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Detail

Dyadic International, Inc. - Special Call

Event Details

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Company Name	Dyadic International Inc. NASDAQCM:DYAI
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Event	Special Call
Advisors	NA
Situation	To discuss Regulatory considerations and advantages of the C1 platform, Case studies describing the successful production of high value antigens for both Schmallenburg Virus and Rift Valley Fever Virus in relation to the performance in other production platforms, The efforts being undertaken by Dyadic to address the emerging SARS-CoV-2 variants including Dyadic's development efforts advancing a SARS-CoV-2 receptor binding domain (RBD) vaccine candidate – DYAI-100 plus the rapid engineering of C1

Call Details

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Company Details

Contact Name	Ping W. Rawson
Title	Chief Financial Officer
Phone Number	(561) 743-8333

Email	NA
Description	NA
Other Contact	NA
Job Title	NA
Phone Number	NA
Email	NA
Description	NA

Transcript

Dyadic International, Inc. - Special Call

Dyadic International, Inc. (NasdaqCM:DYAI)
Tuesday, May 4, 2021 10:00 AM

Executives
Analysts
Presentation
Operator
Good morning, and welcome to the KOL Fireside Chat on the Potential of The Transformative Dyadic C1 Protein Production Technology in Helping Meet Global Health Challenges Sponsored by Dyadic International. [Operator Instructions] As a reminder, this call is being recorded. And a replay will be made available on the Dyadic website following the conclusion of the event.

Dr. David Bramhill of Bramhill Biological Consulting will be the host and moderator of this discussion. In the past, David has worked on numerous expression systems, including 3 splines, Tetrahymena, insect cells, E. coli, HEK and CHO. His consulting projects have included antibodies and vaccines to coronaviruses and other viral pathogens. And with that, I'll now hand it over to you, David, to begin the discussion.
David Bramhill
Thank you. We should move to cover the forward-looking statements. This Dyadic statement cover this situation. And let me outline the agenda for you. So that we will be looking at the various aspects with the problem of a COVID vaccine, as a challenge that needs to be able to address even the poor countries in the world, not just the wealthy ones. And look at how the solutions that are out there could be augmented and helped greatly by a Dyadic's platform. And the speakers that we have lined up are Dr. Alain Townsend. He's a well-known immunologist who's done extensive work on viral peptide presentation by MHC class I, particularly with flu antigens. And has engineered a vaccine to flu. And obviously is involved in this current COVID-19 vaccine project.

Next up will be Dr. Albert Osterhaus. And he's at the University of Veterinary Medicine in Hannover. He's discovered dozens of human and animal viruses, including coronaviruses and others. And he's worked on the development and testing of various intervention strategies, antivirals, and diagnostics. But particularly including vaccines. And our third speaker will be Cecil Nick. And he's the Vice-President of Technical Matters at Parexel. And he's got over 30 years of regulatory and clinical experience and has been involved with over 20 different biologics projects. And multiple submissions to the EU, USFDA, and other agencies worldwide. And then finally we will have Joris Vandeputte. And he's the President of International Alliance for Biological Standardization. And over his extensive career, he identified H1N1 in swine. And has since gone on to be involved in numerous vaccines from discovery stage, all the way through regulatory. And particularly with his animal vaccine work, this has given him a view on the importance of the cost of goods being kept down in order to deliver effective and cost effective treatment for animals.

So with that, we will go listen to Alain Townsend. And he will begin by framing the problem and looking at the possibilities for a solution for a COVID vaccine, and explaining how we decided to use that particular strategy.

So with that, it would be over to Alain.
Alain Townsend
Thank you, David. I'm just going to talk for a few minutes about the basic immunological principles involved here. And just start by saying, this is a virus, SARS-CoV-2, as you know. Viruses infect cells and replicate inside your cells, and then spread. And all viral infections have certain things in common. One of which is obviously to induce panoply of immune responses. And probably in most cases, all of these responses are involved in protection. However, what we know is that sometimes an individual component of the response can play a particularly large role. And it can be the basis for designing a vaccine.

In the case of SARS-CoV-2, we don't know all of the answers yet. We know very well that the innate system, the T-cell system, the antibody system are all involved. But what is absolutely clear at this stage of the research is that the antibody response can be critical. So in animal experiments, we know that antibodies directed against the sub-component of the spike protein, the receptor-binding domain, can be highly protective. Both in antibody transfer experiments as is clear, or in various experimental vaccines that induce antibodies that bind this domain, and prevent the virus from binding to its receptor on cell surfaces. Now obviously it's not the only thing going on in the immune response. I ought to underline that. But it is a critical component.

We know that probably something in the order of 80% of all of the neutralizing antibodies do bind this domain, and act probably simply by blocking binding to its receptor. That makes it a very good target for a vaccine. And as it turns out, this virus is tailor-made for this approach. Because unlike many other viruses, the receptor minding component within the spike actually behaves almost like a separate protein. It can be detached from the spike. It retains its confirmation perfectly. And can be used to induce immune responses. This was understood many years ago with the SARS virus, and is true also for this relative or cousin of the SARS virus. So as a starting point for designing a vaccine, it makes a great deal of sense.

There's also good experimental evidence in the literature that animals immunized just with BRBD can be protected from infection, both in the mouse models and also in the NHP models. Now, what is the best way of doing this? Well, the simplest way of approaching this is simply to take purified RBD and immunize with it, with an appropriate adjuvant.

And that is a very good starting point. And in fact, that works. We know that works again, both in mice and in the NHP model. But what is clear if you're just using the protein on its own, then you need quite a large dose. But if you have a production system that can manufacture very, very large numbers of doses, very cheaply. Then again, that seems like an extremely logical and sensible starting point. So in this context, Dyadic are intending, or have achieved already the production of the RBD in the C1. It should be possible to make it in quantities and at a price that really is capable of immunizing billions of people. And if that can be done with the cheapest and most straightforward adjuvant, then that would be a great success, and very much worthy of support.

Of course, all of these things, you can't always immediately go from mouse, NHB, human, and expect it to work perfectly. But there are many options for developing it if the immune responses turn out not to be as good as you want, it can be multimerized. The adjuvant can be strengthened in various ways, as we know. So for me, scientifically it seems highly logical to start with a pure RBD with alum adjuvant as a starting point. If that works on its own, game, set, match in a sense. Because you can adapt it very easily and rapidly, mixtures of RBDs, for instance, and certainly new sequences. So that's the basic principle of what's being proposed. And it seems to me like a very, very good place to start. Finished that. I think you're muted, David.

David Bramhill

Yes. Yes. You were so succinct. I can commend you, Alain. Yes. So thank you for outlining the rationale for the approach. And we will move over now Albert to ask how this has begun to be potential practice and the various testing and results with the vaccine candidates so far.

With that, would you like to tell us about that?

Albert Osterhaus

Thank you, David. Also for the introduction. After the contribution by Alain, I think he made it quite easy for me. He explained quite well what we would need for a good vaccine. And the question is, we have vaccines at the moment. And we have had a great success, I should say, at the speed with which new vaccines were being made was unprecedented. Yes. So basically we have now messenger RNA vaccines, the big champions at the moment. I think we should realize that these things were considered 2 years ago, things that might be used for cancer, and in the veterinary world. And now we have seen this technology exploding. There are some drawbacks there, as we have seen. But these are good vaccines. They're safe and they are efficacious. We also have seen the advent of the [VaxIt] vaccines, where for instance, [adenoviruses] are being used, relatively mild viruses, that express part of the genetic material of the spike proteins of COVID, of the SARS coronavirus type 2. And there is still work ongoing with subunit vaccines. And that is coming about.

So of course, first of all, we have to ask ourselves, what do these vaccines do? And basically, Alain told us quite well that we have to go most probably for the spike protein that really covers about 80% of the antibody response. And in principle, the receptor-binding domain, that is definitely going for 80% of the neutralizing antibody response. So in principle, we have 2 options there. And we see that both are being used in most of the vaccines today, use the whole spike protein. So that's for the antibodies. For the T-cells, it is a little bit more up in the air. We don't know completely what's going on. But we know for other coronaviruses, but also for other viruses like influenza virus, and what have you, that also the internal protein may play an important role.

So basically those are the [indiscernible]. So we have to have most probably a good antibody response. That's a given. And preferably good antibodies against the receptor-binding domain. Although other antibodies against the rest of the spike also contribute to a certain extent. So when we have these good vaccines, as I said, we have messenger vaccines, messenger RNA vaccines, we have VaxIt vaccines in the meantime. What is missing? Why do we need another vaccine? Why do we need more vaccines? And well, there's 2 things I would like to stress today. Because future vaccines, what are they going to be directed against? And especially when we get these new variants of the virus, the variants of concern as they are being called of this particular virus? And it is reminiscent of what we have seen with flu. At the moment, every year, we have to vaccinate individuals in the risk groups, at least against flu.

And we are making in the more classical way, we still use embryonated chicken eggs there. And that's what our great-grandparents used to do. And we are still doing that today. So we really have to do probably better than that. Although these are quite good vaccines. So we have to adapt thereby strain selection every year, the 4 variants of influenza vaccines. And the interesting thing is that we may be moving in the same direction now with COVID. Because once the world or at least the industrialized world has been vaccinated against COVID or has had the infection, the only way for the virus to persist is to change all the time. And we see that happening that we get new variants. So that's an important thing. That's one part of the equation. The other thing is that we have to vaccinate the world. And I dare to say here and now, that it will be very difficult to do that with a messenger RNA vaccine.

Yes, because the technology is fantastic, but it should be affordable, et cetera. I'll come back to that. Now, I'm speaking about the assets, the possibilities of the C1 system. And I think it is a solution for, it could be a solution for this next generation of vaccines that are not only very rapidly able to represent new strains that are forthcoming like we're doing in flu. But also, they can be scaled up and they can be used for the world. So we need vaccines for Africa. We need vaccines for Southeast Asia, for many parts in the world that have not been vaccinated yet. So what are the options? And we and others have been doing quite a bit of work on C1 in the meantime. We have already worked on a MERS corona vaccine that was based on the receptor-binding domain. And that was produced in the C1 system.

And this could be used either in the way that Alain just said, just simple use this one component, the RBD with an adjuvant. For instance, with alum. But you could go also glue it up to nanoparticles. And we did all that work, and we got very good protection there in animal models. We could

do that with the RBD. But it's also possible to produce the whole spike with the system. And also to make the nanoparticles, as I said. So this versatile system that I was talking about is indeed able to make these different variants there. And then of course the other advantage there is that very rapidly, and Alain already told us, it's a very small part of the spike protein that we need.

We can actually present them together as a multivalent vaccine, 2 variants, or 3 or 4. That's all possible with this technology, even by co-expressing after we have done the strain selection, as we do for influenza. And then what we may need in the future similar to what we're doing for influenza, is boosting the immune response repeatedly in the winter months. We don't know if it's going that direction. But the expectation now is that this virus is not there to disappear. It will most probably stay for a longer period. We don't know how long. But it might well be. And it's not unlikely that in the coming years, we will have to continue vaccination. And that means boosting by adapting the strains of the vaccine. And this system that we are talking about is very well suited to do that.

And then the important thing of course, the cost production of these things. And I think Joris Vandeputte will be talking about that as well. This is a production system that is relatively cheap. You can produce huge amounts. Let's say almost a gram of the substance per liter, which is unprecedented. So that is an enormous asset, at a very low cost. A relatively low cost. It's a very simple or media. And the other thing is that also the production can be done at different places in the world. It's not a very sophisticated technology, the production technology, at least. So very rapidly, you can represent new strains. And you can produce huge amounts of these vaccines in a way that you can even do that in relatively simple fermenters. And the purification processes is relatively simple as well.

So when I look at this whole technology, and obviously after the successes we have seen by the messenger vaccines, the messenger RNA vaccines but also the vaccines based on the vector system, the adenovirus and the poxvirus. These vaccines are good vaccines, but for the future, we may need an additional asset there, a vaccine that can be reproduced all over the world in principle in huge amounts, so that we can vaccinate the world. And I think we have an option here to do that with this technology.

So in principle, in conclusion, I should say, we have a global potential here for not only monovalent, but also multivalent recombinant antigen vaccines. And what is even more interesting, the technology can also be used for antibodies and antibodies are used for preventive treatment as we know and early symptom treatment that's forthcoming as well. But talking about the vaccines, I think we have an asset here that has already proved itself in laboratory experiments, and human trials should be going on as fast as possible to see whether we can indeed use this technology to vaccinate the world in the end. Thank you very much. And I hand back to David.

David Bramhill

Thank you very much, Albert. That's very clear. So with this new system that we're using to produce the vaccine antigens, I'm going to hand it over now to Cecil Nick and ask him to put on his regulatory hat and tell us how he sees the pathway forward using this system and what are the challenges and advantages that it would offer.

Cecil Nick

Okay. Thank you, David. So clearly there are plenty of vaccines around, but there isn't enough, and things can be improved. And so the regulators are certainly interested in the development of new vaccines. And in this respect, the dyadic vaccine ticks the boxes. We've heard that there is certainly a need for affordable vaccines to meet the global need. Also, as you've heard, and this is very important, the ability to rapidly modify this vaccine to target evolving variants and there are regulatory processes in place to do that once you have established vaccine, similar to flu. So once we have the vaccine, it would take several months really at the most to generate a vaccine against a new strain. So this product will enable us to keep up with the evolution of the disease.

Another very important aspect that potentially hasn't been mentioned is the fact that this is a relatively stable protein, and therefore can be stored in the fridge. And that clearly is an immense advantage when we're starting to go into the developing world. It uses tried and trusted technology, potentially the Alhydrogel based Agilent, which there have been decades of experience with. Also, the fermentation is based on simple substances, such as glucose. There is no need for complex starting ingredients, which again makes this easily available.

The use of the receptor-binding domain will potentially maximize the ability to generate neutralizing antibodies because as you've heard, it's the antibodies against the receptor-binding domain which play a major role in neutralizing the virus. In addition, using the smaller fragment will reduce the overall protein load and potentially facilitate the multivalent vaccines, as you've heard is done in the case of flu and may well be needed here if we end up with multiple strains circulating. The C1 System, there has been experience with it. And we have talked to one of the regulatory agencies I'll go into a little bit more detail later, about this and there was no concern about the expression system. It is going to generate a pretty standard protein. It glycosylates the protein in the same way as the human cells do, which is important. It means that the protein will look exactly, or not exactly, but pretty much the same as it does when it's produced in the cell as a result of viral infection. The expression system is highly efficient. And in fact, the standard 2000 liter fermentor could provide a 100 million doses within days.

Now, as I said, we would expect a high level of interest from the regulatory agencies, and we've spoken to the German regulators, and indeed they were very interested to hear about the product. And we had a highly constructive interaction, discussing the quality testing, the stability data, the nonclinical program that precedes clinical testing and the design of the proposed clinical trials. And that was very useful. And we can be hopeful that first-in-man studies will start later this year. Clearly, there is an urgent need for effective vaccines. And as a consequence, we would expect that the regulatory review process would follow an accelerated path. The exact path is depending on what else is out there and the specific needs at the time. We could be getting emergency use or it could go through an accelerated review process. This is all to play for in the future.

So in summary, this C1 expressed subunit offers the benefits potentially over existing vaccines, potentially improved storage ability. We don't know about the tolerance yet, but we could have enhanced tolerance. So there's plenty of benefits that we may see over existing vaccines as we move forward. And very importantly is the ability for developing multivalent vaccines and the ability to allow for max vaccination. So thank you very much.

David Bramhill

Thank you very much, Cecil. So our final panelist is going to be Joris, and he's going to give us an overview and looking at how this technology, how this vaccine, could be applied to vaccinate billions of people worldwide.

So with that, let's hear from you, Joris.

Joris Vandeputte

Thank you very much, David. And thank you, Alain, Ab and Cecil, because you said almost already everything I was thinking to say. But I will do my best to put it a little bit in another perspective. The key thing here is we have, I think, a game changer in our hands. So a little bit coming back to the COVID-19 pandemic. Before the pandemic, the existing global lack of production capacity was already crying. Just before COVID emerged, the world had a production capacity of around 5 billion doses for all human vaccines, everything. And the sudden global demand to triple this capacity to protect the world population has quickly demonstrated how critical the situation is.

We should keep in mind that the urgency for the production of COVID vaccines poses extreme stresses on basic vaccinations already, like polio, measles, DTP, because of the competition for production capacity, at least at this moment. That means that solving on one hand COVID coverage should, on the other hand, not replace the problem to vaccine availability elsewhere by decreasing coverage for other diseases, particularly childhood diseases, which could destroy the fantastic work that has been done by Gavi and the United Nations organizations during now the last 20 years. Therefore, we urgently need, as has been said already, innovative, versatile platform technologies that can respond quickly and cost effectively.

Of course, the production of antigens is the first key step. The international situation now shows that it must be robust, flexible and globally applicable. The point of raw materials is also critical. They should be easily available everywhere, which as I can confirm what Ab said, is unfortunately not always the case today. This is the case with the C1 production system, because media [indiscernible] readily available everywhere. They are very importantly very well-defined and devoid of animal origin material, which is of major advantage for quality control and the regulatory. It is important to keep in mind that quality assurance and regulatory processes represent a very important part of the time in the path to getting a vaccine on the market.

C1 can produce large amounts, as been said already, of a huge variety of antigens belonging to different viruses or different infectious diseases. Results show already today that it is able to produce large amounts of, for example, the receptor-binding domain of SARS-CoV-2 or even the complete spike, and that for different variants. It also glycosylates very well, which is a very time-saving element comparing to previous classical production times. You had to try and error, upscale and then drive the right process, which could take months, even years. This is not the case here. It's a game changer to reach global coverage of vaccines. Ab and myself in our ZAPI experience, we could see how quickly at least potentially 1 billion doses can be produced. It's a question of months, even probably hopefully not months, only 1 month. The flexibility allows them to combine the antigen, if needed, with particles, what we call multimeric protein scaffold particles [indiscernible] as has been said for subunit. So the results will show which of both is the most indicated. Both solutions are highly flexible and highly price competitive asset.

As said, the versatility of the system is really very appropriate to adapt the vaccines quickly to variants in case of need. And again, in our experience, C1 fits to almost any steel bioreactor, single-use bags, anywhere in the world where there is fermentation experience. Even in the case of particles, the system allows high flexibility. For example, you can produce the particle in one production site in the north. You can produce the antigen in another different production site in the south. And somewhere in the middle, if needed, you can mix and you have the vaccine. This can contribute highly to global coverage.

Stability, it has been talked about. Indeed these vaccines already can be conserved at fridge temperature, which is extremely important. And we think there is a fair possibility, but we have to prove it, that it could even be stored at higher temperatures. Very importantly, this type of production allows a very high degree of definition of the vaccine. So we really are here like in RNA, but with additional flexibility in those vaccine when we talk about vaccines by design. And this is very excellent when you are in the case of a pandemic. So when you have a new virus and as we know today, if you have the methodology to detect the genome very quickly that codes for the right epitopes and the right corresponding antigens, then you can produce with the C1 System high amounts of it. So you go from an in silico detected genomes, the antigens, and you can go very quickly. We talk again in a couple of months, which has been unforeseen.

Also importantly, these vaccines are extremely well-defined and that means that for all quality and batch control release, all this can be done in vitro with robust in vitro tests. This way of working increases the control and the insurance of the consistency and the robustness between batches of the production process. That also means significant shortening of the batch release processes in process control, helping to reduce costs, increase access and the availability of the vaccines globally.

Now a little bit about the regulatory in addition of what Cecil already said. Keeping the very high standards of regulatory files, this type of vaccines allows to go quicker. We can really talk about regulatory innovation, and I explain myself, in the European project ZAPI, we... Well, invented. We call it the Platform Master File. That means that for the first file, the first platform, you go through all the process for toxicology, safety, efficacy, clinical trials, with one or a couple of antigen. You present it to the regulators. And once this basic file has been accepted, then normally adaptation to new antigens and other antigens should become relatively easy, because you have proven everything for your backbone. Then you have to only complete the file with what is new specifically linked to the new antigens.

This approach, of course, adds to the flexibility and the maximal use of the versatility potential of the process. So in principle, this is extremely practical to put in place vaccines and to combat very quickly a new pandemic, a new challenge, while you behave and keep the production capacity for the classical vaccines in place. So the regulatory authorities already use more or less this principle when you see the guidelines that were issued by the ICMRA, and the European Medicines Agency, in spring of 2020.

In conclusion, I would say that the C1 production system is not only a potential game changer in the global access to much needed vaccines. It is a must, where we have to focus on. Thank you very much.

Question and Answer

David Bramhill

Thank you, Joris. So I think everyone's done a great job covering the project and the platform. We have quite a number of questions here, so we'll move to the question time now. And maybe -- let's see, and I'm going to go, the first question: "Is RBD better than full spike trimers as a booster? Influenza vaccines are not adjuvanted, do we need un-adjuvanted RBD subunit vaccines, for people more than 60 years old?" And I think probably we'll go to Joris for this question.

Joris Vandeputte

Thank you for passing the honor to answering this question, but I'm sure Albert is much better placed than myself to answer that very technical question.

David Bramhill
Okay.
Albert Osterhaus
Perhaps if I can try to answer the question, we know that adjuvants, as already Alain said, are quite important to increase the response, the antibody response, and we also know the T cell response, against new pathogens that come in. So, if you want to vaccinate a young child or a person who has never seen a certain infection, you would use an adjuvant. Unfortunately, the adjuvants do not work so well in people who have already mounted an immune response to a pathogen. So we know for instance, that there are adjuvanted influenza vaccines for older adults, and they do make some difference, but the effect is not as extreme as we see in non-primed individuals.

So I think that if you look at influenza vaccination, the nonadjuvanted influenza vaccines, which are usually the most frequently used, with the exception of the elderly sometimes, I think that we do not necessarily have to use an adjuvant in the future. So, for now, when a lot of people are still not primed, the majority of the human population has not seen the virus yet or has not yet been vaccinated, then an adjuvant is quite useful. I think in the longer run, when we are looking into the future, depending on what this virus is going to do, it's here to stay most probably. But if it comes back every year with variants, I think we could probably do without an adjuvant there. Although again, for the first immunization or the first contact with the antigen of the virus in this case, yes, it's quite important to have that combined by an adjuvant. Is that an answer to the question?
David Bramhill
Yes. I think that, that should be good. Thank you. So maybe we don't rely on my expertise on who should answer different questions. Let's go down the list, and one of the questions from -- missing the name, [Lee Alpaugh]. "Would the final product have to be an injectable, or do you think you could make a pill for this technology?" And maybe we should expand it to inhalable, for a respiratory virus, is another way to deliver. Would one of you like to choose to answer that?
Albert Osterhaus
I think Alain would be a good person to answer this question.
David Bramhill
Okay. Alain?
Alain Townsend
Thank you. I think the answer is, of course, don't know. And you just have to do the science, and then do the trials and look for equivalence. It's very attractive to sniff something or swallow it, but there are theoretical things one could say. But in the end, I think we know so little really, about what's going on in many of these situations, you just got to try it and see. Each protein, each vector, each particle seems to behave slightly differently, so you've got to try it. Do the research, do the clinical trials, look for equivalents.
Albert Osterhaus
I'd like to add to that. I think indeed, I fully agree, you can only say after you have done the experiments. Of course, a lot of experiments have been done with locally administered vaccines for influenza, for instance, and the problem is rather similar. Let's say the influenza vaccines that are being administered locally, so in the nose so to say, or as a spray. So basically these vaccines, they consist of live attenuated viruses, so virus that can replicate in the upper respiratory tract. If you are going to use the subunit vaccines that we are talking about, then it will be, of course, the best thing to do would be to go to the place where the first immune response is necessary. But we know in general, that non-replicating vaccines, you need much more antigen there. You need much more stimulus there.

So, I think the technology will in principle, be more used for injection, for injectables. Although there are a lot of trials have been done with influenza vaccines with no live vaccine. But if you look at what the state of the art is today, it's only live vaccines that are being used locally for influenza at least.
Joris Vandeputte
If I may add to that, there is indeed a lot of experimental with subunits, topical administration, but it remains experimental.
Unknown Attendee
Yes, inhaled may well be a way to investigate.
David Bramhill
Okay. Well, thank you. So the next question that we have up, I can answer the first part: "Are rural populations at risk?" And obviously, they are, anyone who breathes is at risk. "How large are the populations compared to urban, and how effective would C1 be, in making vaccines available to such rural populations versus other platforms?" And that's a question from Ted. I'm not sure who is best to answer this. I think a combination might be the best way to go on this as well.
Joris Vandeputte
I can try to start.
David Bramhill
Yes, thank you.
Joris Vandeputte
So basically, the C1 allows first of all, as we all have said, to produce amounts of antigens and doses of vaccines in such a short period, that we have never seen before. Secondly, the system allows the multiplication, it means it allows quite easily to set up quite simple production sites of different places in the world. And also, even if we need particles, we know already that the production of particles if it were needed, is relatively simple. So, that means that here we have a vehicle where potentially we can produce huge amounts of vaccines, and deliver them everywhere in the world. I like to remind, the Gavi experience. So Gavi was started, now just 20 years ago, and I had the pleasure and honor to be part of the first team in 2005.

So, Gavi together with international organizations and local authorities, arrives and successfully delivers vaccines really everywhere. In the bush, everywhere, in the most difficult places. The condition is of course, to have the vaccines available, which this new system can do, and to have them stable. So we know already the temperature average, is able to transport them in a very... And control the quality. So, here we have something that really fits to global coverage, whether it's urban or rural. Albert, you want to add something?
Albert Osterhaus
I think you covered it well. I think when I gave my introduction, I spoke about the limitations of the current vaccines, and you just summed them up. So, it will be very difficult to have local production of these sophisticated vaccines that we were talking about, messenger RNAs, but also the vectored vaccines. And as a matter of fact, I think that indeed, if we manage to, you mentioned Gavi there. If we managed indeed, rurally, at many places in the world to manufacture these kinds of vaccines in high amounts, I think this technology would indeed allow us to do that. Stable

vaccines, cheap vaccines that can be produced worldwide at remote locations.

So I think it is a technology for second generation COVID vaccines. I think they will not primarily compete with the messenger vaccines and with the vector vaccines. But they will definitely compete with vaccines that should be used all over the world. And I think we should realize, that if we really want to control this particular pandemic in the longer run, we cannot neglect those parts of the world that are not being vaccinated today, because the viruses will keep circulating there at a very high level, and then new variants will be popping up. So, I think we have a responsibility towards the world at large, to also vaccinate those areas that cannot afford or are not within the system to be vaccinated today. So Joris, as you said, stable, cheap, worldwide production. And I think those are key factors that are lacking in the current vaccines that we have today, no matter how good they are and how well they are able to control the infections in the Western world.

Joris Vandeputte
Fully agree.

David Bramhill
Thank you. So we have another question: "Is it reasonable to expect that the spike protein will be conserved among variants, as any variation in the RBD will itself affect the virus infectiousness?" And I don't know... I can give a quick answer to that, perhaps. So, the spike protein has 2 pieces, I'm going to move a bit further back from my screen because I'm going to illustrate it here. And here is the main part of the spike protein, and hanging off it, is a domain that flexes on my wrist. And this includes the binding site for the receptor. Now, to avoid easy antibodies against that, the virus tucks it into the top of the spike protein. So this isn't normally exposed, but it has a chance to come out and bind when it reaches the target area, so the ACE2 receptor. And coronaviruses bind various different receptors, and then can mutate to engage different surface receptors on different cells, and SARS happens to have chosen ACE2, but this binding site can vary.

Now, to keep hidden. It actually uses the knuckles part, engaging my left-hand fingers, and that's the tether to stop it flopping around all the time. And this surface, this interaction is conserved and it's a closer engagement. And so, the variation can occur here to bind a different target, but the tucking in, the locking or retaining of it in the closed confirmation is mediated by a different surface. And this is an ingenious system, if you give the virus intelligence, and what it means is that this surface is often conserved. So, even between MERS and SARS and the latest SARS, this surface is one of the more highly conserved parts. And becomes exposed as the virus tries to engage its receptors, so that the RBD actually represents 2 of the most highly conserved surfaces of the spike protein. And that's the basis for it being such a good antigen, to raise neutralizing antibodies that block the infection process.

Albert Osterhaus
Perhaps you could also say the situation is a little bit reminiscent of what we see happening in flu as well. The most important antibodies that protect from time to time, if you've got new variants, they are definitely against the globular head of the hemagglutinin, which is another spike protein. We know at the stem, that there is another antigen there that that is very well conserved, so if you make antibodies against that, you're protected against many more strains of the virus. The problem is that it's very difficult to generate antibodies against those structures, that is one of the problems.

And we should not forget that about 20% of the antibody response against the whole spike protein, 20% is not against the receptor-binding domain. And we may have to rely on that response, if indeed new variants are popping. Because the variants, they have mutations in the flipping part that you were just showing. So in principle, I think it's more than the IBD, but less of the binding domain. The rest of the spike protein is also important, although it's not as potent, but I think we should not completely neglect it. And there is with these viruses, yet another story that some of the antibodies against other parts of the spike, might not be so beneficial as we hope.

David Bramhill
Thank you. So we have another question here: "Can the C1 platform be used for manufacturing antibodies and/or other drugs?" I guess biologics is what specifically is meant. And so I'd open that to the panel.

Joris Vandeputte
I can say yes, it can be used to produce monoclonal antibodies, for sure.

David Bramhill
So there is direct experience of doing so? Yes. Okay. Thank you.

Albert Osterhaus
[That’s a real] technology that should be further worked out because obviously antibodies are being used currently, but they're so expensive that they can only be used by limitedly, let's say in a hospital situation where you want to prevent somebody to get infected, if he has to go into a hospital where there is infection. Obviously, when we have more of those antibodies that are very potent, especially for prevention and very early treatment, it will be the best thing. But the high cost there is really the limiting factor. And I think as it has been shown that this technology works for production of antibodies, it's definitely time to put effort into that as well.

David Bramhill
Yes.

Albert Osterhaus
Effort into that as well.

David Bramhill
Yes. Okay. Thank you, gentlemen. The next question with the new South Asian variants, which seem more virulent, would it be suitable to prepare a multi-virulent vaccine, say every 6 months and administer a dose of that and develop a strategy that would address say some periodic, whether it's 6 months or a year, interval. Is that a reasonable plan?

Alain Townsend
Okay. Should I say something to that?

David Bramhill
Yes, please do.

Alain Townsend
Just going on the data that's visible at the moment and the literature, if we accept that neutralizing antibodies are actually protective, I think is a reasonable assumption that's not been absolutely demonstrated, but I think neutralization in vitro is a reasonable yardstick. Charles Mangum might disagree with me, but I think it's reasonable. So if you look just at people who for one reason or another, have a very high titer against the original virus. So the people with the highest titer are probably those who were infected and who then received the first dose of vaccine, they make probably more antibodies than anybody else.

They almost always those sera, at least in our experience will cross-react and neutralize the variants at about tenfold lower titer, which probably means that those people are protected from those variants. Again, we have to be very cautious because all the data isn't in. But that would be my expectation. If however you have low titer, so let's say you've just had one dose of vaccine or you've had a mild infection, very often you can't detect any neutralizing activity against the variants in those sera. So one thing that points to is possibly, rather than having to make lots of new vaccines to new variants all the time, if you're stuck, then one thing you can do is just try and make sure that people have a very high titer to the original before you even have time to make new variants of new variant vaccines.

And I think that's a very sensible starting point. But of course, if you would prefer to have antibodies deliberately induced by the new variants, but we may end up with a situation even more complicated than the flu. It's already getting pretty complicated that there might be multiple variants. And then the technical issues of producing vaccines that cover all of the variants using the principle of one vaccine for each variant might get difficult. Whereas I think just getting a very good high titer against 1 or 2 of the variants would probably do the job. But you have to do the experiments and find out. That's the only way of going.

David Bramhill

Okay, we've got a question from Lee. And they say, "This technology seems to be what the world really needs, especially the third world. What has been the delay in getting it into testing and how do we get around those barriers?"

And maybe I should say a quick word since I'm not involved in the team and this project at all. And that's to note that this question assumes that you already have however many billion dollars of Warp Speed money to help you super accelerate the rate of development. And as an independent observer, I'd say this team's done a pretty good job in getting where they are with the project. And that it's only because they haven't got the abundance of financial support that they haven't been able to go as fast and set up all the clinical trials and everything at the rate that Moderna and Pfizer and others have done. Okay?

Cecil Nick

Yes. I think also at the beginning of the story, we really didn't know whether the vaccines were going to work and therefore the focus was in developing as Alain suggested, the responses which were very robust in order to maximize the opportunity of controlling the virus. Now we are there and the focus is shifting to technologies that can actually be used to mass-produce the vaccine. And the studies into these protein vaccines are perhaps trailing a bit, but they're looking very promising. And I would hope that at this point in time, we will have the strong focus to bring this to market as quickly as possible.

Albert Osterhaus

Well, perhaps it's also good to say that exactly the money initially was lacking. Yes? Because the proof of principle was not really there to such an extent. But it all came from the collaboration with Dyadic and also a European project that was being paid basically by the European Commission. And what we were doing there is develop this technology, and it was just before the pandemic struck that the first proof of principle was proven with the MERS coronavirus doing exactly this. And so then it takes some time to gear up. But on the other end, I could say that the first human trial is about to happen in a couple of months. Yes? So by the end of the year, we will have that.

And of course, we would have loved it to go much faster, but then still, of course, you have to convince the authorities and the people who have the money to do this and you have compelling evidence now that indeed we have to speed up and make a second generation of vaccine that actually targets a different type of population, especially for vaccination of the world. This will be a much better candidate than the ones we have at the moment.

Joris Vandeputte

To complete that. So I fully agree with Ab. We're part of the same very successful ZAPI project. So if we could, I do not dream of the billions of the Warp system, but if we could invest within a couple of years, between 50 and 100 million euros already, we could go very quickly and go, I think, including 2 Phase II, at least very quickly.

David Bramhill

Thank you very much. And I know that there was a question that is on the list that you've just answered that the plans for human trials are coming up. So we haven't yet tested though in human yet. So a couple of questions, how many companies are currently using this technology and as a closely related to that, what do you feel is the opportunity for a new manufacturing platform for cell lines like C1 that industry's regulatory timelines now being more streamlined?

Albert Osterhaus

Obviously, this is the next step to go. Yes? So where proof of principle has been made and small Phase I trials are forthcoming now, and definitely as Joris already said, we have to plan for the Phase II, Phase III trials. And basically, that can be done, but of course, large-scale manufacturing, that's the thing that has to be done.

And that is an expensive thing, obviously. Although the technology is cheap relatively, but still going for Phase II, Phase III trials, it's not the technology of producing, but it's really the conducting clinical trials is the expensive part, of course.

Joris Vandeputte

I fully agree with that. And in addition to that, in fact, physically, we have the building blocks for production, even under CGMP circumstances, they are available. So it's just a question of a little bit, I should have courage to say, we go for it. We can set up a relatively small high profile team that manages it and we can start if we have the results. Yes, we can start and in 6 months, we can be ready for Phase II, at least.

David Bramhill

Thank you. And so I think the next question is pretty similar. So looking at when, wait a minute, I'm just getting... Sorry. Got new questions. Let's see. Oh. Are there plans for researching a cancer vaccine? And if so, what would be the goal?

Albert Osterhaus

I think this would not be the highest priority at this time. So basically perhaps it's interesting to note that the messenger RNA vaccines that at the beginning of the pandemic, nobody really believed in. Yes? It was only for veterinary use, but also for cancer use. And I think that's the interesting thing that the messenger RNA vaccines that were being used in humans were all cancer vaccines or candidate cancer vaccines. Obviously this technology, if you identify the right targets, they might serve as cancer vaccines as well in the long run. But I think for the time being, I think it would be good to focus all the attention at this moment, at the COVID vaccine indeed.

David Bramhill

Okay. Thank you. Well, we have time for one more question, I think. And I'm just trying to... Let's do this. So if we're already using CHO cells, what would be the barriers to moving to C1 as a platform in its place?

Cecil Nick

Do you want me to take that one?

David Bramhill

Yes. I think that would be a good one for you.

Cecil Nick

Okay. I don't see there are any barriers. Basically, there is the experience. There is the familiarity with CHO cells and that's really what the barrier is. Moving away from familiarity to something which is promising, exciting and potentially a much more effective production system. And clearly, as we gain experience with this technology, there will be less reluctance to embrace something which is new. So I would envisage that there's huge potential for the C1 production platform in the future.

David Bramhill

Thank you. Thank you, Cecil. [So we now] would see that the productivity and the low cost of the media, but also because of the productivity, the amount of stainless steel tanks that you need to invest in would be a major incentive to try something that you only need to build something a 10th of the volume or whatever, even given the same volumetric productivity in the system. And obviously, all the data that I've seen suggests that it's, the C1 is a very good productive platform. So that for any new product, your greenfield plan would be far smaller and thus a fraction of the cost to invest in before launch.

Cecil Nick

Yes. We'll get around a lot of the issues in terms of scaling up and the complexities of the CHO cell process.

Joris Vandeputte

I fully agree with that. So I would even say it's almost not comparable. We are in 2 so different systems. The advantages of the C1 system are so huge in volumes and in flexibility, and then setting up and in standardization also. So you'll see it in the production already in CHO cells with the monoclonal antibodies and the transgenic adaptation and so, et cetera, et cetera. It's a huge process. So while here in the C1, apparently, it's much more simple, straightforward.

David Bramhill

Thank you. Well, I think that's all the time we should take, and we appreciate. Like to thank all our panelists for their contributions. And I found it very interesting and informative. Of all the different systems I've worked on, c1 is not one of them yet, but I hope soon it will be. And thank you everyone for attending. And I don't know if Tara has a brief concluding thing or if we, if we say goodbye to everyone.

Operator

Yes. Thanks David. So thank you everyone for joining. This concludes today's fireside chat. You may now disconnect.

Albert Osterhaus

Thank you so much. Bye-bye.