used and contributed to having better solutions and better vaccines for COVID.

DENIZ

Thank you for that detailed explanation. I also believe that community involvement is crucial in HIV research. **What are your thoughts on the importance of community engagement in vaccine research, particularly concerning the perspectives and experiences of people living with HIV?**

BEATRIZ

I think that the HIV community has been pivotal for all developments in HIV, both for treatment and now for the vaccines as well. If you think about all the HVTN and trials...there's always community involvement. Now, to test the efficacy of therapeutic vaccines, as we do not have biological markers of cure, our participants need to interrupt their treatment for a short period of time, for instance. All this requires a lot of community support because it is not easy to perform these trials and you cannot design and implement trials without having community involved. It is totally critical.

DENIZ

But how can researchers engage and collaborate effectively with people living with HIV, ensuring community voices are heard? Activism was very different in the 80s and 90s compared to now.

BEATRIZ

That is a very good question, and I would probably rely more on your reply. I would love to be able to engage the community more in our studies and in our research. It is true, activism in the '90s was needed to move forward with antiretroviral treatment development and access. And I think that in terms of access, it was actually activism that made the difference.

Now, for cure, for example, there is a debate going on: we hear from some community members that they are less interested in cure research because antiretroviral treatment works perfectly and they have a perfectly healthy life, which is true. And we often hear the same about all the long-acting regimens. Sometimes it is not easy to get community involvement in cure trials because there is less of a feeling of need. We as scientists – and many other community members – still think there is a need for a cure. As a doctor, I do not want to be treating people lifelong. I want to cure them.

For prevention, something similar is happening with PrEP and HIV vaccine research. PrEP trials are being so effective, and now I see a lot of advocacy efforts around pushing for the implementation of PrEP, which is perfect, and I fully support it. But what about vaccines and what about choices? As a scientist, I would like to have a vaccine that I can administer when people are 12 or 13 years old and be protected for life, instead of needing to take medication to prevent HIV. Since we do not have a vaccine yet, PrEP needs to be implemented, it is great that all efforts are directed towards making PrEP available and accessible. But if all community focus is on PrEP implementation, then we lack community involvement in vaccine development. The same applies to cure. Without community, we cannot move forward because we are unaware of your needs.

DENIZ

Thanks a lot for those answers, Bea. They were really insightful!

BEATRIZ

It was my pleasure. Now, I would like to know your opinion. What is the community perspective? How do you think we could engage community more in our research on cure and prevention? What steps should we take, or what are we doing wrong that prevents community and patient engagement?

DENIZ

Patient organisations play a vital role in all HIV-related developments, from daily life to scientific studies. As a member of a community organisation, I would like to say that I expect pharmaceutical companies and researchers to actively involve patient organisations throughout the research

process, share findings openly and take their feedback into account in the development of an HIV vaccine. In addition, patient communities from different cultural backgrounds can provide valuable information about patient experiences and priorities, help develop research protocols, and participate in data collection and discussions on the ethical and social implications of the vaccine. This active collaboration enables researchers to develop a vaccine that is not only effective, but also responsive of the needs of the people it is intended to protect.

BEATRIZ

I totally agree with you here. Thanks a lot for your input! It was a pleasure to talk to you today.

DENIZ

Likewise. It was a really interesting conversation.

Disclaimer: This activity was developed under the RBDCOV Project, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101046118.