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CORPORATE PARTICIPANTS

Aris Baras Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Ryan Crowe Regeneron Pharmaceuticals, Inc. - VP of IR

CONFERENCE CALL PARTICIPANTS

Brian Corey Abrahams RBC Capital Markets, Research Division - Senior Biotechnology Analyst

PRESENTATION

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

Thanks again for being here. I'm Brian Abrahams, 1 of the senior biotech analysts here at RBC Capital Markets. Our next feature company is Regeneron. And since I picked up coverage of the company, I'd be getting more and more questions about what's going on in Regeneron's pipeline? Of course, I get a lot of questions on EYLEA and Dupixent. But people I think are more and more interested in learning about the R&D engine.

And so we're really pleased to feature today, I think, a different aspect of Regeneron than many people get a chance to see and understand. We have with us Aris Baras, who's the Senior Vice President of the Regeneron's -- Regeneron Genetics Center, as well as Christos Kyratsous, the Senior Vice President of Research; and Ryan Crowe here on stage as well, who's their Vice President of Investor Relations. And they're going to walk us through a little bit more about what goes on behind the scenes at Regeneron that enables them to maintain one of the broadest pipelines in all of biotech. So thank you so much for being here and joining us.

Ryan Crowe - Regeneron Pharmaceuticals, Inc. - VP of IR

Thanks, Brian. Just a quick forward-looking statement. I just want to remind the folks that remarks made today may include forward-looking statements about Regeneron, and each forward-looking statement is subject to risks and uncertainties that could cause actual results and events to differ materially from those projected in such statements.

A description of material risks and uncertainties can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update any forward-looking statements, whether it is as a result of new information, future events or otherwise. I think Aris and Christos going to have a little open and then we'll go to your questions, Brian. Thanks for having us.

QUESTIONS AND ANSWERS

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

Great. Well, maybe just to kick things off. Can you start by telling us more about the Regeneron Genetics Center. How does it work? What are some of your overall responsibilities?

Aris Baras - Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

Absolutely, Brian. Thanks for having us, and thanks for coming out to meet with us and hear from us about our genetics medicines efforts at Regeneron. So Brian, maybe I'll take a moment. I'll start. Christos will add and finish up, talk about 2 things: the genetic center, we don't mean to confuse and also genetic medicines. So 2 different things that we talk about at Regeneron, and we want to raise awareness for them as well.

So briefly about the genetic center, something we've been doing for a very long time in the last 10 years or so, large-scale human sequencing, very simple goal is looking for identifying new targets genetically validated targets that have much higher probability of success in drug development. That was the initial goal, and we've been very productive in terms of the number of new targets we've discovered at Regeneron and advance them across lots of different modalities and programs, antibodies, genetics medicines. And since the initial efforts, we've also added to that, where it's not just target discovery, and we'll get to this later today, but also how we can use genetics to guide the development of our existing programs, and a really simple and great example, we use genetic mutations, genetic variants that many of us have, and we sequence millions of people. So we've got lots of data on this as surrogates or mimics of what a drug is doing.

You have a drug that blocks a target, we've got thousands of people that have a mutation that is basically a knockout of that target. So we can look at real human data to see what the prediction is, what the effect is? Is it going to have a benefit on heart attacks or asthma or COPD. That's the basic gist of it how we've been using genetics, at a scale that doesn't really exist in our industry, and we'll talk about examples.

This is distinct from but leads in nicely to genetic medicines, where Christos and I have been -- Christos has also been at Regeneron. We've been -- I guess we're not the old-timers, funny story about a dozen years we've been at Regeneron.

About 5 years ago, maybe even longer than that, we really started to kick off efforts beyond antibody technology platforms. And specifically, what we talk about in genetics medicines are things like siRNA, our big collaboration with Alnylam, gene therapies, CRISPR-based editing and other enzymes and approaches that are being used today.

And I'll just say 1 last thing and Christos take it away from there. The reason why we made a big investment and made it a priority area for us about 5 years ago when we started doing this, a couple of things. We really believe in technology platforms. We invest heavily. You know Regeneron as a company as a technology development company, antibodies, TRAPs been prolific in that over the last 30 years. And we like technology platforms that are not a single product opportunity, but they can be multiple product opportunities from the platform.

Number two, we also like in Genetics Medicine. They have a lot of features that antibodies have in terms of their precision, their specificity. In contrast to a great field, medicinal chemistry, small molecules, but very hard to get really specific inhibitors or activators. And so just like antibodies, we can get really specific blockers or sometimes agonists. Because of these being genetic medicines and a lot of sequence base, it's very precise. You can design a sequence to inhibit something with siRNA or to deliver a gene, obviously, right?

Those are some of the hallmarks of why we like these genetics medicines platforms and why we've invested so heavily in their development at Regeneron. You want to add to that?

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Sure. Thanks, Aris, and thanks, Brian, for the invitation. Very happy to be here. So 2 things to add. One from the technology development side, that's a very nice synergy between antibodies, what have been traditionally doing for the last 20 years or so, and genetics medicine, meaning that you can take antibodies and specifically target genetic medicines, the viruses or siRNAs or other components, and we can talk about that in a bit.

So in terms of technology development, it's a very nice follow-on story for what we've been traditionally doing with antibodies. And the second thing I want to add is by expanding our modality portfolio to genetics medicines that gives us a very vast array of modalities to choose from, from the traditional protein therapeutics, mostly antibodies. Again, we've been working with those for several years now to siRNAs, CRISPR, gene therapy, you name it, and we can let the biology we can let the biology areas at Regeneron do their work and then choose the best modality for your indication, the best modality for the disease, you're not restricted to the single modality you have available. We have the entire array to choose.

Aris Baras - Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

This is a huge point and 30 seconds here that Christos always talks about correctly. We are not stuck to a certain modality. So whatever we think is the best modality or if you need to take multiple shots on goal, for a fantastic target, we can do that given the different modalities that we have.

The other point that we always make is precisely because we have a very productive genetics and biology effort at Regeneron. We have lots of targets we've uncovered. And in the past through protein therapeutics, we really could address predictions are 1/4 or 1/3 of the human genome because those gene products are secreted or available to antibodies. Now we can really access a lot more target space through this.

And we should also add, this is a big research and technology development effort, but it's also a big drug development effort. So these efforts over the last 5 years have led to -- we have now 6 programs in the clinic. Happy to talk about these. All the way into proof-of-concept studies and late-stage development and a very rich pipeline that could be from preclinical development into the clinic.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

Got it. No, that's great. And you mentioned with some of these modalities you mentioned siRNA, I know you guys alongside your partner Alnylam recently reported proof of principle data from an APP targeted RNAi. And so I'd be curious if you could tell us maybe a little bit more about what those data mean for your approach, both for this program itself and then maybe even bigger picture use of RNAi to get at neurodegenerative neuropsychiatric diseases. And then maybe if you could also kind of weave in the next steps for this program and your confidence in the overall safety.

Aris Baras - Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

Thanks for that question. Obviously, we're really excited about what's going on in siRNA in the brain, in central nervous disorders. The data, as many of you heard from Alnylam, their last time around, they did a very nice presentation with some data from the human study and also some of the background data from the preclinical development in the primate studies. It's early days, right? We have to remind everyone, this is the first, first time we're getting siRNA into the brain in human studies. Honestly, this really exceeded our expectations in terms of what the potential, what the possibility is, right? Emphasizing it's early days, but up to 90% silencing was seen in the highest doses tested there. That's quite profound in terms of the potential of this technology and platform. There's lots that still has to be done. You alluded to that we have to complete studies in terms of the single dose cohorts and they're advancing to multi-dose and really establishing the safety profile of that platform.

But you can remember decades ago when they were first developing siRNA technology in the liver and how far that has come, right? So there's nothing more we can say on that other than we have to continue this development with our partners with Alnylam, but so far, everything looks really hopeful.

And to your point about potential, if this all holds up and we can get as it looks really profound platform in terms of silencing of target genes in the brain and hopefully have the type of safety profile that siRNA has had in liver. The possibilities are fantastic. We know a lot of great targets for neurogenic diseases that affect very large patient populations without really any treatment effective treatments available. And the discovery pipeline through genetics and a lot of other work is really rich in that space. So this could unlock a big opportunity on drug development in CNS.

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Two things to add here. Aris, you talked about the level of knockdown, about 90%, but let's also not forget the durability, right? You get multi-month durability so far, okay? We don't know exactly how long it's going to last, but the status of course, have been going, which is really exciting. A single dose can knock down expression for more than 90% or about 90% for multiple months. And 1 more point I want to make about the safety here.

First of all, the -- when we -- our partner Alnylam, we're designing a lot of the preclinical toxicology studies, we had no idea how the platform is going to perform in the humans, right? So you have to guess a little bit about your dose, guess a little bit about the frequency of dosing and things like that. And you also want to push the system. So sometimes you want to see toxicity in your animal so you can understand your margins, right?

So -- and it's always a data set that is hard to explain unless you have the totality of the data and you combine all this preclinical data with the emerging human data. And I think that's exactly what we are planning to do now with Alnylam, we look at everything collectively and assess how we're going to be progressing forward, this hold here in the U.S. The studies are still recruiting as well in the world, which also shows how different

the regulatory agency sometimes see the same data set in different ways. This is not a black and white thing. This is the very first time you see biology and technology like that translating in humans. So it's actually unknown territory, right, that Alnylam is trying to curve here, which is really exciting.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

You mentioned at the beginning, some of the targets that have been discovered through your efforts HSD17B13, I think was 1 of the more interesting targets that was deriving from your efforts that you were able to really go from target identification to proof of concept in humans very, very quickly.

Can you talk more about that program? I guess, where you are now with regard to the ongoing Phase II and continued dosing work in Phase I? What you're looking for in terms of histological benefits to guide next steps. And I guess how you're thinking about the NASH space overall because it's -- you sort of have this interesting element here where you have a very novel target that no 1 else is going after. It's a field where there's some regulatory and commercial uncertainties, but there seems to be sort of growing momentum as things move into late stage and mature. So where does this fit into your prioritization, what are the next steps here? How excited are you on this program?

Aris Baras - Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

It's a major priority for us. Favorite question, so thank you for that. One of the things we love to do back to the genetic center is 1 of the things that was new in the field about 10 years ago was look for these protective genetic mutations. Really, genetics has before that, been mostly about what genetic mutations cause disease, right, and pioneers in the field, examples in heart disease and some infectious disease had done the opposite.

They discovered mutations that make you superhuman, they protect you from certain diseases. And 10 years ago, we started on a big campaign to not find 1 or 2 of these, but to find dozens of these. And we have done that now. And you're highlighting 1 of the early stories. We focused a lot on NASH because of, as you said, the big opportunity there, right? No treatments. It's now the major cause of liver cirrhosis and liver transplant.

Unfortunately, it's been a graveyard of drug development, but we're starting with these protective genetic starting points. So we know in humans, when these genes are knocked out, they have a tremendous benefit, reducing your risk of getting NASH or if individuals have NASH, it dramatically reduce your risk of progressing in NASH.

HSD was the first -- but I also want to remind folks, we have a very complementary portfolio with our collaborators at Alnylam. So we're leveraging the siRNA approach in the liver for the most advanced program, HSD17B13. The next 1 is PNPLA3, it's a different mechanism, very complementary. And the third, which is we've talked about is in the latest stages of preclinical development, moving quickly towards the clinic is CIDEB, which actually had the biggest effect we've ever seen in terms of reducing risk of NASH in our genetic sides published information.

So that's your question about HSD. We did finish the early human studies. There was a Phase I study and then a 1B that Alnylam reported out on last year in NASH patients, not powered, obviously, for these types of things is a Phase I study, but we got a sense an early sense of being able to look at not only kind of dose and target silencing, but importantly, some early biomarkers. So they were seeing numerically lower transaminases, liver enzymes biomarkers of that. And we've now started the proof-of-concept Phase II studies where, yes, we're absolutely looking at in biopsies, looking at elements of inflammation, fibrosis, the core type of information that we'll need to advance drug development there.

Just to round it out, PNPLA3 has also started clinical development. And there, the opportunity will be similarly to look at in the Phase I, is also to get a component of that where there will be patients with fatty liver. And there, the mechanism is looking at liver fat, where we hope we expect to see very -- there's been some competitor data there, some large reductions in liver fat pretty quickly through that pathway.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

We're looking forward to seeing those data. You talked at the beginning about being modality agnostic and all the different the growing suite of modalities that are enabling you to interrogate and explore these novel targets that are coming out of the genetics efforts.

Can you talk a little bit more about the modalities, the new modalities that you're most excited about? And I'm curious to maybe go beneath this maybe a level deeper, I mean, it sounds like the RNAi efforts are in full force and obviously have antibody technology. But tell us more about what else you're excited about? What's novel beyond some of the ones that we're already kind of seeing in the clinic?

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Sure. So first of all, I want to mention that for all these modalities, we see them more as -- all of them are evolving first, right? So you can see siRNA, for example. It was something that was utilized quite a bit in the liver. You can very efficiently deliver siRNA to the liver. Now with Alnylam, we were able to unlock CNS as a new space, which is an entire new area. Our collaboration with Alnylam is also expanding to VI. So we have another tissue that we are hoping that we're going to get data in the future, and we are able to unlock. And then you can see the modality evolving into other extrahepatic tissues by different types of targeting.

CRISPR therapeutics are similar, a couple of years ago with our partner in Intellia, we announced, we published that we were the first to actually deliver systemically this CRISPR components, knock out a gene in the liver in hepatocytes, TTR very, very efficiently and reduced levels of circulating TTR by more than 90%, about 90%. Again, CRISPR is currently systemically administered CRISPR components are mostly targeted to the liver, unlocking and delivering these CRISPR enzymes to other tissues outside the liver is a huge area that we are planning to -- we are working on very, very actively, and we have multiple different targets outside the liver.

On the editing space, in addition to targeting these enzymes outside the liver, CRISPR/Cas9 outside the liver, you also have availability now of newer generation supports enzymes. So there are more and more types of enzymes that are available that allow you, when you utilize them properly to make different types of edits. So you don't go and you make a blunt cut into your DNA, but you can make more precise modifications.

With our partner Intellia, we are making actually very directed CRISPR an AAV-mediated gene insertion. And we have programs like that, we have shown some of the data, the preclinical data for hemophilia in certain Factor IX. We also have some data that we published for enzyme replacement therapies by expressing these enzymes from the liver.

And then when it comes to gene therapies delivering AAVs, okay? We partner with Decibel to deliver AAV for a genetic deficiency otoferlin, we pick that because it's a very defined genetic lesion. And we have very strong preclinical data that restoration of expression of otoferlin restores hearing functioning of these preclincal models. We are very excited about that. Our partner Decibel very recently announced that we are in the clinic. So hopefully, we're going to have some -- we're going to start recruiting patients and announcing data soon.

So -- and then we can take all of this into the next level by unlocking again the delivery, right? So you can see that all of these modalities have progressed very, very fast. But what we are lacking in many, many places is how to deliver them properly to the right tissue specifically. And that's exactly where we believe that antibodies can actually play a major role. We have published some preclinical data in both mice and nonhuman primates, that you can conjugate antibodies to AAV. For example, you can strip them of their natural tropism so they don't go to the liver and where they normally go to. You all know that liver is a huge theme for all these AAV therapies that results in loss vector, but also sometimes some toxicity is being seen.

And then you can add an antibody on the surplus of these viruses and you can let the antibody, take the virus to your favorite tissue. And that is a technology that works extremely efficiently in both mice and nonhuman primates. There's a conference going on in Los Angeles this week, the American Society for Cell and Gene Therapy and a lot of the data that we are presenting there during this week. We are very excited about this technology. You can imagine that you can encode your favorite enzymes, your favorite transaminases into your AAVs and target them with antibodies to your favorite tissue so that you can unlock the use of these enzymes and use of these genetic medicines to these tissues.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

It's super interesting. How far away is that -- I know you've had some proof-of-concept data in animals and nonhuman-primate models. How far away from the clinic? Is this antibody-directed gene therapy, would you say?

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Yes, we are finalizing now a lot of the preclinical data sets to validate the precise target that we are talking about, and we are trying to prioritize the first clinical applications where we can use them. We are in the process of doing a lot of scale up that is required to develop all these processes so that you can produce all these vectors in the right quantities and at the right scale. And then both internally and with potential partners, we are thinking about how to best position them in the clinic. So we're not too far away from that.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

And is this something you imagine or envision developing utilizing sort of your own vectors and payloads for delivery of or using, I guess, have making external collaborations for -- to try to improve the specificity and biodistribution of others' gene therapies?

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Both. I mean, additionally, in the genetic medicine space, I think as Aris mentioned, there are a lot of like homegrown efforts, both on the target discovery side, from the RGC and other efforts within Regeneron, a lot of effort on the technology development side that are homegrown efforts to take some of these programs and put them in the clinic, but we also especially in genetics medicines. We really enjoy these very productive collaborations with like-minded companies that have been extremely fruitful for us. So we hope that we're going to be continuing collaborating with those companies and potential orders in the years to come.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

Great. I know we've only got a couple of minutes left, but I wanted to ask about your COVID efforts. You obviously had a very successful antibody that really helps mitigate some of the morbidities at the height of the pandemic. We're all here now unmasked. Obviously, we've come a long way since then, but there's always a threat of a mutation and an outbreak kind of lurking around the corner. Can you talk about the process by which you were able to find a conserved epitope for COVID, what you've observed preclinically. It looked like from some of the recently published patent filings, you see good binding connects and consistent neutralization potency across a lot of different tested COVID variants. I'm curious, the next steps for your lead compound there or lead antibody there [14287] enters the clinic mid this year.

And I guess, how you discovered it and what you think the challenges might be now from this point forward, where we are in the pandemic to develop a COVID antibody and sort of generate the same sorts of returns that you've got in the past?

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Right. So the process here is very similar to what I think Aris was describing for genetic diseases where you rely on a huge data set of sequences to try and understand patterns, right? So it's the same thing that you are trying to do when you are starting virus evolution. And what we've learned is that over the last more than 2 years now of available sequences of the virus, you can see that there are certain regions of the virus that are changing very, very frequently for the virus to evolve spread faster amongst the population, but also as a result of the immune pressure.

All of us, when we are vaccinated on where we are infecting infected -- the majority of the antibodies that we are developing are against this region of the virus that is called the receptor binding domain. They are very potent neutralizing antibodies. They block the virus very, very well. But also the problem is that this is the region of the virus that is changing very frequently.

So the clinical development of these antibodies is very challenging because you are basically chasing an ever evolving target. It's very difficult. So what we were able to do is we were able to identify sequences that over the multiple years of the evolution of the virus did not change very much or didn't change at all, and then we were able to isolate antibodies against those sequences.

And out of those antibodies, we only chose the ones that are very potent, as potent as the antibodies that are targeting the receptor binding domain, and we chose one, the 1 that you mentioned as the 1 that is going to be our clinical candidate. The antibody has been scaled up, and we've already discussed all these things with the regulatory agencies. We are going to be in the clinic in the next few months. And we are hoping that by the end of the year, we are going to start collecting data as these antibodies being tested in patients.

Brian Corey Abrahams - RBC Capital Markets, Research Division - Senior Biotechnology Analyst

Got it. I feel like we can talk for another hour or 2 on all the things that are going on, but this has been a fantastic overview and deep dive Aris, Christos. Thank you guys so much for being here.

Aris Baras - Regeneron Pharmaceuticals, Inc. - SVP of Regeneron Genetics Center

Thank you.

Christos Kyratsous - Regeneron Pharmaceuticals, Inc. - SVP Research

Thank you.
