Science Translational Medicine Podcast

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Host – Orla Smith
Hello, I'm Orla Smith. Welcome to the *Science Translational Medicine* Podcast for July 24th 2013. In this show, I will be speaking with Dr. Raymond Langley from the National Center for Genome Resources in Santa Fe who has developed a molecular test to help identify patients with sepsis most at risk of dying.

Sepsis is an insidious, often fatal, disease. Patients with sepsis may arrive at the hospital with vague mild symptoms but become seriously ill only hours later. A big challenge for ER doctors is to identify these patients as soon as they arrive so that life saving treatment can be started immediately. Dr. Langley and his team combined proteomics and metabolomics with clinical data to come up with a molecular signature that may help ER doctors to identify these high risk patients.
Here now is Dr. Langley on the line to tell us more.

Interviewer – Orla Smith
Welcome, Dr. Langley, and thanks for joining us.

Interviewee – Raymond Langley
Thank you, Dr. Smith. I really appreciate the opportunity to discuss this project.

Interviewer – Orla Smith
So how big a problem is sepsis?

Interviewee – Raymond Langley
Well, it's quite large. If you think about it, over 10 million patients arrive at the hospital every year with an infection, and of that you see about 750,000 that develop sepsis. It becomes very important for the doctor to determine, first of all, if they have sepsis or not, and then what sort of outcomes that are going to take place. We see about 300,000 deaths per year because of sepsis and the cost is over $16.7 billion per year. And as the population ages, we expect actually more and more patients to become septic and have risks for severe outcomes.

Interviewer – Orla Smith
So what type of treatments are available for patients who are at high risk of dying from sepsis?

Interviewee – Raymond Langley

Well, the main thing right now is early goal-directed therapy, which was developed by Dr. Emanuel Rivers, and primarily it's a management protocol that states if you start antibiotic treatment, if you make sure that you use vasopressors to control blood pressure, you'll do ventilator assistance to help improve oxygenation. All of these things need to be taking place in the first 8 hours for the best chance of success, and they've actually reduced that down to about 4-6 hours. But that's the main thing. Right now we're left with patient management. Unfortunately, there is not any effective therapeutics for severe sepsis or septic shock.

Interviewer – Orla Smith
So what was the rationale behind your study?

Interviewee – Raymond Langley
There aren't very good diagnostics to date. The majority of them have been based off of cytokines and chemokines and they're typically single molecule assays. Unfortunately, they lack a lot of specificity and sensitivity so they're basically just not very accurate. If you panel them you can do a lot better, but the patents are owned by a number of different companies and it's very difficult to license all of them together. So what my mentor, Dr. Kingsmore, decided to do was let's take a multi-data set approach, data-driven, and see if we can't develop our own diagnostic that has the potential to improve diagnosis.

Interviewer – Orla Smith
So tell us about the study design.

Interviewee – Raymond Langley
We worked with three hospitals—Duke University, we had the Durham VA, and we also had Henry Ford Health Systems under the direction of Dr. Emanuel Rivers who developed early goal-directed therapy. From that we collected about over a thousand patients. And we selected 150 patients from our original discovery that we could look at, as you mentioned, proteomics as well as metabolomics. We used Metabolon for the metabolomics and they were able to basically identify about 400 distinct metabolites. And then Monarch did our proteomics and they could accurately detect about 200 proteins.

Interviewer – Orla Smith
And what did you find?

Interviewee – Raymond Langley
Well, what we found was quite surprising is that we were able to differentiate patient survival at presentation, so that would be even though the patients may die anywhere from 2 to 28 days out, there was definitely a signature of death that was very specific, and it was much more accurate than current models such as APACHE II, SOFA, or what's currently used for triggering early goal-directed therapy, lactate. Basically, our model performed much better. We were able to reproduce it in a number of different internal validation data sets, and we also were fortunate enough to be able to validate in a very

similar study with the Brigham and Women's Hospital where they had looked at patients as well. And, again, in almost all situations we outperformed APACHE II, lactate, and SOFA.

Interviewer – Orla Smith
So what is this molecular signature that you discovered?

Interviewee – Raymond Langley
Primarily what we found is that we saw changes in acylcarnitine esters, or basically fatty acids that were of various chain lengths that were bound to carnitine. Typically carnitine esterification is done to transport long-chain fatty acids across the mitochondrial membrane into the mitochondria for beta-oxidation and ultimately energy production. What was quite interesting in what we found is that we saw a lot of various lengths of these fatty acids bound to carnitine. Typically, this would be unnecessary because carnitines can freely cross the mitochondrial matrix without having to have carnitine bound to it. So this led us to the idea that potentially there was a backup in beta-oxidation.

Interviewer – Orla Smith
So how would fatty acid breakdown help patients survive?

Interviewee – Raymond Langley
Under sepsis you're under an energy crisis. The body needs a lot of energy to basically battle the infection that's taking place. If you have a problem with the ability to produce energy, there's a good chance that the organs can start to fail, they're not going to be able to basically just do their normal functions. And this could be linked to the fact that not enough oxygen is delivered to the patients, and this is sort of a basis of early goal-directed therapy—you know, respirate, keep the blood pressure up, and keep the oxygen flowing to the system. Well, without oxygen fatty acid oxidation can't take place. So this is potentially one issue. There also seems to be some functional issues based off of… if you look at some animal models, there looks to be some enzymes that are actually turned off during sepsis. It's not understood why, but this is where I think potential therapeutics can be discovered.

Interviewer – Orla Smith
And will ER doctors be able to use this test anytime soon?

Interviewee – Raymond Langley
That's a good question. Right now we're still very much in a discovery phase. There are some limitations to this study, the main one being that it still may not be as clinically relevant as doctors would prefer. But we did find that as the patient neared death, the signature became much more pronounced. So what we want to do is we want to run some more temporal analysis of these signatures to see how well they improve and how sensitive the signature actually is for predicting outcomes. And then we also need to work with companies to develop a point-of-care device. For this to be effective, it really needs to be in the clinic where a doctor can do a simple blood stick and get the results

within, you know, within less than an hour for the best positive results for patient management.

Interviewer – Orla Smith
And finally, what has been the driving force behind your interest in sepsis?

Interviewee – Raymond Langley
I'll start with Stephen Kingsmore. About 12 years ago he was in a skiing accident, had surgery, and developed sepsis. It was rather severe, I think he spent a month in the hospital and nearly died from it. So he took it, I would say, very personally and went out and started the EL-1. For myself, just recently my brother came down with West Nile neuroencephalitis. He was in Dallas, Texas, one of the first victims that got really sick. It nearly—well, it did kill him. His heart stopped twice. They were able to restart his heart and he was unconscious for over a month. He's still recovering, he's still—you know, this was a year ago—he's still trying to gain his strength back to walk. But needless to say, it was a very strong motivation for me to make sure we get this out, because I would like to see that hopefully if something like this happened in the future doctors would have a much better chance of helping these patients. And hopefully this will lead to new therapeutics as well.

Interviewer – Orla Smith
Dr. Langley, thank you so much for joining us today, and congratulations on a landmark paper.

Interviewee – Raymond Langley
Thank you, I appreciate that.

Host – Orla Smith
That was Raymond Langley from the National Center for Genome Resources in Santa Fe, New Mexico. Check out his *Science Translational Medicine* paper online by going to our Web site at stm.sciencemag.org.

I'm Orla Smith. Thanks for listening!

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This Podcast is a production of *Science Translational Medicine* and the American Association for the Advancement of Science, working together to advance science and serve society.