

Disruptive: Confronting Sepsis

Host Terrence McNally interviews Donald E. Ingber and Michael Super. Podcast published October 7, 2015.

McNally:

Hello, I'm Terrence McNally and you're listening to DISRUPTIVE the podcast from Harvard's Wyss Institute for Biologically Inspired Engineering.

The mission of the Wyss is to: Transform healthcare, industry, and the environment by emulating the way nature builds.

Our bodies — and all living systems — accomplish tasks far more sophisticated and dynamic than any entity yet designed by humans. By emulating nature's principles for self-organizing and self-regulating, Wyss researchers develop innovative engineering solutions for healthcare, energy, architecture, robotics, and manufacturing.

They focus on technology development and its translation into products and therapies that will have an impact on the world in which we live. So the Wyss is not interested in making incremental improvements to existing materials and devices, but in shifting paradigms. In this episode of DISRUPTIVE, we will focus on: CONFRONTING SEPSIS.

Sepsis is a bloodstream infection in which the body's organs become inflamed and susceptible to failure. The leading cause of hospital deaths, sepsis kills at least eight million people worldwide each year.

It can be caused by 6 species of fungi and 1400 species of bacteria. Diagnosis takes two to five days, and every hour you wait can increase the risk of death by 5-9%. The treatment challenge grows more complex as the prevalence of drug-resistant bacteria increases while the development of new antibiotics lags.

"Even with the best current treatments, sepsis patients are dying in intensive care units at least 30% of the time," says one of today's guests, Wyss Senior Staff Scientist Mike Super.

A new device developed by a team at Wyss and inspired by the human spleen may radically transform the way we treat sepsis. Their blood-cleansing approach can be administered quickly, even without identifying the infectious agent. In animal studies, treatment with this device reduced the number of targeted pathogens and toxins circulating in the bloodstream by more than 99%.

Although we focus here on treatment of sepsis, the same technology could in the future be used for other applications, including removing microbial contaminants from circulating water, food or pharmaceutical products.

Now let's explore the development process with Mike Super and Wyss Founding Director, Don Ingber.

[02:25] Ingber leads the Biomimetic Microsystems platform at Wyss in which micro-fabrication techniques from the computer industry are used to build functional circuits with living cells as components. He's authored more than 400 publications and over 100 patents.

[02:40]

The seeds of Wyss's therapeutic sepsis device go back over twenty years. I ask Don to talk about some of the earlier explorations and findings that laid the foundations for the current work.

Ingber:

[02:51] I was interested in mechanics and biology, this idea that mechanical forces are as important as chemicals and genes, and that the shape of the cell is important. To get at testing that, I come up with the idea of using little magnetic particles that I would coat with molecules that would bind to specific receptors on cells.

You know, I had developed this technology with getting very specific interactions between magnetic beads and cells, so we had ways to pull on cells, to collect cells, to move cells, and many labs have used that for diagnostic tests.

McNally:

In the early nineties, working with chemistry professor George Whitesides, later a Wyss Founding Core Faculty Member, Ingber imported the use of photolithographic micro-fabrication from microchip construction to cell biology.

Ingber:

[03:34] So that now got me into this world of micro-fabrication and cell biology. And I think that was the first time I think those two fields really connected in a big way, and I think that was a major opening of a spigot that's become a fire hose.

McNally:

Whitesides's group later developed what they called microfluidic channels with tiny inlets and outlets.

Ingber:

[03:56] Very interesting thing about it is that if you put, let's say, a red dye in one inlet and a blue dye in the other inlet, when they join in the bigger river, they don't mix. And they pass out the outlets and they don't mix. And that's because turbulence - which you'll learn about in high school like you'll see smoke mixing in the air - is a function of radius. If you have a very small radius, less than about a millimeter, there's no mixing. It's called laminar flow.

So that George and others have used to miniaturize all kinds of instrumentation, and big things the size of a refrigerator are now the size of an iPhone and toaster, and used for analytic labs and diagnostics.

But I have a medical background, and I thought this is really interesting, you have two things moving by and they don't mix. Well what if you had blood mixing by sterile saline in like a dialysis type of a format, what could you pull out of blood that would be cool and how would you pull it out of blood? Well I have these magnetic beads and I know if I've got magnets I can pull things, so what if we could have magnetic beads bind to things and pull them out? And I thought, what would be useful to pull out? And I thought of sepsis.

[05:10] And I started to talk to clinicians, and basically it was very interesting. The medical clinicians said, "No that's not sepsis. Sepsis is an inflammatory cascade. That's what kills patients." And all of them were working on modulators or inhibitors of the inflammatory cascade.

The surgeons said, "This is a great idea, I'll test it on a patient as soon as you have it," because they're just like, can-do cowboys.

One of them actually said, "I had a small child and everything was failing, and we did a complete blood transfusion, and it actually saved the patient. And I think it's because we got rid of the toxins in the blood."

So here's critics - 99% of the medical people because that's who funds sepsis and reviews grants. I went to medical school. I saw patients. Some of them get better just with antibiotics. Well, that means that what triggers this inflammatory cascade, it's the bug and the toxins it releases, so it's got to help to get rid of the source because it's all an equilibrium.

[06:08] One of the amazing things about medicine, people don't realize, and everything in biology, it's all tipping points. So in medical school you learn, if you think a patient has a urinary tract infection, you do a urinalysis. If you do a urinalysis and you count the number of bugs, if you have 100,000 bugs you treat that person with antibiotics, they have an infection. If you have 99,999 you send them home and you watch. Because empirically, experientially, they know that above about 100,000, it's going to propagate, and if not, your body will bring it under control. Well to me that must be what sepsis is like, except you have these bugs proliferating more and more toxins you're fighting. And if you can get rid of them, it's got to help.

McNally:

And it's not just the live bugs, right, it's also the debris of the ones the body has already killed...

Ingber:

When the bugs die, they release toxins, and the toxins are often cell wall molecules. So yeah. So this is another key point, which is that the reason that the clinical people say it's not important is that their blood cultures are almost always negative. So I think they thought, because again - no questioning their assumptions - they thought there are no bugs in the blood culture, so the bugs must have started a cascade and now they're not really there...

McNally:
...They're not relevant any more.

Ingber:
...they're not relevant any more. It's like 70-80% of blood cultures are negative, so they treat blindly, which is one reason why people die.

But, that was hard for me to believe, and the more you learn about it the more you realize that, even if your body is killing the bugs, they've released these toxins and the toxins are what trigger the cascade.

[07:35] I got some funding to explore this, and we used these little microfluid devices and, in fact, we could pull bugs out with magnetic beads if we put antibodies to the known bug on it. And then we even put human blood through, and we could pull bugs out of human blood in this little device. The problem was, (a) incredibly slow and (b) incredibly low volume, and (c) the device with that laminar flow, if we were off at all in the flow rates, we would dilute the blood or lose blood, so it's not very robust. And then finally - I know this clinically - when a patient comes in with sepsis, 80% are blood culture negative. You don't know what the bug is. I can't use an antibody against them.

So we had to think of something that would capture the bug without knowing what it is, and this is really where the key technology enabler is. Now, I being trained in medicine, know that there are things in your blood called opsonins, that are part of your primitive immune system - your innate immune system - that nature has evolved before antibodies to kinda' capture bugs. Now I didn't know much about them, but I did write that in my grants, that if this worked, that's how we'd get over that problem in the future.

Now we're getting close to around 2008, 2009, which is when I started the Wyss Institute. And so I had this little project going, but I knew that it really wasn't going to go anywhere unless we could get around the efficiency and the flow problems.

McNally:
[09:00] In other words you had the principles working but they weren't working in a way that would actually be useful.

Ingber:
Not be translatable exactly. So when we did the Wyss Institute, it really needed to be an institute that focuses from fundamentals to translation, and the translation was the most novel thing that is not normally done in academia. And to do that, I set out to hire people from industry that had ten, twenty, or more years of product development experience and integrating with students, fellows, post docs and so forth.

One of the first hires was Mike Super, who had been in the infectious disease field and worked in monoclonal antibody therapeutics for drug companies.

McNally

[09:33] Mike Super grew up in South Africa, and then in Namibia, which was then called South West Africa, and got a Ph.D. in Medical Immunology at the Institute of Child Health, University of London.

Super:

In my PhD work, which was at Great Allman Street Children's Hospital, I took on a group of children who had what they called non-specific childhood infections in the first 18 months of life. They had otitis media; they had fungal infections; they had bacterial infections; and then they seemed to get better.

So for my thesis, the purpose was to find out what was missing in these children, and to find out if eventually one could come up with a therapeutic application to help these children. The thought was that there was something that was wrong with their complement system. Complement is a very ancient part of the immune system. And we knew this because we could treat the blood. We could heat it, we could cool it, we could do things like that, and we could actually show that this protein - we thought - in the blood was sensitive to let's say 56 degrees heat inactivation, whereas an antibody could withstand that. So we knew it wasn't an antibody. So to cut a long, long, long story short, what I found was that these kids were missing this protein, which we later called mannose-binding lectin.

McNally:

Mannose-binding lectin - or MBL - binds to sugars on the surface of pathogens, and it's also involved in the activation of complement and clotting.

Super:

I was invited to Harvard Med School to do a post doc based on the mannose-binding lectin work that I'd done in London. And unfortunately Harvard wouldn't get me a green card, and so I had to go to industry. And that actually was a very good switch, in that I learnt certain things that are necessary and which I use day-to-day now.

McNally:

[11:32] Mike Super spent 17 years in the biotechnology industry, in companies ranging from start-ups to large Pharma. His industry work focused on the design, development and production of therapeutic antibodies for cancer and autoimmune disease therapy. I ask why he decided to leave industry

Super:

I decided to leave because industry was getting very, very restrictive. I had worked in biotechs where essentially I had five to ten different hats. One moment I was talking to the FDA; the next moment I was traveling the world looking at production sites; the next time I was talking to the protein engineering group or the molecular biology group, and really had a broad reach and enjoyed that very much. But as my company got bought by larger and larger companies, my role got smaller and smaller. So that at the end they just wanted me making monoclonal antibodies again. And it didn't suit me, let's put it that way.

Then the offer of the Wyss came along, and this was transformative to me, to hear about something that was in Harvard, so with access to that tremendous brain power of Harvard, but wanted people like me who had a track record in industry, who'd actually led teams.

So this fitted very nicely, because the idea of taking a well-developed project from academia and move that quickly forward to something that could be presented to the FDA, really appealed to me.

McNally:

I've read before, you said you were also finding that industry was getting risk averse -

Super:

So when I was in biotech, we weren't risk averse, we had to take risks. The whole field is not risk averse, but as my company got acquired by larger and larger pharmaceutical companies, that's when the risk aversion became very clear to me.

McNally:

[13:25] How did you get involved with the sepsis project?

Super:

Don Ingber sent around an email that said, "I've been writing my grants and all the time I talk about an opsonin that could be used to bind pathogens." The proteins which are opsonins will bind to a pathogen and will tell the immune system, "Oy, here's a foreigner, let's attack him, let's clear him out of here."

Now, antibodies are opsonins; MBL is an opsonin. Antibodies are different in that they bind to a specific target. What Don was asking for is something where you didn't have to know what the pathogen is before you started to remove it.

McNally:

And...with your background...

Super:

And I wrote back and I said, "Well Don, I did my thesis on mannose-binding lectin. I think that we can use that to address your question."

McNally

[14:27] Inber explains how in the human body MBL works with the spleen -

Ingber:

So normally it's in your blood. It will bind to foreign things like microbes - over ninety different pathogens and toxins. And what happens is, they bind, and then, because other parts of the molecule are exposed when it passes through the spleen - and the spleen is this incredibly vascularized organ that literally has sinusoids where it trickles slowly - just like a marshland can filter water because it slows and has huge surface area on the reeds. Your spleen does the same thing. It slows and has a huge surface area on the blood vessels and slits in the blood

vessels and macrophages sit there. They capture this compliment-MBL-bound bug, and then they engulf it and kill it. So that's how you normally clear.

And when we were doing studies, we actually tried this device in a rabbit, and we gave it a huge amount of pathogen, of fungus, and we could never detect it in the blood. And when we stained the spleen, it went all in the spleen. The spleen is incredibly efficient. It's just that when you get infected, you overcome that balance.

McNally:

[15:33] But Mike Super wasn't satisfied with MBL as it naturally occurs in the body –

Super:

What I then did was to take what I had learned in academia and what I'd learned in industry and put them together. What do I mean? I made a fusion protein, an fcMBL fusion protein that had the capability of binding that MBL has, so it binds to many different pathogens, but it also has the high level of expression, the ease of purification of the fc protein. We made a fusion protein of that. We have managed to put that on magnetic beads and on other surfaces, and we have shown very nicely that it binds and captures pathogens from many different media.

The first thing to do was then to see, did it bind to all these pathogens that normal wild type MBL bound? So we set up what has turned out to be the largest collection of pathogens in private collection, and we have been testing systematically to make sure that the fcMBL binds to all of them. That's one point.

A second point was when I was working in industry with therapeutic monoclonal antibodies, I was actually often making something called immuno fusion, I was fusing a cytokine to the antibody, and I was trying to use this in cancer therapy. The problem that I found is that the standard of care for cancer therapy and our new therapy worked against each other.

McNally:

How so?

Super:

The standard of care was to do chemotherapy which turned out kills the immune system, so if I added an immune stimulating therapy at the same time as I just killed off the immune system, that wasn't going to go anywhere.

Interestingly enough, immuno-therapy is becoming a big deal in cancer, as you know...

McNally:

Right.

Super:

...now, a bit late. Maybe I was a bit ahead of the curve, I don't know.

McNally:

- Or an opportunity for your next project.

Super:

Ahhh, good point. Very good point. So what we found that's very encouraging with fcMBL is that treatment with antibiotics actually sensitizes gram negative bacteria for binding of the fcMBL.

McNally:

How does that come into play?

Super:

That means the standard of care that they are giving at a hospital is actually helping our dialysis machine take out the pathogens.

McNally:

[18:02] But that was just step one. Don Ingber picks up the story –

Ingber:

So he bought some and it worked really well. But then, being somebody like Mike, who's a development guy, he had a team of people. They took it, they genetically engineered it, because there could be problems... There are parts of the molecule that induce blood clotting. There are parts that induce a thing called complement fixation, which is part of the inflammatory cascade.

Super:

We wanted to retain the binding function, but we wanted to remove completely complement activation and coagulation activation.

Ingber:

This is where engineering comes in. Biologically inspired engineering is being inspired by the way nature builds. Then we want to take the best technologies we have from man-made approaches and engineering and science, now do it even better for our purpose.

So yes, so he took out the bad parts, kept in the good, put a bit of a molecule from an antibody at the bottom, because in the pharmaceutical industry they learned that that makes it incredibly easy to isolate it and purify it, so you can make large amounts of it cheaply. It also stabilizes it if you ever want to inject it in blood.

McNally:

So there again is where that translation approach, you wouldn't have done that in academia, but when you're thinking translation, you pick and choose and do what will move things forward the most.

Ingber:

[19:18] And the fastest...So he basically made that, we tested it, it worked incredibly well.

And about this time, DARPA, which is the Defense Advance Research Project Agency, the part of the Department of Defense that is tasked with keeping America ahead technologically by thirty-fifty years for the defense of the United States. And this means economic defense, medical defense, everything. They put out a grant opportunity that used my papers and my review article's pictures, my device, as a paradigm, and basically said we need to have dialysis-like therapeutic devices for sepsis, because our soldiers in Afghanistan and Iraq... We're discovering that they're getting injured, but then they're getting infected and they're dying of sepsis. And also, we used to think we have to fly them home to be dialyzed, to go into intensive care, but now we have these little portable devices, you could do it by the bedside at a distant site.

So they wanted to have things that would integrate into a dialysis unit that would be able to cleanse their blood, and they also wanted us to do it without use of anti-coagulants, because injured soldiers can't have an anti-coagulant, they bleed out while they're on these machines

McNally:

[20:27] I ask how they solved the problem of keeping the dialysis moving without anti-coagulants?

Ingber

Joanna Eisenberg at the Wyss in another platform for non-medical purposes, literally to prevent ice from sticking to airplane wings, developed, something she called SLIPS, which is inspired by the way a pitcher plant in Africa can have insects walk over it when it's dry, but when it's wet, they just slip and slide and fall into it like a black hole, and it eats it like a Venus flytrap - which is kind of amazing. And she realized that was due to surface texture and topography, and with a liquid held on sort of by capillary action, she made artificial substrates by using micro-manufacturing to etch substrates, and then put liquid oils on it that were biocompatible. And she could prevent anything from sticking, and that was commercialized in a company called SLIPS Technology.

I was aware of this and had this grant opportunity - and actually was speaking at a meeting on architecture. Ben Hatton, who was working with Joanna, was there, and I said, "Do you think we could use your SLIPS for preventing blood from sticking?" And we went back, tried it, and it worked.

McNally:

[21:36] Mike Super -

Super:

I'm not saying that we prevented clotting. I'm saying that we prevented clotting from sticking to the surface. Now this is a big deal in medicine because you don't want clots to form in artificial valves, you don't want clots to form in dialysis. There are many places where clot formation is terrible, but also it has been shown that clots form and bacteria clump in the same place, and what we've been able to show with this slippery surface is that bacteria, fungi, etc. do not stick to this. So we have done hours *in vivo* and weeks *in vitro* in the lab, to show that we can have

very high levels of bacteria, a sticky bacteria like pseudomonas, which is not sticking to the surface.

McNally:

[22:26] Ingber tells me Wyss got the DARPA grant and exceeded everyone's expectations.

Ingber:

We hit four-year milestones in nine months. Largely because we had this team of guys from industry who knew what milestones were and how to bring full force to bear. Whereas academia graduate students, postdocs, they get a little derailed. You have to let them follow the paths, as you should. But by this mixed model, it really worked incredibly well.

McNally:

[22:49] Add to the mix the FDA -

Ingber:

FDA has been a partner. We talk through a lot of issues about if you want to bring this to the clinic, what are the challenges you're going to face? And the challenges you're going to face, now thinking on the translational side is, you've got a biological molecule with engineered MBL. It's a natural protein, that's okay, but then you have magnetic beads, that's a danger, what happens if it clots a vessel if it gets out? Then you have this flow system and all the surface contact area. So can you simplify it? You know, bringing it to... simplicity and impact. So can you make it simpler, simpler, simpler?

And so in this case, we decided, you know, it's a dialysis-like therapeutic device. Why don't we just put it on a dialysis part? And it works incredibly well. And so, we have papers in review, but we're already in pigs and we're about, hopefully to do a start up very soon called Opsonics. Opsonin is what MBL is, so Opsonics... that will bring this through the large animal testing to get to humans.

McNally:

[23:47] So they've overcome the project's inherent obstacles, others that emerge in the translation process, and still more in response to input from DARPA and the FDA. They're now testing the device with large animals.

Super:

...because we basically want to use a human size dialysis machine and a human size filter with the fcMBL protein, and to check this in a large animal model of sepsis. Unfortunately, for the animal that is, we have to make it sick, but fortunately for the animal, we then cure it.

McNally:

[24:23] Don Ingber says they're beginning to see some promising results with pigs...

Ingber:

It's still early. We had a lot of success in rats. The other things that's interesting, the rats have shown that it synergizes with antibiotics. So if you use an antibiotic, you actually kill the bugs but you release the toxins. Because we capture both the bugs and the toxins, when we release toxins we capture both.

Now the other exciting thing is that, I told you, 70-80% of patients are negative blood cultures.

McNally:
And what that means is...

Ingber:
You've taken a blood sample...

McNally:
... you've waited for it to culture all that time, and now it doesn't tell you anything.

Ingber:
So there's a couple of things. You mentioned earlier that the mortality rate can increase 5-9% every hour you're on the wrong antibiotic, and they just give you a broad spectrum antibiotic when you come in, because they don't know. And if 80% they never know, so they just keep trying things to see if it works and it often doesn't. But even if you have a positive blood culture, it could take two to seven days, so every day with that kind of mortality rate.

So we found that, because we're pulling out live and dead, if we just measure MBL-binding material in blood... We've now done a large number of patients in a study in the lab with human patients from emergency rooms, and it looks like we can take a very high percentage of those. We can't yet tell you what the bug is, but we can say, "Yes, you have sepsis." [

Now, for our device, what's valuable again for going to clinical trials is...it's very powerful to increase the likelihood of success of a therapeutic - whether a device or a drug - to have what's called a companion diagnostic, which means make sure that this patient you think really will benefit from your therapy and show that when your therapy's working, it scales with what you thought was causing it.

So if this ever goes to clinical trials, which we hope, if we have a diagnostic, we could say, 'Well, here are ten patients but you know, we don't detect this, these MBL binding materials in these two, but these eight we do, so let's test those,' because we think we'd help, and then we could follow it, and we say, "Oh it's high, and now we try to treat it, and now it's going down, down, down. Now we can stop therapy."

Like you don't know when to stop therapy. And then you could see if it comes back, and then we need to start again. So that's how we're thinking about it right now, is as a companion diagnostic, but in the future it could be used in any lab to basically determine whether there really is sepsis and this patient should move to

the intensive care unit and be watched and really be tried with antibiotics or go home.

And that's a big problem. Clinically, you see a patient, they're old, sometimes they don't get a fever, they don't really express the way a young person does if they're sick, and things go very quickly. So I think it has real value.

McNally:

[27:05] And so just to bring it up to today, what are the next steps, the next developments, and tentative time line you're looking at?

Ingber:

For you to move towards clinical trials, you have to show safety in an appropriate animal model and some degree of efficacy, but you also have to be able to manufacture materials that are quality controlled that would be appropriate for clinical use. So that's something we are starting to do and we need to really form a company to get that done right. So that's one thing that's being done.

The other is developing an animal model for sepsis, which, believe it or not, there really are not any good animal models, so that's one thing we have done with a pig model. We have a pretty good model of sepsis where they have clinical signs that look like in-patient. And then this diagnostic, similarly, get it in a form that's robust, that can be mass manufactured, so that if it works, it can then go out clinically. All of that requires a different know-how with dollars, big dollars, but also people who have regulatory experience, people who know how to do manufacturing.

McNally:

I ask Mike Super - If everything goes well, how soon might human clinical trials start?

Super:

Usually we're talking about two years from now.

McNally:

As you say, in some ways this process started in 2006...

Super:

Yes.

McNally:

So we're talking 2017. Things move quicker at Wyss than other places, it's still eleven years.

Super:

Yes I know, but, let me push you back on that, because Don's ideas on the microfluid in 2006 and my ideas on MBL, which were also way back, were working in isolation. But from the start of the project at the Wyss, we're talking less than four years, from the start of the project in August 2011 till now.

McNally:
Then plus two.

Super:
Then plus two. Now that is incredibly fast. [

McNally:
[28:56] I want to know – Does he have visions of the future, of how things might be different or better because of the work he and his colleagues are doing -

Super:
I hope so, I mean one of the things that we are also working on is being a guinea pig with the FDA. Why? What do I mean by that? They are very interested in other examples of coming into a project early to see how to transition that through the FDA. For example, here we have a protein on a device. Which department of the FDA does that go? Is it devices? Is it CIDA? Is it CIBA? Is it protein?...How do you deal with that? And this could get lost in the weeds.

So having good advice, hopefully, in examples like this, when there are huge unmet clinical needs like sepsis, will allow us and the FDA to work together to getting drugs and devices approved much more quickly, go smoothly through this difficult process, where you still have absolutely their requirement and ours, of course, of safety for the final treatment, for the final device, for the patient, but at the same time find a way to do this in an interactive, collaborative even, way, to speed this up.

McNally:
[30:22] As Super and I discussed, some of the discoveries, the research, the academic papers go back years. I ask Don Ingber how the Wyss model accelerates their coming to fruition -

Ingber:
We call it a technology translation engine. Measures of success in our original founding included IT portfolio patents, and we're up to 1000 patents after six years; corporate alliances; licensing agreements; and new start-ups, and having impact, because you can't have an impact... Academics don't produce product, you have to develop a seamless interface with the industrial world. Now, we did that partly by bringing in technical expertise for product development.

We have a program we call Institute Projects, where essentially, we use a very organic approach, so people often say, "How do you decide what to fund and what to kill?" And we don't. We use self-assembly and self-organizing principles, biological principles, which is basically faculty and students come up with exciting technologies for them, and they start interacting with these guys from industry, and the guys from industry will either say, "You know, it's already been done," or "I've heard of a technology that's about to come out no one's ever heard about, but it does this better," or they'll say, "That is really exciting."

If they say it's really exciting, we start submitting intellectual property and patents, and lawyers who look in the outside world say, "This is novel,... this is unique." Then we put more investment in, and we call it what we call a Platform Project.

Now, if we start talking to industry...Why do we talk to industry? We talk to industry because they know what the real challenges are. They know what the competition is. They know what has been done before. They know the regulatory issues that have nothing to do with technology.

Some people say that the success of a start up is only contributed about ten percent by the technology, which academics don't get. It really...You've got to get good management, and regulatory, and marketing, and business and manufacturing, etc. So we actually bring entrepreneurs-in-residence in when we're getting feedback from industry and the venture capitalists which basically says, "Really exciting. We want to see more de-risking. ...more importantly commercially."

McNally:

[32:26] And that's one of the things that I hear, I would imagine is one of the real distinctions of Wyss. Others will de-risk scientifically or de-risk academically. You want to de-risk commercially so that you can hand it off.

Ingber:

Do both. So that is the valley of death that everyone talks about, right? Which is, you have this great technology, but basically the investors won't take risks any more, they want it validated. So how do you get over that? So we get over that by bringing in people like Mike Super to do the technological de-risking.

But then, when we really see, we think this is really exciting, we have strong intellectual property and patents, we have strong interest but they want to see it de-risked, and we're getting the same message. We triangulate and we're getting the same message - you need to do this, this and this from all these different groups, then we'll move it to what we call an Institute Project, where we form a triad with the faculty inventor (in this case was me), with a member of our staff with industrial experience who's the technology leader, which in this case is Mike Super.

And then we'll either use one of our internal business development people who've been in the outside world as entrepreneurs, or we will recruit an entrepreneur that has experience and is excited and we think can bring it all the way, who will be our interface with the outside world and understanding what they're talking about when we sometimes don't. And that was Eric Devroe on this project. And that... It takes time, but you are constantly iterating in the process. And that has been quite successful. We're very close to closing on a start-up that will be very focused on commercializing a sepsis therapeutic with a diagnostic as a companion diagnostic.

McNally:

[34:02] How many of the Wyss Institute's platforms and how many of its novel technologies does this one effort draw on?

Ingber:

It involves my platform, biomimetic micro systems, which started from the floor with the bio-spleen concept. Mike Super is now in my platform. He actually started in what's called biomaterials evolution, where we're going to do protein engineering, so that's when we first built the protein engineering group. But as this project grew and that platform moved more towards genome engineering and synthetic biology, he joined my platform.

And then Joanna's platform on the anti-stick surface is called adaptable materials technology.

We're now collaborating with the anticipatory medical and cellular device platform. They developed a way to diagnose Ebola with... They literally engineered gene circuits in microbes and then break the microbes open, put all the chemicals on a piece of paper and dry it, and then add water, and they could get programmable activities. And they can program it to sense Ebola very quickly, but MBL may be a front end capture agent.

The way technology has developed at the Wyss, and I think in all good scientific labs, is that there's a natural flow. It's like a blood vessel with branches and branches and branches. And so you have creative people and we have a goal, but then it's like, "Oh, we've developed this technology, it could also be used for that or that or that."

It's like I developed magnetic beads, I wanted to pull on receptors, but, "Hey I have these magnetic beads, I could use this for other things. What else could I use it for?" And it's who's around you that usually not only... You can think of a hundred ideas, but you only pursue ones that you have tools to pursue. It's like, you can think of great ideas in your house to build something when you have some free time, but you never do it because you don't have the right materials.

At the Wyss, we have the right materials to do anything because we do medical, non-medical, we do synthetic biology, genome engineering, polymer chemistry, nano technology, material science, computer engineering... So there's someone around to do everything and bring their own creativity to it.

McNally:

[36:03] You've been listening to DISRUPTIVE: CONFRONTING SEPSIS. I'm Terrence McNally. My guests have been DON INGBER and MIKE SUPER. You can learn more about this sepsis therapeutic device as well an exciting range of other projects at the Wyss website - wyss.harvard.edu - that's W-Y-S-S dot Harvard dot edu - where you'll find articles, videos, animations, and additional podcasts.

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with you again soon.