EPISODE TWO:

Enabling Precision Oncology Using RNA-based Information and Technologies

Dr. Dave Messina, Cofactor Genomics | December 26, 2018

Welcome to The Precision Medicine Podcast, where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows, and consider solutions for advancing the quality of patient-centered cancer care.

Jerome Madison: Hello, I'm Jerome Madison, Vice President of Provider Relations at Trapelo and one of the hosts of the Precision Medicine Podcast, and today I have David Messina, Chief Operating Officer of Cofactor Genomics, and we'll be discussing how to enable Precision Medicine using RNA-based information and technologies. Dave, thank you so much for being on the podcast, and welcome.

Dave Messina: Thanks so much, Jerome. Really great to be here.

Jerome Madison: Absolutely. So, Dave, we met at the Harvard Medical School at the Personalized Medicine Conference, and we're doing our man-on-the-spot podcast interviews for the Precision Medicine Podcast. And when we met, I learned something really unique about you and your leadership team at Cofactor Genomics. Many of you have experience from the Genome Center at Wash U., which was really predating the Cancer Genome Atlas Project. But, can you tell us about that experience, and how that led to you founding Cofactor Genomics?

Dave Messina: Yeah, yeah, absolutely. So, we were fortunate to be really in the thick of it during the heavy days of the first Human Genome Project. So, we were there actually a little bit before that started, I think, just at the beginning, when with the first large genome to be done in that center and collaborating with other centers was the worm genome. And Bob Waterston, who was one of the leaders on the project and on the Wash U. Side, was a worm biologist, and some of us liked to joke that maybe he wanted to get the worm genome done first.

Dave Messina: So, you can imagine what it was like to be around a large research center where there was a factory or a military-type approach to generating the massive amounts of data that was necessary. And a lot of new technology had to be developed along the way. So, when the project began, the investigators who started it knew that they would not be able to complete it without the creation of new types of technology, both on the hardware sequencing side, but also in terms of the molecular and computational approaches.

Dave Messina: And so it was, at that time, sequencing was a much slower throughput endeavor. So, this was the days of the ABI 3730 and 377-sequencer where you'd have to cast a slab gel of acrylamide and [inaudible 00:02:50] load 96 samples at a time, and you could only get about 600 bases per read. So, on a good run you could get maybe 60, 70-thousand letters of DNA generated at a time. And the reason why it took, give or take, ten years and $3 billion to do it the first time is that it really took an army of people or research institutions across the world to be able to generate all of those gels and process—all that data—and stitch together what was the largest jigsaw puzzle in human history.

Jerome Madison: Yeah. What was it like using the different technologies? Now we have technologies that are very efficient, and they have high throughput with what they are measuring, but what was it like in the limitations of the technology and the platforms you guys were using during that time?

Dave Messina: So, the manual process did involve a lot more skill than we think of today. Today, you load a sequencer, most of them are cartridge-based formats. So, you load the sample, it automatically can do millions or even billions of sequencing reactions. And, in parallel, the next-generation sequencing machines at that time in loading this gel manually, you had a very fine, flat-tipped pipette that you had to load.

Dave Messina: So, I had come from the University of Chicago where I had been involved in a human genetics project which was involved ... it was a pre-human genome, right? So, we didn't have the map of the human genome, and we had to figure out where, out of all the billions of bases of human DNA, where the gene that was likely to be responsible for the disease we were looking at was going to be. And, so, I loaded a genotyping gel, a sequencing gel, just about every day for a year to generate the data. And we were thrilled that we were able to narrow down the location of this putative disease gene to about one million bases of DNA. So maybe 50 or 60 genes in there, and we really didn't know how many.

Dave Messina: And I got pretty good at loading those gels, doing it about every day for a year. When I got to the Genome Center at Washington University, I loaded some gels there as part of the Human Genome Project with some of the folks who had been doing that three shifts a day there. They were way better than I was and way more accurate and way faster. They were able to load a gel in about twice as fast as I could and do it more accurately.

Dave Messina: And, so, there was that level of skill there even just in generating good quality data by having a good load on the gel. So much different than today or even just a few years later than that when the next-generation sequencing machines started to come online in the mid-2000s.

Jerome Madison: Yeah. A lot of the work that you guys did then, and of course with the emergence of NGS technology, much of the focus has been on cracking the code of DNA. But your work there at Cofactor Genomics goes beyond DNA, focusing on the importance of RNA. Why is it important to examine RNA, and how does that differ from what DNA can tell us about a patient's disease?

Dave Messina: Right, so DNA has unquestionably been critical in our understanding of human biology. And knowing the entire parts list, if you will, of what makes a human being from its DNA is essential information. But DNA fundamentally is about potential. It's what might be. When we look at DNA we talk about risks, we talk about estimates, because DNA is really just the master instruction book. And very rarely does DNA mean destiny in the way that we think of it. And, so, that's why if any of you have done the 23andMe® or that sort of home testing, you'll see things like your likelihood of developing a disease based on your DNA.

Dave Messina: So, that information is really helpful, but wouldn't it be great if we could get more of real-time readout, a barometer of your health? And that's really what RNA provides. So, if we think of DNA as the master recipe list, we know that in any given cell in the body, all the 20-thousand genes that exist in the human genome, not all of them are going to be turned on in every cell in the body. And if we identify, say a variant or a mutation in your DNA, that doesn't necessarily mean that the gene with that variant is expressed in the tissue where it matters or the cell where it matters.

Dave Messina: So, RNA being the active form of DNA that DNA gets copied into RNA, so you have lots of copies of RNA in a cell that are then turned into proteins, which actually do the work. And, so, the real advantage of looking at RNA instead is that you can use the high-throughput technology that was developed for DNA sequencing with RNA, but you're really getting a readout that's much more like the protein that's actually doing work in the cell, which is what you really care about. But the technology today doesn't exist to be able to read proteins directly in a high-throughput way.

Dave Messina: So, RNA occupies a sweet spot in the middle where we can use high-throughput technology but understand really what's going on in real-time in the cell and get a picture of whether that cell is healthy or sick or whether it's likely to be responsive to a treatment.

Jerome Madison: I think that's a really important distinction, because a lot of the conversations focus on DNA sequencing today. And just to quote what you said, "DNA can only tell you potential." It's about risk, where RNA tells you what's happening today with that patient's disease and whether the cell is healthy or potentially carcinogenic.

Dave Messina: Exactly. And, so, except for scenarios like cancer, our DNA really doesn't change much from when we're born 'til we die. It is mostly stable. And, yes, we see changes in the cancer genome, but by and large our DNA doesn't change, but your RNA does. Your RNA is changing all the time. It's a dynamic molecule. And so being able to look at what genes are turned on and off and in what combination in a cell or tissue gives you far more information of a much richer source of information about what's going on inside your body.

Dave Messina: And so that's why it makes such a powerful molecule for so many areas from drug development right on through to diagnostics to being able to use it in treatment decisions.

Jerome Madison: Absolutely. And the technology to make these measurements, to make these findings, is key. And that's what's going to enable Precision Medicine. And technology is now catching up to the imagination of scientists like you. And, in fact, I read somewhere where you compare where we are in Precision Medicine today to pre-internet computers.

Dave Messina: Yes.

Jerome Madison: I thought that was very, very poignant. Can you explain a little bit more what you mean by that?

Dave Messina: Sure. So, here we are at the end of 2018. If we rewind 30 years and think about what computers were like in 1988, so, in 1988, you could get your state-of-the-art computer would be maybe an Intel 286 or 386-processor. You'd get less than a megabyte, 600 KB of RAM maybe. You'd be storing stuff on floppies. If you had a hard drive, it was going to be maybe 80-megabytes. Your monitor was going to be maybe 16 colors, if it was color at all. And, you'd spend about $2,500 in inflation-adjusted dollars for that.

Dave Messina: So, pretty primitive compared to the computers we have today where we essentially have super-computing-like performance on the mobile phones in our pockets. We have pocket computers that can access essentially any information on the planet. And, nevertheless, the computers in 1988 were extremely useful. We had…already at that point about 15% of homes in the U.S. had a personal computer. And, so, we got a lot done with them. And it certainly wasn't the beginning of personal computing, but it was so primitive compared to today.

Dave Messina: If we were sitting in 1988 and trying to look into the future—30 years of what personal computing would be like—we might be able to guess that things would be cheaper or faster and those kinds of broad strokes. But it would have been difficult, and I would expect very few people at that time really had a clear conception of how much computing has changed our lives over the last 30 years and what advance we have seen in really every area of our lives. The internet existed in a primitive form, but it wasn't at all like it is today. Email existed, but hardly anybody outside of government labs used it.

Dave Messina: So, if we then try to use that as an analogy for where we are in genomics or, let's say, Precision Medicine today, so, Precision Medicine in 2018 is kind of like that 286-computer 30 years ago. We have a lot that we can do with Precision Medicine, and we know that it's going to be hugely important in the future, but it's very difficult for us to see, to understand, really the full breadth of how that's going to be true. We can start to think about some ways in which it might be true. And that really underscores for me what an amazing time it is for us to be in biology and really in this burgeoning area of Precision Medicine. We're at the beginning mostly, but we're far enough along that we're already starting to see some of the value and some of the power.

Jerome Madison: Yeah, I just think that's a fascinating illustration about pre-internet computers compared to the smartphone that most people carry in their back pocket. It's just amazing, just as next-gen sequencing capabilities have made tumor-cell profiling and personalized cancer medicine a reality, here comes immuno-oncology, which is a whole new world with respect to biomarker function and detection methods. How does this affect or should it affect pharmaceutical companies' approach to drug development?

Dave Messina: So, immuno-oncology—and most of you listening to this probably know this—but, this is really this amazing new class of drugs where we have the body's own immune system able to fight the cancer. And we have built up techniques, which ... and I should say, when they work, they're incredibly effective. So, the success rates or the overall response rates or survival rates that we see, when these medications are effective for people with devastating cancers, is remarkable. And the problem is, though, that although they work really well when they work, they don't work well for everybody.

Dave Messina: And, so, immunotherapies, on average, work say in roughly, let's say 30% of patients. And that's an average. It's in some cases and in some cases much less. So, in order to understand how best we can take advantage of this and really develop new medications that extend the advances that we've seen with immunotherapies, we've got lots and lots of folks who are working very hard at sort of the next generation or different ways of taking that same approach and building the next generation of immunotherapies.

Dave Messina: And one of the ways that they're approaching this is by trying to understand which patients are going to be likely to respond well to these treatments and which won't. And that's a difficult question to answer. The primary biomarker, if you will, the companion diagnostic that is used most widely with immunotherapies, is called PDL-1 antibody, which really the field has come to learn with its widespread use is not really a great biomarker. A pretty high correlation with response to immunotherapies, but far from perfect.

Dave Messina: And, so, there's been recognized a need to develop better biomarkers. And really, I think what we're seeing in the field is a shift overall from the classic single-biomarker approach where we're trying to capture all the complexity of what's going on in a patient with just measuring one thing and hoping that will correlate well with something as complex as response to a treatment.

Dave Messina: We're moving to this era where we're not only thinking about using multiple analytes to understand patient response to therapy, but multidimensional markers where we're actually taking many signals, say from RNA, and are able to combine them in a sophisticated way with computational models that allow us to capture all the complexity of what's going on inside a patient and better understand their likely response to a treatment or their prognosis or any other number of things that we use biomarkers for.

Dave Messina: So, it's this ability to take complex information, say it's from RNA, combine it with highly-sophisticated software models, and use that to inform treatments and be able to see which patients are likely to respond, even in the drug-development phase.

Jerome Madison: Yeah, you know, it's our goal at Trapelo to provide greater access and scaled Precision Medicine by eliminating the obstacles: prior authorization, insurance denials. Because it's been said by many that reimbursement of diagnostic tools is the major hurdle to facilitating Precision Medicine. So, Dave, we ask everybody that comes on the podcast, what are your ideas on how and why these diagnostic tools that companies like Cofactor Genome are developing should be covered by insurers?

Dave Messina: Right. So, in order to unlock the potential of these groundbreaking medicines, it's essential to have sophisticated diagnostics to pair with them. It makes no sense to continue to treat patients based on the law of averages, which is really how it's done for the most part today. Patients get prescribed medications based on what works most of the time in most patients with that disease. And we can do better. We can do so much better. And, so, it's critical to be able to take advantage of the new technology such as multidimensional biomarkers to be able to have just as sophisticated a diagnostic to pair with a treatment decision, to be able to pair with these amazing new medicines like immunotherapies that we see.

Dave Messina: So, there's no question that this will come. And really the challenge for us today in the industry and with, this includes the regulatory and reimbursement bodies, is how to bridge the gap from the world we know where we are a single ant-like world, and we think in terms of trying to reduce the complexity of a patient to one marker to where technology is going, and at today, where we have the ability to use multidimensional biomarkers in diagnostics like Cofactor has developed.

Dave Messina: So, there's no question that it's coming. It's going to be, I think, a battleground. And there's an opportunity for forward-thinking in insurers and regulators to really enable that. And it's possible, I think, to do that in a safe way. We can still apply all the same standards of efficacy, all the measures that we apply towards approving new diagnostics today. We don't need to create, I think, a whole new language around those or a whole new set of regulations, we simply just need to take advantage of the approaches that we have that are emerging and really adjust to that new reality. It's not going to be possible to think in single-biomarker terms for much longer.

Jerome Madison: Right. You know, those in the space are dedicated to challenging the norms. And I noticed that Cofactor Genomics, you guys did that even in your office design. I saw where you have musical instruments, bicycles, and even ski gondolas in the office. And that's not your typical setup for a highly scientific group of folks that are working on a genome. How does this impact the work your team is doing and the overall culture?

Dave Messina: Yeah, we do have a beautiful office where we have musical instruments. A lot of folks from Cofactor have a musical background. Our Chief Scientific Officer, my partner and dear friend, John Armstrong was a professional musician and actually signed to a major label many years ago and still performs and records music in his spare time. And there are other folks at Cofactor who play music outside of science.

Dave Messina: And, I think one thing that we see—and a lot of other folks probably recognize this too—is that there is a lot of similarity between the creativity that comes in the form of music and the creativity that comes with great science. And, so, it's totally natural for us that our workplace reflects that interplay and that we have a space that fosters creativity and is enjoyable to be around. And we want people to do their best work at Cofactor, and so it only makes sense to us to have an environment that encourages that.

Jerome Madison: That's awesome. Well, we want to thank Dave Messina of Cofactor Genomics. And, of course, all of our listeners for joining us today. We hope that you'll tune in for the next episode of The Precision Medicine Podcast. And don't forget, you can download full transcripts of today's episode at precisionmedicinepodcast.com. If you enjoyed this episode, you probably know someone else who would, so please tell them. They'll thank you, and so will we.

About Our Guest: Dave Messina, Ph.D.

Dr. David Messina is currently the Chief Operating Officer of Cofactor Genomics in San Francisco, California.

Dr. Messina has spent the last 20 years in computational biology and genetics. He worked on the Human Genome Project at Washington University in Saint Louis, mapped disease genes at the University of Chicago, and co-developed the first comprehensive atlas of human transcription factor genes. As COO of Cofactor Genomics, Dr. Messina is pioneering the use of RNA-based diagnostics, enabling personalized treatment for patients.

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