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4. The Future of Diabetes Research: Thoughts from JDRF CEO Alan Lewis

We recently spoke with Alan Lewis, PhD, the new President and CEO of the Juvenile Diabetes Research Foundation (JDRF). Dr. Lewis discussed the future of diabetes research, the companies he believes will play a role in that future, and how diabetes therapy will change on the road to a cure. The JDRF, of course, has great influence on the direction of diabetes research – we appreciated Dr. Lewis' candor and are eager to see where he will take the organization. He comes into the position with a long history in drug development and discovery and most recently served as the President and CEO of Novocell.

- **Though encouraged by new technologies and treatments, Dr. Lewis acknowledged that finding a single "cure" for type 1 diabetes would likely take longer than expected, likely longer than a decade.** He noted that definitions of "cure" vary and that some patients may consider a fully functional artificial pancreas as a cure – Dr. Lewis anticipates success with the JDRF's Artificial Pancreas Project within five years. However, he indicated that

the ultimate goal is "beta cell preservation and restoration." He was enthusiastic about crossover treatments, which are being used for indications other than diabetes; if they work for diabetes, they would have an accelerated approval process.

- **Notably, Dr. Lewis explicitly stated that one of the top near-term priorities of JDRF is developing a closed-loop device – reflecting a shift in focus to more "here and now" therapies to complement its research on far-off cures.** Dr. Lewis believes this priority will address the immediate need of the patient to maintain health and live longer. However, he noted that JDRF is still committed to the ultimate goal of beta cell recovery, with a particular focus on antigen-specific therapies (therapies targeted for a particular substance that causes an immune response). He expressed hope that JDRF would be seen as a leader in this field, just as JDRF's leadership is now broadly acknowledged in CGM and the movement toward the artificial pancreas.
- **The JDRF continues to support smaller companies in both treatment and cure-based research and encourages larger companies to invest in the field.** Dr. Lewis was intrigued by many of the current approaches by smaller companies, highlighting Macrogenics, Tolerx, SmartCells, Bayhill Therapeutics, and Osiris Pharmaceuticals as having programs reflecting significant potential progress (we note that Genentech has now taken over Bayhill Therapeutics' work in diabetes – a success story for JDRF's "bridge" funding). He also emphasized the need for big pharma to play a role in the commercialization and future success of cure-based therapies, citing J&J, Genentech/Roche, GSK, and possibly Novo Nordisk and Lilly as potential major contributors to the field in the near and long term. Last, he emphasized that JDRF would work to foster more relationships between bigger and smaller companies in the future, as well as discussions with other patient-focused organizations.

FINDING THE CURE

Kelly Close: Dr. Lewis, we really appreciate your taking the time to speak with us today. We'd like to start with the million-dollar question: is a cure something we can reasonably expect to see in the next decade? As patients, of course, we have been hearing that it's around the corner for the last few decades.

Dr. Alan Lewis: As you well know, JDRF's mission is to cure diabetes, so one of the first questions I asked when I joined the organization was where this stood – i.e., what is the cure and when can we expect to see it. Clearly, the cure represents different things to different people, and there's probably no such thing as a single cure for all patients with type 1 diabetes. I also realize there's always a danger in increasing the hope for something sooner that it actually will occur. Some people say that they realize that if they could maintain their blood sugar within normal range, they wouldn't have to worry about hypoglycemic events and complications. That for them is a cure. Thus, I think in actuality a closed-loop artificial pancreas will be considered a cure for many of the people who I've described, who tell us they are more concerned with maintaining their blood glucose levels within a tighter range than they are worried about wearing devices and whether their beta cells are functioning.

But we really believe that you need to restore and preserve the beta cells and protect them from future immune attack. That is ultimately the cure. So the question is, how do you do that? There are multiple ways to pursue that goal, such as encapsulation, which Novocell and others are working on, for example. We've also recently announced a major collaboration with the Genomics Institute of the Novartis Research Foundation (GNF) in beta cell regeneration. We have a number of programs with small molecules and biologics that were first used to treat other diseases, which often accelerate the drug development process – they're not final cures though, so if we talk about IL-1 receptor antagonists, or an

anti-CD3 antibody, for example, they come more under the category of treatments. In terms of a time frame, it's going to probably exceed 10 years, certainly longer than we would like. But from my vantage point, it's not that far away, when you consider that it often takes 12-plus years to develop a new molecule for clinical indication. My feeling is we will see a lot of benefits beyond the decade.

WHO IS DR. LEWIS?

Kelly: Great, thank you – we hope so, and we so appreciate all that JDRF is doing. To step back a moment, could you give us a little more personal insight into your background and what led you to this position? What interested you particularly in diabetes?

Dr. Lewis: I moved into diabetes research when I became involved with stem cell research while at Celgene in San Diego. At the time I was running Celgene's Signal Research Division. They had acquired a stem cell company that focused on cord blood banking and placental cell delivery, and that sparked my interest in stem cells, which were obviously closely tied to diabetes research. You probably remember that California at that time was a hot-bed for stem cell research, so I connected with many of the researchers in the field. Around the same time, in 2003, the proposition that led to the California Institute for Regenerative Medicine (CIRM) was introduced, with Bob Klein driving a state-wide initiative to create a fund for regenerative medicine and stem cell research. Bob is a former board member of JDRF, and the Foundation was closely involved with those issues.

My full-time involvement with diabetes research began at the end of 2005. I was approached by Novocell, a stem cell engineering company in San Diego, that was focused on creating a cell therapy for diabetes. I took on the CEO position there in February of 2006, and we worked on islet cell technology.

As you know, islet transplantation has been possible for some time as an experimental therapy for type 1 patients, particularly people with brittle diabetes. But transplanted cells, which come from cadavers, don't last long, and the patient has to take high doses of immunosuppressive drugs to prevent rejection. Novocell took a different approach to replacement. They took those donated islet cells and encapsulated them in a polymer that protected them from attacks by the immune system. In that way, people undergoing transplants wouldn't have to take immunosuppressive drugs for the rest of their lives. Novocell was also developing a proprietary protocol to coax human embryonic stem cells into insulin-producing cells. This was my first entry into cutting edge stem cell research, and I realized immediately that this was the future of medicine.

Kelly: Well, a natural follow up is, what lessons have you learned/experiences do you have that you feel helped prepare you for the position?

Dr. Lewis: There are some clear parallels between leading JDRF and running a start-up – you need to find great ideas that have a clear path to becoming treatments and cures, and quickly but systematically move those ideas through the product pipeline. And you have to be smart about placing bets on what will work and what won't – and on what people with the disease will use and what they won't.

In many ways, the volunteers at JDRF are like your investors at a start-up. They have a huge personal interest in seeing you succeed, and they have an extreme sense of urgency about bringing home that success. But at the same time, they understand the complexity of what you are trying to do and are willing to support that as long as your path to success is clear.

From my earlier research background, I know the advantages of managing a large portfolio of research, but also the difficulties of managing a big scientific staff. We need to be big enough and smart enough to be the go-to organization in diabetes research – but at the same time, not so spread out that we can't actively manage our science, and mass our resources behind the most promising ideas. We need to take some smart bets.

Kelly: Dr. Lewis, we'd love to hear more about your views on the Artificial Pancreas Project (APP). What is the biggest barrier right now? Is it the insulin action? The accuracy of the devices?

Dr. Lewis: Broadly speaking, it's a combination of issues, none of which can't be overcome. From a mathematical perspective to run these systems, there are algorithms that we are helping to create. They involve a variety of factors around food intake, size, etc., all of which clearly are things that we're working on. The sensors probably need to be further improved, even though we have seen so much improvement already. And you've mentioned fast-acting insulin – clearly, if we could further improve the speed, then we'd be in a much better position to closely mimic the physiological response.

We've been talking with companies and people to accelerate CGM, pump and algorithm development, all to the end of getting a first-generation artificial pancreas. Obviously, there are companies that have made more extensive progress on the technology front, and they're all very keen to see this happen. Our goal is to make sure that many companies and academic groups can develop this program. I think we're optimistic that we will be able to form collaborations around the world, in the not-too-distant future. I think that support will go a long way to ensuring that short-term timelines will be met and that we won't be waiting longer than five years for success.

ON JOINING THE JDRF

Jen Lesser: How did you decide to join JDRF? How did you think about the decision and what did you think now that you've arrived and are six months in?

Dr. Lewis: Number one, JDRF is a great brand with a great reputation. Number two, it had a portfolio of research with both academia and companies that was much broader and more interesting to me than those in my previous life, and I've always been involved with multiple projects at once. They cover topics from glucose control and the Artificial Pancreas Project, to immunity, beta cell replacement and regeneration, complication therapies, devices, biologics, and small molecules. And then third is this incredible army of people that we call volunteers. They all have passion and are absolutely supportive. They always say the same thing to me: anytime you need anything, let me know – I'll do anything I can to help. I can assure you that sentiment is incredibly motivating for somebody who's in charge of an organization, and I never had that in my life before. [And the board members] are not looking for a financial return on their investment. They just want a cure.

Kelly: It's an amazing team that you have both in the US and globally and what you are doing on so many fronts is truly inspiring. So from patients, thank you for doing that.

Dr. Lewis: And you know, that's so meaningful for me to hear: Thank you. Nobody ever tells you that in a biotech company! This is a very different world.

THE JDRF'S RESEARCH PRIORITIES

Kelly: The JDRF has made some real strategic shifts to focus more on improving things for patients in the here and now. Can you discuss the changes that have been made and what the implications are for the organization?

Dr. Lewis: As I said earlier, the simplicity of the idea of a single "cure" is very appealing and therefore the mission has been very straightforward. But realistically, patients have to maintain their health, and they need to live longer while that research is ongoing. Work aimed at more current breakthrough therapies is critical – it will help more people to benefit from an ultimate cure. So we have made an absolute commitment that we intend to do both, getting better treatments in the short term while focusing on the ultimate goal of a cure through beta cell preservation and restoration.

One top priority right now is developing a first-generation closed-loop system for glucose management, with faster-acting insulin. We're also looking at other hormone therapies, which may be included eventually in a new type of artificial pancreas.

Another priority is the beta cell. The JDRF is incredibly supportive of replacement therapies, supporting research on cell therapy, embryonic stem cells, adult stem cells, beta cell precursors, and reprogrammed cells. Cell transplants for diabetes, however, are an incredibly difficult thing to do and to commercialize. So what we decided to do is focus energy on beta cell regeneration. We've been investigating and investing in regeneration for years now, and have made progress to the point where we can now move to translation. The collaboration that we talked about with GNF is obviously huge for us in addressing those translation challenges; a multimillion-dollar collaboration with the idea of generating multiple investigational new drug (IND) applications. We're looking for other, similar partnerships to advance research in this field.

That, we believe, is the way forward. We've got to exploit the physiologic mechanisms of beta cell expansion, which has been observed in pregnancy, obesity, and childhood growth. Clearly, that's something that we think we can do. And obviously, we feel we're well positioned to drive the future of medicines. Working with GNF and other academics in the field, we really believe that, like we did with the Artificial Pancreas Project, we will be seen as the leader in beta cell regeneration. Regeneration will also be very effective, we believe, for people with type 2 diabetes.

In addition, for a cure for type 1, we need to modulate the immune system. We believe perhaps the most important and effective area of focus for us in terms of immunity is to create antigen-specific therapies to suppress the immune system response that causes diabetes.

We're already involved with a number of immunotherapies that are nonspecific or from the anti-CD3 class – rituximab is another example. But some of these kinds of programs tend to have a risk of adverse side effects and don't address autoimmune memory effectively. So our approach now is trying to regulate the autoimmunity of the disease safely and with durability with antigen-specific therapies. We really believe it's critical for us to have this kind of therapeutic, both to modulate the immune rejection of transplanted cells, and more importantly, to regenerate beta cells. It's a one-two – regeneration plus a targeted antigen-specific therapy. Now, what is that today? I can't tell you because it's relatively new. There are a number of approaches that we are investing in and investigating, and we believe the combination will be the really exciting way that people will see a cure down the road.

Eric Chang: Dr. Lewis, how have you felt about all of the work that the JDRF has done on the reimbursement side? We know the organization has been lobbying to increase reimbursement for devices and provider time. Some of this is actually newer work for JDRF, is it not?

Dr. Lewis: Yes, it is. You know, we have an incredibly valuable Government Relations staff that has been instrumental on the research side. They are a key component of the artificial pancreas project and the CGM studies we have undertaken. Our connection with insurers and with the FDA also helps.

One of our objectives with the CGM studies was to convince insurers to increase their coverage. Since the first results from those trials were published more than a year ago, most of the top insurers now reimburse for CGM devices. When it comes to the regulatory environment, obviously, that helps with the Artificial Pancreas Project. Most companies have their own regulatory capabilities. But when we create the first generation artificial pancreas, I think we can do a lot of the groundwork with the FDA, like we've done for CGM, and I'm optimistic we'll be able to help speed the process for the artificial pancreas/closed-loop.

We keep the FDA very aware of what we're trying to do, and I think we have a very good relationship. I think our role is seen very positively by these authorities and by Congress. We are lobbying in the best

sense for patients and trying to teach people when we can. We know what the issues are and I think we have seen incredible progress – and in the same breath, I will say there is so much more to do, and we aren't looking up for a microsecond.

COMPANY COMMENTARY

Kelly: Tell us a little more about your thoughts on the companies JDRF is currently funding – we'd love to hear your opinions, especially since you've so recently led a company yourself.

Dr. Lewis: Well, so many different companies are onto very exciting tracks. It's a terrific complement to our academic research. I think Tolerx and Macrogenics are doing a fantastic job. They're very smart; they have great clinical trials with anti-CD3 therapies. Novocell – I think what they're doing is phenomenal, and many of our volunteers like the approach. Bayhill Therapeutics is a very interesting one as well. They started off in multiple sclerosis and then made real strides in diabetes and recently Genentech/Roche made a great deal with them. And the list goes on with companies like SmartCells and Osiris and others.

Kelly: That was great to see – a classic case of JDRF funding working really well as the bridge between companies.

Dr. Lewis: Yes, there are gaps in the development pipeline, and we want to help fill them by supporting the right companies. I think we've made smart moves in funding several companies.

A few have had pharma take up their projects for late-stage testing – Tolerx with GSK, Macrogenics with Eli Lilly, Osiris with Genzyme, Transition Therapeutics with Lilly, and Bayhill Therapeutics with Genentech.

With Transition Therapeutics and Lilly, gastrin-based therapies have been used in regeneration, and there are things we intend to do beyond gastrin, such as trying to activate gastrin endogenously by using proton pump inhibitors in combination. It also has application for both type 1 and type 2 diabetes.

I love what Osiris Pharmaceuticals is trying to do with mesenchymal stem cells. Wouldn't it be wonderful if you could have a general anti-inflammatory cell that is not going to be rejected, that you could put into patients – not just type 1s but other patients, too? I'm keeping my fingers crossed that this approach will work.

Now Novocell is another example of a company that is moving aggressively towards the clinics that has been supported by JDRF. All in all, we funded more than 25 different small biotech companies over the past few years. Ultimately, you need lots of shots on goal to be successful. And so the more shots we have, the better chance we'll score with some. So far, we have had four companies move on to commercialization agreements with pharma or diabetes companies. That's pretty good.

Kelly: What interest have you seen in the field from larger companies?

Dr. Lewis: I think Genentech is making a major commitment to move into diabetes. It's exciting, it's new, and I'm encouraged by them immensely. Clearly, there's also incredible commitment to diabetes from Novo Nordisk in their collaboration with Cellartis. Lilly has been very supportive of biomarkers research, and I'm optimistic about their two collaborations with our partners Transition and Macrogenics. GSK getting involved with our partner Tolerx is exciting for us too – it's another big pharma company getting in the field.

All of those things are very positive. But the one I haven't mentioned is Johnson & Johnson. Clearly, they are exceptionally well placed. They've made a commitment to diabetes research and product delivery, and their stem cell program with BetaLogics has been moving nicely in that direction. They've got some very smart people in their organization.

That's one of our goals – to encourage companies like J&J to take a very close look as to what's out there. It's great for biotech companies to do early clinical trials but it's essential for the commercial wing to come from pharma, the big companies that have the money and the ability to take these products into the marketplace and support them. So we've really been trying to encourage big pharma to get in the space. But as you well know, they're a bit risk-averse. They will do it as long as there are biotech alliances to start with. These companies that I've mentioned, they're all clinical stage companies.

Eric: **What do you think will motivate larger companies to invest in more cure-based research?**

Dr. Lewis: I think the notion that there isn't just a single cure, and that there are ways to approach patients on the way to the ultimate cure. Large companies are risk averse, and the ones involved in diabetes therapies would have large markets to lose if there were one single cure. However, the multiple shots on goal approach, with combination therapies, devices and solutions for patients with diabetes, makes it more attractive to large companies.

THE FUTURE OF DIABETES – AND MESSAGES FOR ALL

Kelly: A last thing for patients specifically: How do you think diabetes will look five years from now and ten years from now?

Dr. Lewis: Well, there's going to be incremental changes and improvements over the years, and it will vary according to what stage of your disease you are in. The next five years, we'll be trying to slow progression of this disease by improving A1c with less hypoglycemia, so you have more time within your target glucose range. Hopefully, this will also reduce long-term complications. We will likely have drugs on the market that preserve some beta cell function in the newly diagnosed. And there will likely be improvements in treating diabetic eye disease and hypoglycemia unawareness.

If you talk about the next five to ten years, then you're getting into keeping people within your target range longer, with minimal interventions. We'll be preserving beta cell mass earlier in the disease, and maybe even increasing beta cell mass in some patients with established disease. And obviously, there will be some better treatments for certain complications. Beyond that, we're going to try to prevent and reverse this disease. The goals are clear.

Finally, it's also clear that we'll have better biomarkers and know how to better image these cells that we've talked about. What we don't know today is what the technologies are that might actually make a huge difference. They probably exist, or they may exist in other fields, and we just haven't used them in diabetes. We will be aggressively looking at drugs which we can reposition because obviously that's always the quickest way to get a new product into the field.

Kelly: And, do you have any other messages in particular for the corporate community? The investor community? The patient community?

Dr. Lewis: Diabetes is large market, and I don't only mean the type 2 market. The corporate and investor communities will realize that type 1 therapies are on their way. Insulin has been around since 1921, and we need alternative products. Importantly, this is a receptive patient group often diagnosed at a young age so their support system is well established. Also, given the nature of type 1 diabetes, compliance is likely to be better than in much of the type 2 marketplace – that should be appealing to the corporate community. I think there will be a far greater focus on type 1 patients due to the growth in numbers, the accelerated innovation landscape, and the characteristics of that patient group.

For people with diabetes, these are exciting times. We have a portfolio of research aimed at benefiting people at all stages of diabetes – those who have been living with the disease, sometime for decades. Those with complications. The newly diagnosed and those at risk. We are focusing our research so that we

can deliver both near term and longer term treatments and cures. Our aim is to cure, treat, and prevent diabetes – with emphasis on cure.

Kelly: That is fantastic. We hope you will be at JDRF as long as it takes to achieve all of these goals. Thank you so much, Dr. Lewis, for sharing your valuable time with us.

— by Eric Chang, Jenny Lesser, Katherine Wu, and Kelly Close