**SEASON TWO: Episode 36**Dr. Roy Symthe Explains the Importance of Protein Expression in Practicing Precision Medicine

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Producer, Karan Cushman: Welcome to season two of the Precision Medicine Podcast sponsored by Trapelo. This is the 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. Be sure to subscribe at precisionmedicinepodcast.com to get the latest episodes delivered straight to your inbox.

Jerome Madison: Welcome to another episode of the Precision Medicine Podcast. I'm Jerome Madison, host, and today we have Dr. Roy Smythe, the CEO of SomaLogic, who has a vision not just to heal patients through the use of precision medicine, but also to use it to keep people from, I guess, becoming patients at all. Dr Smythe, thank you for being a guest on the Precision Medicine Podcast.

Dr. Smythe: Jerome, thanks for having me. It's great to be here.

Jerome Madison: We were talking before we got on, and you have a fascinating background with your training as a physician-scientist. Can you share a little bit of your background and what made you transition from practicing to come into leading companies in the industry?

Dr. Smythe: Sure. Happy to do that. You're right. I did originally train as a physician. I trained, went to medical school of course, first, you have to do that, and then trained as a general surgeon. Also trained in surgical oncology, did a fellowship in cardiothoracic surgery and a postdoctoral research fellowship in molecular therapeutics. All at the University of Pennsylvania.

Actually, in medical school though I had a really seminal experience that had an impact on what I did later in my career. The individual who founded the Robert Wood Johnson Scholars Program, a guy named Sam Martin, was at the University of Pennsylvania. And the Robert Wood Johnson Scholars Program is a program that has postgraduate medical trainees, people that are in their residency programs, spend a period of time, 18 months or so, outside of the training at a business school and medical school to learn things you don't learn in medical training about healthcare economics and delivery science, healthcare policy, and so forth. The goal over time has been to train those individuals to do things that might change the trajectory of healthcare.

Back in the 80s, Dr. Martin decided to get a grant from the Charles A. Dana Foundation and train a group of medical students on the same curriculum. I was in a group of students that did that. I was a Dana scholar at Penn. I was a medical school student in Texas. But came up to Penn and did this Dana Scholarship Program at Horton in the University of Pennsylvania and medical school.

This is the mid 80s, and the people that were there were saying that Medicare is not sustainable and the healthcare funding strategy in North America is not quite right. The delivery structure has not been constructed to deal with most of the problems that individuals really have. I thought these guys were crazy when I started, the conservative kid coming up from Texas, but by the end of the 18 months, I thought they were right.

Despite the fact that I had this relatively traditional successful academic surgical and clinical, both academic research and clinical career, I watched everything happen that these individuals said was going to happen during this fellowship.

Basically what happened late in my career, even though I was successful and had checked basically all the boxes you could check on that a career, I decided that I really wanted to work on that project.

So, I stepped out of healthcare proper in my late 40s and transitioned to industry, because I thought that was the best place for me to actually work on that project.

Jerome Madison: Well I heard you speak at the Precision Medicine Leaders Summit. I've actually heard you speak other places too. It sounds like you're taking that knowledge and what you've experienced into the industry to solve bigger problems. Your keynote that I listened to was titled *Moving Precision Medicine from Rhetoric to Reality*.

You spoke about the value of proteomics, which is the larger … large-scale study of proteins. I'm not sure that this conversation is as prevalent maybe as it should be in the industry. But years ago I remember Brian Van Tine, Associate Professor in Oncology at Wash U, when NGS as a technology was just launched and there was a big frenzy about it.

He said, and I'm basically paraphrasing, that a gene mutation causes downstream action or non-action of a protein being made or not made. So protein is the product of the action. We should pay attention to protein expression.

Yet, at many meetings, you seldom hear a session about the importance of protein expression. So, Dr. Smythe, why is knowing and understanding protein expression an important element in practicing precision medicine?

Dr. Smythe: Well, it's a very important consideration because proteins are the structural and functional molecules of life as it turns out. We spent the last 10 or 15 years focusing almost exclusively on genes and on genomics. There are good reasons for that.

I would say that the scientific reason we've focused primarily on genes and genomics has been that despite the fact that what genes do is so important and compelling—exchange genetic information from generation to generation and propagate the human species, which is pretty important thing to do—structurally, they're really simple. It's four base pairs and a reproducible twisting structure. And actually relatively easy to measure compared to proteins.

As a matter of fact, back in the 30s before Watson, Crick, and Franklin were able to discern that DNA was actually the genetic material, most scientists thought it was protein. They thought it was protein because protein is thousands of different structures, thousands of different half-lives, all these different locations in your body.

But what's been the problem is measurement. We know now that there are 20,000 genes and that there are at least 20,000 what we call canonical proteins. Each gene makes a protein and then of course there's other things that happen to proteins. There are more protein structures than those basic 20,000. But there's 20,000 basic protein structures and, believe it or not, until recently, we could only measure a few hundred of those at a time because it's 20,000 different shapes and 20,000 different half-lives in all these locations in the body.

It's been a measurement problem. If you can only measure a few hundred at a time, then the usefulness of it as signaling mechanism, as compared to genes has been very, very low.

What we've done over the last hundred years is we've measured one protein at a time. So, if you're thought to be having a heart attack, for example, you measure a single protein called troponin, as an example, or if you're getting a blood test to check your blood count, you measure a single protein called hemoglobin.

But if you wanted to get a bigger picture of what's going on in your body or predict what's going on in the future, and you wanted to get a snapshot of thousands of proteins to do that with, it's just been impossible.

But a lot of genomics experts have said over the last couple of decades that proteins could actually be a much better source of information because as it turns out, they are the structural and functional molecules of life. They are what genes make and then a much more important consideration, the thing that I think is most compelling about proteins that's different from genes is they're contextual.

In other words, genes don't change. There's a reason why when you have your genomic testing done, you only swab your cheek once, because if you swab it again, the results going to be the same. But if you test your protein constitution in your body today and you test it a week from now, a month from now, and six years from now, every one of those tests is going to be different and tell you something different about your current health state and potentially your future health state because genes don't change over time. Proteins change minute by minute, hour by hour, day by day, month by month, year over year.

Jerome Madison: What are some examples of how we're using the measurement of proteins to inform treatment decisions and I guess looking forward, what's the promise when it comes to precision medicine, precision health?

Dr. Smythe: Almost exclusively, that's how we've been using proteins up to this time. But what we're doing at SomaLogic is something that is much more compelling, I believe, and that is measuring thousands of proteins at a time and then looking at that pattern of expression to tell you things about disease states that don't depend on us even understanding the relationship of the protein patterns that we're looking at from a biologic correlation standpoint to the disease of interest.

I'll give you an example. We just released our first seven tests into the market a few weeks ago locally, and they were released in a minimally viable product, lean startup fashion, for us to learn about logistics and about how the report should be structured with the clinicians and so forth.

We have about 150 of these tests in our pipeline and one of those tests is a test that tells you what your risk of a heart attack or stroke in the next four years is.

We measure 5,000 proteins of the 20,000 at a time and about 27 proteins of that 5,000 are reproducibly present in an individual's blood. Because of that pattern of expression of those 27 proteins, we can tell you what rich risk category you fall into, high, medium, or low.

The fascinating thing is that two thirds of those proteins have no known relationship to the cardiovascular system. So this is basically pattern recognition. We use machine learning to help us make those inferences about what the patterns mean.

What's happened is we've moved from this single protein association and actually as it turns out, those single protein associations, many of them are very weak and not all that informative. Although we've hung our hat on those diagnostic tests for almost a hundred years.

We're moving now to this more sophisticated pattern recognition where we're less concerned about the biology. We actually believe that those 27 proteins all have something to do with the cardiovascular system, we're just not smart enough to know what those things are. We'll figure that out over time with many of our partners have an intense interest in that. Some of the pharma partners that we work with for example.

But in the meantime, we just happen to measure enough proteins at one time in the body to get this informative signal. We happen to do it at a time when machine learning is available to make sense of those patterns and to correlate them to some outcome.

You can imagine doing this over a whole host of diseases and also things that are a bit more mundane, but also just as informative, like, what's my level of aerobic fitness? What's my level of visceral fat? What's my sleep quality? And so forth. Also things that proteins can inform you about that genes cannot because they're not contextual.

Jerome Madison: We talked about, speaking about pharmaceutical companies and their efforts to create therapies for this, after we measure the proteins, I guess the question is what do we do about it?

There's been recent news about pharmaceutical companies developing therapies that eliminate proteins rather than inhibiting those proteins. Raymond Deshaies, who is now the Senior Vice President of Global Research at Amgen, but when he was the Executive Officer at Cal Tech's Division of Biological Engineering, he predicted that Protex, which is a class of medications that eliminate proteins, may be the next major class of drug development to surpass protein kinase inhibitors and monoclonal antibodies. In fact, when he was there, he said the gold rush is on, and coincidentally now he's at Amgen overseeing the company's drug development in this particular area.

From your view, how promising is this particular therapeutic market and how soon can we expect protein inhibiting or degrading therapies on the market of this new class?

Dr. Smythe: That's a great question. This is another area where what we call high plex protein measurement, which is what we do. The ability to do what we do is very complex, but conceptually it's not all that complex. We just happen to measure five times more proteins in the human body than anybody else in a commercial context.

We also do it at a time when machine learning can tell us, or others that we work with, really interesting things about what those expression patterns mean. In the way that we work with our markets, we just launched these clinical tests a few weeks ago, and we'll be growing that part of our business considerably over the next decade.

For the last several years we have been working with pharma partners, Amgen one of them, whereby during their clinical trials, as they give experimental drugs to patients, they run our assay on the patients because we give them lots of protein data each time.

This question about protein-targeted drugs is a really fascinating one in relation to being able to measure a lot more proteins. Let me walk you through an interesting scenario.

When I was a young thoracic oncologic surgeon was about the time that many of the first targeted therapeutics were released. If you remember, most of those drugs didn't work. It was very disappointing. But we were all so excited, or many, many people were excited. Actually, a lot of people like me, physician scientists that were chest-deep in the science already, weren't shocked because a lot of the first generation of those drugs were targeted in a relatively simplistic way.

We found a mutation in a cancer that was relatively common. We found the protein that that mutated gene made. We targeted that protein in some way… usually inhibiting the effect of that protein. And then nothing happened.

The problem of course is that human biology is not that simple. What often happens are things like what's called the pleiotropic effect, where a mutated gene creates a protein and then has an impact on some other genes somewhere else and therefore has an impact on some other protein that that other gene makes. There's a downstream effect.

I told you earlier that our body makes at least 20,000 basic protein structures. If you're only able to measure a few hundred of those at a time, or if you can't even measure some thousands of those—and certainly that was the case at that point in time. Many of those proteins we couldn't measure at all. Couldn't even find—then the likelihood of your drug hitting the right target was exceedingly low.

What's happening now in some of these studies that we're doing with our pharma partners is that now they know what the mutation is in some syndromes, it could be cancer or something else, and they've worked out, because companies like Amgen that acquired deCODE six years ago has access to millions, at least hundreds of thousands in the case of deCODE, millions of whole genome sequences of human beings.

They've worked out the secondary pathways, which other gene is affected by the first gene, and then because we can measure thousands of proteins at a time, they can find the secondary target.

You can imagine the power of the combination of whole genome sequencing in the ability to measure what we call high plex proteins because that second and third order target will now be able to be found, and then therapies like this, that either eliminate, or shut off, or in some cases where necessary increase the action of a protein therapeutically, will be possible.

My guess is that in the next 10 to 15 years that the effectiveness of the average biologic therapeutic is going to increase dramatically as opposed to what we've experienced in the past, which has been really hit or miss at best.

Jerome Madison: We mentioned cancer, of course, oncology, but you also mentioned cardiovascular disease, that there's a lot of application for the technology. What are some other diseases or conditions that you see research being focused on for protein inhibition?

Dr. Smythe: Well, that's the great thing about proteomics as your aware, and as most of the people listening are aware, clinical genomics has been impactful, but it's been impactful primarily around a somewhat narrow band of disease conditions. It's been impactful for dominant mutation, identification of patients that dominant mutation, cancer-related diseases, but it's only about 5% of cancers that fall into that category.

It's certainly been helpful for pharmacogenomics, helping tailor cancer therapeutics based on some of those mutations and some polygenic risk assessment as well, some cardiovascular disease risk. But it's a relatively narrow band of conditions that germline mutations tell us a lot about.

So far, polygenic risk assessment again has had some impact but has not been something that's been able to tell us a lot about a broad range of things because as it turns out, most disease processes are a combination of low level genetic predispositions, which are incredibly complex polygenic risks and then all the things that we do to ourselves or that happened to us over the course of our lives.

That's, as I mentioned earlier, that's context. Genes aren't sensitive to context necessarily, but proteins are exquisitely sensitive to context. Across basically every disease category that we have looked at here, respiratory diseases, sleep conditions, cardiovascular, oncologic, immune diseases, musculoskeletal diseases, and then, as I mentioned earlier, even predisposing health conditions, things like aerobic fitness, body composition, dietary composition, and things like this, things that genes are never going to be able to tell us about because they are just not informative about those real-time things that we're doing to ourselves, when we've tried to create models for these things so far we've been successful 90% of the time.

We think that it's somewhat, and of course as my freshman biology professor always told me in biology, never say never and never say always, we think it's somewhat unlimited that they’re across disease categories, because again, proteins are the structural and functional molecules of life.

When you're either at risk for, or have, a respiratory condition, there's probably a protein signal for that. When you're taking a drug and you're at risk for an adverse event, we actually know there's a protein signal for that. We've done some research around that. So, we think it's somewhat unlimited.

Jerome Madison: Well here at Trapelo, we do our part to lead the conversation of how we bring precision medicine into routine practice through collaboration. And on all fronts the question is, how do we pay for it?

Dr. Smythe: There's that.

Jerome Madison: What are your thoughts around...

Dr. Smythe: Darn it. Interesting question. When we talk to investors at SomaLogic and they ask us, where do you think your biggest market will be in seven years? I actually begrudgingly tell them that I believe our biggest market could be off the North American continent, because if you look at the constellation of tests that we have in development, things like telling diabetics if they're at high risk for a secondary complication over the next few years, if you're running the National Health Service of Brazil, a single payer system where they're very focused on how they're going to spend their money next year... or let's use Japan.

Japan's an even better example because rapidly aging population, they've got probably the sharpest Sword of Damocles hanging over their head from the standpoint of healthcare costs in the medically developed world. They're keenly focused on where can we spend our money in the most effective way.

You can imagine saying in your population of patients in congestive heart failure, we have a test that will tell you who's at greatest risk for a secondary complication. In a population of diabetics, we have a protein pattern that will tell you who's at risk for a secondary complication. You can imagine the power of that information for an organized system of payment, which we don't have in North America right now, to be able to deploy resources in a way that has the largest impact, both financially and from a human value standpoint.

That's not the way North America is structured. We have a very perverse reimbursement system. We have pockets where the payment system aligns activities to produce both financial and human health outcomes that are both salutatory, but not everywhere, as we're all aware.

In the short term we'll be focusing a lot of our efforts on Medicare Advantage Plans. On health systems that are managing both financial and medical risk. We'll be talking to the Veterans Administration, because that's a single payer system that has a big interest in spending its money in a way that has the largest both financial and human value impact at the same time. We'll be focusing a lot of our efforts in that market, on those entities, as we move forward over the next couple of years.

If you ask me what I think should be done to change this and make it better in North America, I'll tell you there are two things. The first is I would change the payment system to a system that that rewards much more substantial health outcomes. If you did that then a lot of things would happen very rapidly.

We do that just a little bit now. Even in our value-based payment systems, it's much more about penalizing people for not doing things than it is rewarding them for true health type outcomes. It's a lot of process for the outcomes that we reward people for, they're process outcomes. Did people come in and get their vaccinations?

We actually have now the ability to collect data around real outcomes and reward health systems, or providers of care, or even physicians, for those outcomes. But what it would do is it would focus innovation on things that matter. There's a lot of innovations still. That's directed at generating revenue. A lot of that revenue generating innovation that's done to the expense of innovation in healthcare that could improve outcomes. That balance would tip in the right direction.

And then other things. The second, and we would move into the second area now that I think that would be important and that's the democratization of technology and information to individuals.

When we actually plan the third market, we plan to move into over the next few years is direct to consumers, then healthcare providers would embrace democratization rather than struggle. There's just a little struggle with it right now. I don't think that there's a fundamental concern as much as just a struggle of how I coordinate this democratization of technology and information direct to individuals.

I think that the way to make healthcare most effective is to empower individuals and make them feel more responsible and effective. I think providers would embrace that if they felt like that would improve outcomes and they would be reimbursed for that.

It sounds a little pie in the sky, but that's what really needs to be done over time. In the meantime, we'll direct our efforts where we think it makes the most sense, and we'll also be talking to people outside of North America.

Jerome Madison: Well, we appreciate the contributions that you are bringing to this space to really change healthcare and add to the value of precision medicine. We have a lot of conversations with brilliant people like yourself, Dr, Smythe, but I will say that I have a great appreciation for you because you're the only guest that's been on who really understands the importance of Texas High School football. As a former football player and an athlete myself, I celebrate the path you've taken after football. Thank you for that.

Dr. Smythe: Well, it's an interesting comment. Usually what people talk to me about is whether or not I'm concerned about when I'm going to develop CTE, but actually, and I told you earlier, I've got a son that, I've got four children, but my oldest son is a player in the NFL.

Athletics, there's a lot of interesting lessons you can learn from athletics and one of them that's come in very handy in my life as a clinician, as a researcher, and certainly has come in handy on the corporate side of healthcare, and people talk a lot about all the things you learn from sports. You learn teamwork, sacrifice, repetition, and discipline. But I tell people the most important lesson I learned in athletics was how to recover from failure.

If you're on national television and you miss a block and the quarterback get sacked, and this happened to me once when I was playing in college, you have this impulse to lay on the field, to fake an injury, and to be carried off.

But what you know is that 30 seconds later there's another play, you have to get up, go back to the huddle, line up again and man or woman up. That's the way life is. That's the way medical life was. Patients get sick. Things don't work. That's the way research was. Every experiment certainly doesn't go well. In corporate life you win some, you lose some. But the people that win in the long run are the people that recover from failure. I would say that experience has been very valuable to me.

Jerome Madison: Very well said. Dr. Smythe, we really appreciate your insights and thank you for being a guest on the Precision Medicine Podcast.

Dr. Smythe: Thanks for having me. I enjoyed it.

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**About Our Guest**

**Roy Smythe, M.D**

**Chief Executive Officer of SomaLogic, Inc.**

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Dr. Smythe is the acting CEO of a leading-edge, biotechnology company headquartered in Boulder, Colorado. During the course of his career, he has been an internationally recognized surgeon, biomedical scientist, academician, health system administrator, and healthcare business entrepreneur.

While in medical school at Texas A&M, he was a Charles A. Dana Foundation Scholar at the University of Pennsylvania School of Medicine and the Wharton School of Business. Following medical school, Smythe trained in general surgery, surgical oncology, and thoracic surgery and completed a postdoctoral research fellowship in molecular therapeutics at the University of Pennsylvania. His medical and translational research career then began at the University of Texas MD Anderson Cancer Center, where he was the recipient of NIH and numerous other funding awards. He subsequently chaired the Department of Surgery at Baylor Scott & White Health System and the Texas A&M Health Science Center College of Medicine where he was the Roney Endowed Chair. Dr. Smythe later became the Medical Director of Innovation and Executive Vice President for Institute Development before moving into expanded roles in corporate healthcare.

Dr. Smythe came to SomaLogic from Royal Philips, where he served as Global Chief Medical Officer for Strategy and Partnerships. Before joining Philips, he served as Chief Medical Officer at Valence Health, a Chicago-based healthcare company. He held the same title previously at AVIA, a healthcare technology accelerator.

A highly sought-after lecturer and the author of more than 300 papers, abstracts and essays in academic, literary, and humanities publications, Smythe is also currently a member of more than 20 U.S. national learned societies.

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