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Oligonucleotides: Technology, Strategy, Collaboration
The Essential Fundamentals For Success
A Conversation With David Corey

David Corey, Rusty Kelley Professor of Medical Sciences, UT Southwestern Medical Center

ABOUT

David Corey is the Rusty Kelley Professor of Medical Sciences in the Department of Pharmacology and Biochemistry at UT Southwestern Medical Center and President of the Oligonucleotide Therapeutics Society. In this presentation, David recently sat down with Scott Merz, Asahi Kasei Bioprocess Sales Manager for the Americas to share his experiences and provide advice on technology strategies to accelerate oligonucleotide R&D.

David Corey, Professor of Medical Sciences, UT Southwestern Medical Center

Scott Merz, Sales Manager, Asahi Kasei Bioprocess America, Inc.

Scott Merz: David, how does one select better targets, based on disease indication and competitive advantages?

David Corey: That's a really critical question in this area. As you've just described, the technology's developed to the point where with antisense oligos and double-stranded RNAs that we have a pretty good understanding about how to knock down genes in animals and humans, a pretty good understanding of what clinical trials are going to be like. The problem is finding the initial target. I guess that's going to be true for any modality for drug development, but it's especially true here.

DC: First of all, you're going to have to get that great insight at the beginning of what's your disease indication going to be. That's going to require the usual discussions between basic scientists and clinicians trying to find some opportunity that other people haven't. then you have to overlay that on top of another thing: how is it going to compete potentially against a small molecule or an antibody or gene therapy? And that's something that you're going to have to think very, very seriously about because you don't want to put all the money in through phase three and then find out someone has an antibody that physicians are going to prefer to prescribe.

And then cost. Those two things, there's obviously an interplay there. You want to do it so that the cost is going to be appropriate so that you can make a profit while still benefiting patients. And even if you have something that's better, our insurance company is going to pay for it, especially if there's some kind of competing treatment. So these are all the kind of things that people need to think about up front.

I'll give you just one concrete example right now. Kynamro, that's a double-stranded RNA that's approved for lowering cholesterol. It has remarkably good properties in humans, both lowering cholesterol and very little toxicity. It would be ideal if that could branch out into a larger patient population. It's an approved drug. You might have seen the commercials on television for it. But how's it going to compete against the existing antibody that targets the same protein? That antibody has to be administered every month. Kynamro could be administered every six months. It would probably be easier for patients. But the antibody has a head start. I believe the antibody also has outcomes data. Kynamro doesn't yet. So which one's going to be used? How is the existence of a competitor going to limit it? Those are all questions that are being confronted right now. These are some things to think about.

SM: Are these questions really at the drug sponsor level, or are they actually having similar conversations with maybe a CRO that they're using? Can you just give us some insight on who has these discussions as far as within the sponsorship or other people?

DC: Well, they would be at every level, right? Because with the CRO, especially if they're the ones who are making the compound, the cost is going to be critical. And again, with Kynamro, you're potentially talking about treating hundreds of thousands or millions of people. How are you going to produce that much compound? There's a discussion that has to be had initially with the people making the compound.

SM: Right. As far as the discussion of which indication, you also have to probably look at which of the technologies and how you use them, the effectiveness of the "bread and butter" technologies. Can you roll into that, the evaluation of the effectiveness of it?

DC: We're talking about what do you want to use? Double-stranded RNAs, antisense oligos. If you use an antisense oligo, do you want to use ones with a negatively charged backbone like Ionis does, or do you want to use a morpholino backbone like Sarepta does? And those are all decisions. I mean, for both of those, a company like Ionis and a company like Sarepta can target exactly the same genes or try to change splicing of exactly the same genes. You're going to have to think about how to evaluate the effectiveness. And again, that will also get down to what the cost of goods is, how the molecules are made, what their toxicological properties are, and whether or not they're tailored for a particular indication. All these things have to be thought about.

SM: Again, at our level, we don't get into the research level of the oligo world. we're obviously in the more process pilot-scale technology. So the idea of tweaking the existing technologies to improve deliverability, can you shed some light onto your thoughts on that and what's the best way to approach that?

DC: If you go to talk to anyone in the oligonucleotide therapeutics world and you ask them what's the biggest problem, traditionally the answer's been there are three answers to that: delivery, delivery, and delivery. That's because right now we're pretty good at delivering things to the liver. We're getting better at delivering them to the central nervous system. We're pretty good at delivering them to the eye. But imagine all of the targets and all of the other tissues. And the big example of improving delivery was the invention of GalNAc to enhance the potency of delivery to the liver. To the extent that basic scientists can figure out better ways to deliver and then process scientists can figure out better ways to synthesize those on a large scale. That's going to be critical. So for example, let's suppose you want to get these compounds to help with cancer. Gonna need better delivery methods. If this field is really going to expand beyond kind of niche applications for a handful of diseases, better delivery is going to be necessary. And that's going to probably mean different chemical entities.

SM: You mentioned GalNAc and we all know the success that GalNAc has had with the ASOs. Are you seeing any specific technology that is forthcoming that you can share so we can address some of those broader cancer therapies or indications?

DC: Well I mean a few labs have talked about carbon chains, cholesterol modifications. These are pretty simple ones that increase the hydrophobicity, maybe give some better membrane binding and permeability. And those do look like they are expanding the range of tissues. So that would be a simple change and you can imagine that it isn't that tricky to add that to a synthesis.

We'll have to see what other people do. But again, in the academic world you see a lot of kind of fancy chemical changes, but at the end of the day for those to be practical they've got to be boiled down into something that you can make on a large scale. We have to consider that filter too. As you know

SM: You're right and it's got to be key because what you can do in your lab, can you translate it into a process that can actually be of benefit to patients?
For leveraging technology to develop transparent quality data to differentiate yourself, this seems like a pretty broad idea. Can you share some light on that?

DC: It kind of seems obvious right. But you know I'm in a position where I'm often asked to evaluate the slide decks that companies bring before me. And I look at those slide decks not so much in terms of what they claim but what the quality of the data is. This oligonucleotide field is not a new field. It dates back 30 years. Why have companies like Ionis and Alnylam survived over that amount of time? It's because they figured out that you had to provide convincing, transparent data to convince people that what they were doing was real. And that what they were doing was believable and would be robust enough to help people in the clinic. So I think that's what's really important. It's not what you claim to try to sway some investor who isn't really familiar with the field. It's providing the cold hard data, the controls, the data that you can interpret so that we know that things are real. Now this may not be so important for the crowd tuned in today. A lot of them are chemists. And chemists are used to having to put all their analytical data out there to meet rigorous standards. That really needs to be the model for everything in this field all the time.

SM: Are you suggesting that we need to have more clinical trials of potential indications? Is that what your vision is?

DC: Even before clinical trials. Before you subject a patient to a clinical trial, your preclinical data needs to be very strong that the underlying hypothesis is valid. And remember that's where a lot of people go for their series A financing. You always want to see that convincing data before you go into the clinic, both from the standpoint of doing what you should be doing for the patients, but also because that's where the costs balloon up. And too often that isn't the case.

SM: Are you suggesting that the preclinical data should be more presented through conferences, symposiums, more papers being delivered? How do you expect, how do you want them to get their data out there for people?

DC: Well, I mean, peer-reviewed data is always good. Presentations at conferences are always good. From my perspective as someone who's been around for a while, sees a lot of talks, I also edit a lot of papers for journals. I can tell within a few minutes whether someone has done experiments well or not. And the standards of the field, there are plenty of guidelines papers for how to present data. I've written a couple myself. People have to read those, they have to understand them, they have to demand that work be done to a high level, both at other companies and within their own companies.

Again, very much the same way is if you were submitting a paper to Journal of the American Chemical Society, they would expect certain standards to be met with analytical data. You should expect that with everything in this field.

SM: Sure. I agree with you on that. So, just a broad stroke of the industry, are we at a good spot with this right now? Do you see more improvements need to be made? Can you shed some light on that?

DC: clearly I still see slide decks that are problematic. But on the other hand, if you go and attend the oligonucleotide Therapeutic Society, which is at the end of this month in Barcelona, virtual attendees are still welcome, then I hope you will find that the science there is as high quality as you will find at every meeting. And that's because there is a consensus and leaders of the field that having high standards is the only way this field is going to progress in this extremely bruising competition with other modalities.

SM: Agree. That's a conference that I know we will be attending as well and will be exhibiting. I think this is our second or third one. Let's roll into the value, what's the impact of implementing new technologies?

DC: When you think about implementing new technologies, it's not enough to be a little cute change, right? People are always going to want to stay with what's proven. So when I see a new technology, I sort of think to myself, first of all, is it going to be practical to scale up and actually have an impact on real world drug development? The other thing I think about is how much is the improvement going to be? A marginal improvement, it's going to be tough to move the dial on that, right? But if something has the possibility for a large improvement in cost, in tissue uptake, in potency, then that's the kind of thing that attracts my attention when I'm looking at something. So for example, if someone could find a way to get some decent uptake in a particular tumor or in a new tissue like kidney or pancreas, that's something that would get my interest. With the synthesis, if someone could find a protocol that would dramatically decrease cost, dramatically make the chemistry greener, those would be the kind of things that would get my attention. And then of course, they support those claims with good, transparent, logical, well-controlled data.

SM: Going backwards a little bit, you mentioned and we talked about the internal discussions within, we'll say the sponsors, of which direction, which modality they're going to try to target as far as indication. We see, to my knowledge, that it's mostly the smaller pharma companies that seem to be forefront in the oligo space, but now big pharma seems to be getting on board with it over the past, let's say 10 plus years. GSK, AstraZeneca, Pfizer, they're all investing. Are they consulting with people like yourself in the industry, trying to help them understand which modality is going to be best for them to go after? If they should use the existing modality, how are you consulting in this area?

DC: They're definitely seeking outside opinion. I mean, I know I've been part of like seminar series that several of these companies have had. I will point out that there's some history there, that big pharma has repeatedly moved into this area. And then at the first sign of failure has abandoned it. And often has invested a lot of money with the expectation of short term returns. I think that the lesson is don't go into this area if you're a big pharma and expect something quickly. You have to be in there for the long haul, solving difficult scientific problems and working toward an outcome that's going to be good for them and good for patients. So hopefully they've learned their lesson and that their involvement will benefit everyone.

SM: That's great advice. And I completely agree that we've seen it all on the way as far as the investment and then the quick decision to back out. We've seen that actually at the CMO levels while companies trying to get into oligonucleotide manufacturing, not have an initial success and then just abandon it and then come back and revisit 5-10 years later and trying to get back into that space. Now that more indications have come along, maybe they can jump into it with a different approach and we're hoping that there's success there.

DC: Yeah. And of course, this isn't just nucleic acid therapeutics. This is probably startups all over the place. There's an expectation that you're going to get success quickly. But you know, this isn't like a software company. There are some, you know, important scientific challenges to solve. And if you take the time to solve them right, then chances are you're going to do well in the long term.

That's also the lesson of Ionis and Alnylam. They managed to stay funded. They kept doing good science, and those two companies and some of the other companies in the field have just gotten stronger and stronger over time and solved some amazing scientific problems as have people like yourself who've done this amazing job of being able to scale up synthesis and provide the amounts of material where we can talk about actually serving hundreds of thousands of people a year.

SM: Actually speaking of Ionis, there's a question that did come in. Let me read it directly. Do you think that if the Ionic guide strand-only drugs did not have a potency problem and the changes needed to achieve this problem were trivial, this would be an important breakthrough?

DC: Potency is always important. And especially with antisense oligos, they are locked in mortal combat with double-stranded RNAs. So if there could be a chemical breakthrough to increase their potency, that would be huge, but easier said than done.

SM: Can you go ahead and give one more shout out for the OTS coming up and maybe you can get some more people to join that conference because it's very critical for us to have this conference so people can understand the science behind it.

DC: The Oligonucleotide Therapeutics Society is the main society for oligonucleotide therapeutics. Our mission is to educate people about oligonucleotide therapeutics, instill high standards of the field and also reach out to young people and foster their careers. Our meeting this year is in Barcelona. It's at the end of October. Unfortunately, the in-person meeting has been capped at 750 and we've already matched that, but you can still do virtual. You can still ask questions online. If you're virtual, you'll have it to play back later. It's really the place to be. If you can attend it in person, it's also a fantastic place for networking. Anyone not familiar with this field, it's filled with people who've dedicated their lives to the field, whether they're in academia or at any company, they are happy to tell you everything. Great place for networking. So please join the community if you haven't already.

SM: Great. Thank you, David. I hope everyone truly does, because I know we've actually gravitated towards that over the past few years. It looks like an exciting conference and I hope to be able to at least do virtual.

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