JEFFREY BUGULISKIS: Welcome to GENcast, a sponsored podcast series brought to you by *Genetic Engineering and Biotechnology News*. I am your host, Jeff Buguliskis.

By any benchmark, Edward Jenner was an excellent observational scientist and practice clinician, yet it is difficult to imagine that he had any clue he was about to make one of the greatest discoveries in science and medicine just as the 18th century was ending. His observations on milkmaids and cowpox, as well as his subsequent development of an effective smallpox vaccine, spawned the field of immunology and irrevocably altered medical treatments.

Vaccines represent one of the greatest weapons we have in the clinical arsenal, so their continued development is imperative to global public health initiatives, especially for those in poverty-stricken regions of the world.

For instance, the World Health Organization notes that neglected tropical diseases, such as schistosomiasis, a parasitic infection caused by a freshwater worm, affect more than a billion people and cost developing economies

billions of dollars each year. Additionally, in recent years, dozens of countries have reported rapid spikes in Zika infections, which is known to cause serious birth defects with pregnant women carrying the virus.

Vaccine development is critical to help control and potentially even eradicate some of these deadly pathogens. Collaborations between academia, industry, suppliers and government organizations is critical for the successful development of these drugs, and knowledge sharing helps accelerate production timelines, reduce costs and increases the chances of bringing important vaccines to market.

This is where the technical expertise and formal training offered by the M Lab collaboration centers at MilliporeSigma is helping support successful vaccine development. In this podcast, I had the privilege of discussing some current vaccine development projects with an array of scientists and technical experts. Let us meet our podcast panel and find out how Edward Jenner's legacy is continuing to help those in dire need.

BART FRYSZCZYN: My name is Bart Fryszczyn. [00:01:56]. I am a process development scientist.

LUCIANA LEITE: Hello. I am Luciana Leiti. [00:01:59]. I am from the laboratory of vaccine development at Instituto Butantan in Brazil.

MARIA ELENA BOTTAZZI: Hello. My name is Maria Elena Bottazzi. I am the Codirector of Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine in Houston, Texas.

ZHUYUN LIU: Hello. This is Zhuyun. I am the Director of Process Development at Texas Children's Hospital Vaccine Center, Development Center with Baylor College of Medicine.

VICTOR ABRAMANT: Hi. I am Victor Abramant [00:02:27], and I am a process development scientist based in Brazil.

JEFFREY BUGULISKIS: Excellent. So we are just going to get into the first question, and we will begin. We have all seen recent news headlines about emerging infectious diseases on the rise to epidemic levels in underdeveloped regions. Additionally, these and many other areas of the world face the challenge of preventing and treating infectious diseases that are either persistent or that can

spread quickly. How are your teams working to solve these problems?

LUCIANA LEITI: Well, here at Instituto Butantan, we have tackled a few emerging infectious diseases that come from time to time. We have been working for some time now with dengue vaccine. It is a collaboration with NIH, and we are at the time finishing a phase 3 clinical trial.

But we have recently also worked on the Zika vaccine, which we had a recent epidemic, which now has gone. But we continue working on it. Butantan worked on an inactivated vaccine for some time, and it continues to work on it, although it is a lower priority.

We also worked with other vaccines that are neglected tropical diseases, such as the schistosomal vaccine, which we have had a previous collaboration with the Baylor group, and we continue to work on it, working with functional genomics and looking for other vaccine candidates, and it is an important project that we have worked for some time. And it is a persistent disease, and it is an important project that goes on.

MARIA ELENA BOTTAZZI: Thank you. So, in addition to emerging diseases of importance, there are also infections

that are primarily caused by parasitic worms, which certainly are highly persistent and chronic, causing huge burdens of morbidity, disease and mortality. But they also afflict billions of people globally.

So Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine is a nonprofit academic-based product development partnership, which leads the development and testing of low-cost and effective vaccines against these neglected and persistent tropical diseases.

So, for example, one of the diseases that our vaccine center focuses is schistosomiasis. The schistosome parasite is a snail-transmitted, waterborne worm that is found in freshwater bodies in tropical ecologies, but most of which are either in low- or middle-income countries, such as, you know, Brazil, as we heard, and other sub-Saharan countries.

We know that there is an estimated 250 million people infected, particularly of importance in children and women of reproductive age. And if we looked even deeper, according to global burden of disease studies, in some

African countries, approximately half of the population is infected.

So this disease is quite important, as you see globally, because it reduces the individual's productivity and quality of life due to its chronic complications of just having the infection, but also because it causes malnutrition, inflammation and pain. So, for example, sequelae like renal failure or other complications in pregnancy can be of high importance.

We do have a current drug, praziquantel, but this drug cannot really prevent reinfection and does not have any direct effects on the eggs of the parasite, nor causes a reduction of the pathology which is associated with its chronicity.

So this is why there is a very urgent and very critical need to develop preventive measures such as vaccines that would serve in a role of an important technology to reduce the burden of these chronic and persistent diseases, such as, in this case, schistosomiasis.

So for our schistosomiasis program, we focus on targeting a protein from the worm's outer surface, which is

also called a tegument in the worm. And we specifically wanted to see if we could express a -- synthetically genetically engineer this protein, and we wanted to use a modified yeast expression system to produce it, scale it and utilize it as a potential vaccine target.

And we really needed to initially do a very rapid production process that would be certainly suitable for testing in the first phases of clinical testing. But clearly, this would eventually need to have much more improvements, further optimizations and advanced product development for us to be able to be suitable for transferring this into industrial production or certainly a vaccine manufacturer, such as Instituto Butantan in Brazil.

JEFFREY BUGULISKIS: So what challenges were you facing that led you to collaborate with MilliporeSigma to solve it?

MARIA ELENA BOTTAZZI: So in our case, for Texas Children's Hospital Center for Vaccine Development, I am going to actually introduce my Director of Process Development, and she will give you a brief of how our collaboration with the M Labs were designed.

ZHUYUN LIU: It is Zhuyun. So there were two major process development challenges we were facing for the production of our recombinant protein-based schistosomiasis vaccine. Firstly, we had efficiency issue. We had low protein recovery rate of only 31% after a three-step purifications process. And the second challenge we have is scalability issue. So the microfiltration method we use for yeast culture clarification was not very reliable when scaling up. And these challenges led us to seek further support and collaboration with the experts in the industry.

LUCIANA LEITI: Butantan has worked for a long time with MilliporeSigma, since the time of the renovation of the production facilities. They were a big support for changing the process, for scaling up, for turning them into GMP. And Butantan relied strongly on these companies to update the process and increase the quality and the production levels of the vaccines and the immunobiologicals at Butantan.

The latest challenge that came up now is for the scaleup of the dengue vaccine. We have produced in GMP the vaccine for phase 1, for phase 2 and for phase 3. But the production for an industrial phase and for all of Brazil

and maybe more will be another step which would benefit from the expertise of a big industrial company.

And so we think that this would be very important to be able to establish a robust process and to be able to get this process, producing with good yields and good process with high quality, and it will be very important to have the expertise of these companies to get this going well.

In the laboratory, we also work on several vaccine developments, and we developed several products in the bench scale, and we have to do the scaleup from bench scale to pilot scale, and we count on the support of these companies to be able to go forward with all of our products in development.

JEFFREY BUGULISKIS: So I want to throw the conversation over to Bar and Victor now, who represent the M Lab Collaboration Center global network of expertise. Can you both talk about your roles and how you address the challenges brought to you by Butantan Institute and the Texas Children's Hospital?

VICTOR ABRAMANT: So, as a part of the M Lab Collaboration Center, I see that the idea of an M Lab Collaboration Center helps to empower this change with

customers, and following the three pillars of learn, explore and collaborate.

The experience enhances their capacities and our idea of showing proper use, specific products or understand their needs and try to give them a sense of how to work at a GMP facility. And most of the case, they are in good shape with their bench scale.

And the idea of a linear dimensioning or linear scaleup with some provider helping the customer, it is really a key point to the relationship. So being a part of this step by step with customers, help them develop their process and reaching their yields and goals.

So the main idea of use, the Collaboration Center is to bring customers and definitely try to increase their knowledge in terms of employees that are working at the facility level and explaining the difference between GMP and GLP. So this relationship is a key point to us.

BART FRYSZCZYN: So, as a process development scientist, I am part of a larger group of scientists and engineers that are based globally. Not everybody has access to the M Lab or is able to travel to one. So we basically act like an extension of an M Lab.

We bring probably combined hundreds of years of experience in bioprocess to our customers wherever they might need it. So we generally work with them on the early- to late-phase process to improve them, redesign them and also show them and educate them how to use our technologies.

It is very important to emphasize the global aspect of the technology management organization. So we can develop a process in one geography, work to transfer it to another one and support the manufacturing at yet a completely different geography.

MARIA ELENA BOTTAZZI: Thank you. So I am going to let Zhuyun Liu to also provide an example from the work that we have been doing with Bar [?] and as part of the M Lab extension program.

ZHUYUN LIU: With the opportunity to work with Bar [?] as part of the M Lab extension program, together we review in detail the production process, identify the purification steps that caused a major yield loss, and redesign the protocols. And more than just consultation, Bar [?] actually came to our lab with the state of our equipment

and developed the protocols with us and showed us how to run the experiments.

So we designed a new cascade tangential flow filtration system based on the Prostak and Pellicon technologies for yeast culture clarification and ultrafiltration. And with this new design TFF system, we could increase the product recovery rate from 31% to 42%, which means 36% increase of the final drug substance.

And in the meantime, the processing time and biofilm consumption and also the filtration membrane costs were also reduced, and which we translate to a 36% of production cost saving.

LUCIANA LEITI [?]: In terms of collaborations, what we feel is that research development production nowadays are extremely multidisciplinary shields. A successful vaccine development or product development, we cannot see that it will ever occur without a lot of collaboration from highly specialized experts in different fields to be able to get a product from the bench through all of the development phases -- scaleup, clinical trials, regulatory, GMP -- to be able to get the product to the population. So collaboration is essential.

BART FRYSZCZYN: I just want to say that I really agree with what has been said. Bringing a molecule to the clinic is really a major effort, and it requires basically multiple teams of highly qualified individuals to be successful. So we were happy to work with Texas Children's Vaccine Institute to kind of bridge that gap from bench up to GMP manufacturing and, you know, bring this lifesaving vaccine to potential patients.

MARIA ELENA BOTTAZZI: I also totally agree with the comments from Dr. Leiti and also Victor and Bar [?]. And especially for these persisting, neglected and emerging infections, we do have some major technical and scientist hurdles that we need to tackle, and we really need to have an urgent shift of the paradigm of how we have this blueprint for the development of leading to sustainability, acceleration and, more importantly, to have access of these new interventions to the communities in need.

So I totally concur that, without having strong, transparent, reliable and sustainable collaborations between not only industry, academia, but governmental institutions, such as, for instance, the vaccine manufacturing networks in Brazil and other countries, that

we would not be able to successfully advance these very important products that could really help in the health of the globe.

VICTOR ABRAMANT: And also, we have a vaccine process development team which discusses deeply about all the process and all the trials that we have been running for different types of vaccines. So this increased our capacity and give a capillarity in terms of information and how to approach some different vaccine or some similar vaccine and try to avoid a waste of time in this really important step of the process of the development.

JEFFREY BUGULISKIS: So we have got our last question, which -- you guys touched on some of this already, but how do collaborations between different institutions -- say, industry, academia or government -- play such a critical role in successful vaccine development?

MARIA ELENA BOTTAZZI: So let me give you an example of how collaborations with different institutions help. As we had been discussing, the challenges and certainly the hurdles are enormous, especially for neglected and emerging and even some of the rare diseases that afflict many people around the world.

So, for that, you need to start learning how to develop much stronger business cases, evaluate better the demand forecasts, increase certainly the engagement with not only the communities that are need of these interventions, but also with the legislatures, those who really advance the policies.

So the only way that we really are going to be able to tackle not only the scientific, but also more the logistical and certainly political, regulatory, financial, ethical challenges is to forge these collaborations and bring in the experts from the different stakeholder arenas, right?

So for us here at Texas Children's Hospital Center for Vaccine Development, the partnerships with institutions in the biopharmaceutical area, as well, certainly the vaccine manufacturers, like I mentioned, and other academia has been transformational for us to really understand the entire ecosystem of how do you bring a discovery from the bench and hopefully leading to delivery and acces?

LUCIANA LEITI: I would just like to add that the collaborations are important, because each sector has a specialty or better information in different areas. So

there is a synergy when you put them together. It is not that we could not do everything if we wanted to, but it would take much more time, and it would be much less efficient.

So when you put the groups together, it works better because the experience of one adds to the experience of the other, and things go much faster and efficiently.

JEFFREY BUGULISKIS: Thanks, everyone, for sharing their knowledge with the general audience, and thank you all for your time today. Thank you.

LUCIANA LEITI: Thank you very much for this opportunity.

MARIA ELENA BOTTAZZI: Thank you. It has been a pleasure to participate with all of you.

VICTOR ABRAMANT: Thanks, everyone.

JEFFREY BUGULISKIS: Thanks for listening to GENcast. For *Genetic Engineering and Biotechnology News*, I am Jeff Buguliskis.

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