

DISRUPTIVE: CANCER VACCINE & HYDROGEL DRUG DELIVERY

Host Terrence McNally interviews David Mooney and Chris Gemmiti. Podcast published November 20, 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 Institute 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.

In this episode of DISRUPTIVE, we will focus on a cancer vaccine and hydrogel drug depots — both being developed by Wyss Founding Core Faculty Member, DAVE MOONEY.

[00:50]

Mooney says the human immune system is the most efficient weapon on the planet to fight disease. Cancer, however, resists treatment and cure by evading the immune system. Unlike bacterial cells or viruses, cancer cells belong in the body, but are simply mutated and misplaced.

Scientists have been trying to develop vaccines that provoke the immune system to recognize cancer cells as foreign and attack them. The approach developed by Mooney's group, in which they reprogram immune cells from inside the body using implantable biomaterials, appears simpler and more effective than other cancer vaccines currently in clinical trials. In one study, 50% of mice treated with two doses of the vaccine -- mice that would have otherwise died from melanoma within about 25 days -- showed complete tumor regression.

On a second front, when it comes to delivering drugs or protein-based therapeutics, doctors often give patients pills or inject the drug into their bloodstream. Both are inefficient methods for delivering effective doses to targeted tissues.

Mooney and his team at Wyss are taking a new approach using biocompatible and biodegradable hydrogels. They've developed a gel-based sponge that can be molded to any shape, loaded with drugs or stem cells, compressed to a fraction of its size, and delivered via injection. Once inside the body, it pops back to its original shape, gradually releases its payload, and safely degrades.

After we explore both of these exciting projects with Mooney, we'll take a closer look at the process of translation of hydrogel technology into products and therapies with Chris Gemmiti, a business development lead at Wyss.

[02:31]

DAVE MOONEY, the Robert P. Pinkas Family Professor of Bioengineering at the John A. Paulson Harvard School of Engineering and Applied Sciences, leads Wyss's Programmable Nanomaterials Platform.

Dave, welcome to Disruptive. Can you share a bit about your personal path to the work that you do today, possibly some turning points or moments of decision along the way?

[02:52]

Mooney:

I went to-- Probably the first decision point I had was when I went to college. Did not come from a technical background, but I received some very good advice when I got to the University of Wisconsin. In my 30 seconds of consultation with an adviser there, and they basically said, "You're good at math and you're good at the sciences, why don't you think about becoming an engineer?"

It actually ended up being a pretty good advice. I went on to become a chemical engineer and I really enjoyed it. It was fantastic. I enjoyed the technical challenge. I enjoyed using my talents to address some of these technical problems.

I worked with companies including Dow Chemical and Procter & Gamble, which are really wonderful places, wonderful companies. But I also began to realize that I wanted to have a bigger impact on people's lives. In this, I think I was inspired by a number of my brothers and sisters who work in fields like social work, education and medical care. This inspired me to take a 90-degree turn and go to graduate school so that I could learn something about biology and figure out how to apply my engineering skills to address medical needs.

[03:57]

McNally:

Before we talk about your work on immunotherapies, can you share a bit about the evolution of cancer treatment over the years?

Mooney:

One of the hallmarks of cancer is that cancer cells tend to grow very rapidly compared to other cells in the body. This was recognized a number of years ago and led to the concept of trying to target that rapid proliferation of cells by using drugs that would specifically kill off rapidly dividing cells or using radiation treatment, that also will more generally kill cells that are rapidly growing versus non-growing cells. Those two technologies, those two approaches, obviously became mainstays of treatment of cancer along with surgery where one goes and directly removes the cancerous tissue.

Those three approaches have had really tremendous impact obviously over the decades. However, they do not target specifically cancerous cells versus other cells that may, for example, be growing rapidly in the body, cells of our intestinal tract or other areas. So there's a lot of bystander damage. Many other cells get killed that we would like to not be killed with these treatments.

Typically, they don't lead to cures. They are treatments, they maybe beat back the cancer for a while, but oftentimes, the cancer simply comes back, maybe in a slightly different form, a little while later. That's the background for where things have been for a number of years.

[05:25]

The alternative approach that's been now coming on and is becoming increasingly important is the concept that cancer cells are truly different in terms of their gene expression from normal cells in the body. They're mutated. Those differences should allow our immune system to be able to recognize that these cells are different and to attack and destroy these cells. This is actually an idea that goes back well over a hundred years, but it wasn't until the advent of modern immunology where we began to really understand cells and their molecules that people can take a rational approach to immunotherapy.

But for the last few decades people have been attempting to create vaccines, sometimes preventative vaccines, but very frequently instead therapeutic vaccines where the vaccine in a therapeutic context is being used to treat somebody who already has cancer. The idea is to use a vaccine similar to how we vaccinate against the flu every winter, to teach our immune system how to recognize the differences between cancerous cells and normal cells and get the immune system to destroy cells that have that signature of cancer.

[08:42] McNally:

And how has that work been progressing?

[06:39]

Mooney:

In the context of therapeutic vaccines, one approach to it that's shown tremendous benefit and actually the first FDA-approved therapeutic cancer vaccine addressed this question of how to get the immune system to recognize and destroy cancer cells by removing cells of the immune system from a patient from their body and manipulating them outside the body.

The general idea here is that the tumor is being tolerated by the immune system normally, it's growing and it's expanding. And so a way to try to break this tolerance is to actually take immune cells out of the body, away from the influence of all those signals, put them in the laboratory, and then to generate the right number of cells and to program those cells appropriately, and then to take them back to the patient, with the hope that they will then generate an effective immune response and kill cancer cells.

[07:30]

As I mentioned a moment ago, this approach has not just demonstrated a proof of principle, but has actually now resulted in FDA-approved therapeutic cancer vaccine. There's been tremendous success from that perspective.

However, with that approach, one has to isolate cells from a patient, you have to

manipulate those cells in a laboratory, and then you have to re-infuse those cells back into the patient. This is a complex process, involves many steps. There's a lot of regulatory burden. It's very expensive and at the end of the day, to this point, it is actually showing limited efficacy. It gives extension of life span by several months.

We said, well, perhaps we could instead create a new microenvironment, separate from the host of the rest of the body... where we did all of this, the same activities, but we actually do them inside the body with immune cells that already exist, instead of having to remove them and manipulate them and return them.

[8:30]

McNally:

This sounds like a big shift. How do you do that?

Mooney:

What we really are highly dependent on here is the understanding that immunologists have developed over the last couple of decades, and we're really trying to exploit and mimic, in this case, what is known to happen during bacterial infection. We create a biomaterial now that we place in the body. It's a little piece of plastic, a plastic disk about the size of baby aspirin tablet. We release a drug from this piece of plastic that will attract the right kinds of immune cells. These cells will sense this chemical and they'll actually follow the source of it and come to the material.

The biomaterial now is filled with holes, it's very porous. It's mainly about 90% empty space so a lot of the cells can then crawl in and more or less live inside this bio material, kind of like them crawling into a house and living inside this new structure that we've created inside the body. Once they are living inside this material, we can then provide signals to these cells to activate and reprogram them. Some of these signals mimic aspects of bacterial infection so that when we also provide a signature of what cancer looks like to these cells, they associate that with infection. They then want to generate a destructive immune response against anything that has this signature.

[10:00] McNally:

So inside the body, you're releasing something that traps the targeted cells...?

Mooney:

Absolutely. Actually, It recruits them, and these cells will then come and live within the material for a period of time sufficient for us to manipulate them and program them to have the desired functionalities.

McNally:

And how do you program them?

Mooney:

The product that's currently in the clinical trial in stage IV melanoma patients, is we actually biopsy the tumor of the patients. So we get a biopsy then we freeze-dry it, kind of like if you talk about freeze-drying coffee, so that we create a powder out of that small tissue sample. That powder will contain all of the different molecules contained in all the

cells.

It will contain all the mutated proteins that may be expressed in these cancerous cells. We do this so that we are able to provide a lot of distinct - what are called antigens - distinct molecules that provide a signature of the cancerous cell, and we can do this in a personalized manner. We actually have the right mix of ...the right signature for each individual person's cancer that we put into the device.

[11:08]

McNally:

How simple is this process for patients? Once the trials are over and you're utilizing this out in the world, what would they go through to undergo this treatment?

Mooney:

From the patient perspective, this is actually quite straightforward. The first part of the experience for them would be that we would require a biopsy of their tumor. These patients are typically getting some surgical removal of tumor already. We would obtain the tumor sample directly from the surgical incision that they'll already be undergoing.

McNally:

You're just piggybacking on that, so far nothing extra for them.

Mooney:

Yeah, so they won't see a change there. Then, separate from the patient, we would manufacture these little tablets that look like aspirins. The patients would simply come in to an office visit and they would have one of these placed under the skin. There's a small incision that's made in an office visit, and then that is closed and they just go home.

McNally:

Wow.

Mooney:

We anticipate doing several vaccinations. So they come in a couple of different times to get subsequent vaccinations, but it would be minimally invasive type of procedure and would not involve ... a very different experience for them than what they already are experiencing in many ways. If this can be successful, it probably has greatly reduced side effects as compared to things like chemotherapy or radiation treatment.

[12:30]

McNally:

And because you're specifically targeting their cancer cells, there may be no collateral damage.

Mooney:

Exactly. The two key advantages here, if this can be broadly successful, is that one, as you just mentioned, we're targeting what's specific about the cancerous cells and we have seen no evidence to date that we are damaging non-cancerous cells. It looks like we really are minimizing any effects that are off target.

The other key feature of your immune system is that it has memory. Once you're vaccinated with the flu vaccine, then you'll never get that particular strain of flu, and the same expectation holds here. If we've generated an effective immune response against a patient's cancer, they shouldn't have to worry about recurrence, because if some of those cancerous cells started to reappear, the immune system would be capable of recognizing and destroying those cells a second go-round so that it would prevent recurrence, which is obviously a very big concern and the major aspect of the lethality of cancer.

[13:26]

McNally:

One of the things that you're saying is that the patient would receive a few of these implants in the course of a month of treatment and, if successful, for the rest of their life they may be free of that cancer.

Mooney:

Yes.

McNally:

Wow. That's exciting. Where do you stand right now? What status are you in terms of trials? What's been successful and what's up next?

[13:50] –

Mooney:

We're still at an early stage in the overall process right now. We've completed a very large number of pre-clinical studies in animals. Those have shown very dramatic potency and effectiveness of this approach. We've also looked at the safety in animals and it appeared to be safe. Based on that data, the FDA gave us approval to do a phase-one clinical trial, which is a physician-sponsored trial. This is actually a trial that is being jointly run and jointly financed by the Dana-Farber Cancer Institute and the Wyss Institute. In this trial, we have an approval to treat a total of 25 patients who have stage IV melanoma.

11 patients have been enrolled, and I believe those 11 have completed treatment at this point in time. It's still very early days, only a few patients, but at this point in time, the vaccine is very well tolerated in these patients. We're getting the response that we would have anticipated based on the animal studies. It appears we are getting a biological response to the cancer antigens and having some impact. Though at this stage, it's still quite early as I mentioned, but very promising.

[14:58]

McNally:

Sounds very good. You mentioned the Dana-Farber Cancer Institute. Can you talk just a little bit about the collaboration between Dana-Farber and Wyss and how that influences or accelerates your progress?

Mooney:

That collaboration between the Dana-Farber and the Wyss is absolutely critical to this

project and to its progress and its success. We bring tremendous expertise on the engineering side. We need to harness that to knowledge of the basic cancer immunology. Obviously we need to also then be able to interact with the clinicians who actually have the clinical experience and the clinical knowledge.

This project would not have gone nearly as rapidly and probably would not have been nearly as successful without that interaction - and now we jointly produce the vaccine that they then place in the patients.

[15:53]

McNally:

What's the big vision at this point? If all goes well, how will this change cancer treatment and what sort of timeline are you hopeful for?

Mooney:

We already have data and pre-clinical models showing that, for example, in models of glioblastoma, lung cancer and other types of cancer, it looks like this also can be quite useful. The hope would be that this is something that could be broadly used in a wide variety of different types of cancer patients to generate a really potent immune response and cause destruction of the cancerous cells, and, as we mentioned earlier, prevent recurrence.

The big picture is that this may have a really dramatic impact in treatment of a very large number of people. I don't expect that this will be the silver bullet that is used all by itself to treat patients. Cancer is a complex disease and this therapy will most likely be used in concert with other therapies, some that have already been developed and others that are undergoing development. Together I think that immunotherapy in general promises to really bring a new era to cancer treatment where we're able to truly cure a very high percentage of patients.

[17:02]

McNally:

Right...As you pointed out earlier, much of the treatment nowadays prolongs life a few months, several months, etc... but few actually achieve cure.

Mooney:

Yes. That's the promise of immunotherapy. It is truly providing cures where patients remain cancer free for very long periods of time.

[17:25]

McNally:

Okay...Let's shift to the hydrogels and gel-based drug delivery. How has this come about? What is the problem for which this is the solution? How does this approach solve or improve on current methods of treatment?

Mooney:

The background for this area of research is that we hear all the time about all the revolutions in the life sciences that have been underway for the last several decades -

genomics, proteomics, the stem cell advances ...All of these have led to a tremendous increase in what we understand about the body, how it works, and about disease.

One of the challenges though is that the potential therapies that come out of these advances tend to be very different types of "let's call them drugs" than what has historically been used in the human body. The new drug entities that come out of this type of knowledge are things like proteins that are big molecules that degrade or are destroyed easily in the body.

And delivery ends up becoming an absolutely crucial problem for a lot of these new types of therapies - whether we're talking about proteins, nucleotide-based therapies like gene therapy, or cells.

Why delivery is such a challenge is because all of these things tend to either die or degrade very rapidly if they're not placed in the right conditions, so their duration of action is really short. But most of these things need to be around for some extended period of time to actually have the desired effect.

The other part of this is that these molecules often are very potent and they can have very big effects on the biology of the human body. We really want them to only be having those effects at certain places. And so this is where engineering comes into play - that we're looking to develop delivery systems that introduce these into the body and get them to the right place at the right time for the right period of time. We use class of materials called hydrogels to accomplish this.

[19:25]

McNally:

How do you create these hydrogels and how have you chosen the substance you create them from?

Mooney:

First of all, I just briefly mention, a hydrogel is, in essence, just a water filled network, typically of a polymer. Why we use these, in part, is because if we look at our bodies, we have cells in the tissues in our body, but then there's also material around those cells. That material is typically a hydrogel. We're actually taking inspiration from the body in the kinds of materials that the body usually builds with.

If possible, we try to start with polymers that are either naturally derived, so there's a natural source to them, or other molecules that have been used in the human body for some period of time so that we know that they're safe and well tolerated in the body. That's one of the criteria.

Another criteria is that we actually have to be able to use these specific polymers to generate hydrogels with the right types of chemical, physical and biological properties for the specific application. For this reason, we end up using a wide variety of different materials because they would give us different types of properties, but in general, what they all do is, once we form a gel and we have placed these, let's say these proteins or these cells within them, they protect the cells from the body. They keep these from being

degraded or from being killed, and then they slowly release the drug or the cell into the surrounding tissue over time, so that we get a long-term durable presence of these agents to drive the biology and drive the therapy.

[21:07]

McNally:

So that's the two problems you were talking about? One was the rapid degradation, and two was the need for long lasting effects. This seems to solve both.

What have hydrogels ... Is there a history? How long have we been working with this sort of thing that you're building on?

Mooney:

if you look at the tissues in our body, many of the tissues in our body could be characterized as being hydrogels. From an evolutionary perspective, the biology decided a long time ago that hydrogels were really useful for building tissues and controlling biology.

From a man-made perspective, we certainly have been using hydrogels for many decades. If you go back to ...When you visit your dentist when you were a child and you were having impressions taken, often times those were hydrogels. There are materials that are used for wound healing that are very frequently hydrogels. A lot of the foods we eat are hydrogels. Hydrogels are all around us and we've been using them for many purposes for many decades or hundreds of thousands of years.

[22:16]

McNally:

And what are the pieces of this that are new in what you're doing that give you new abilities or new properties?

Mooney:

I think there's a few different aspects to what we're doing that's new. One is that we have determined how to appropriately put the polymer networks together so that we get the right types of physical and chemical properties. For example, something as simple as we want the gel to deliver, let's say, a cell or a drug for some period of time, then we would like it to degrade or dissolve itself so that it's not permanently in the human body.

We've developed a variety of means with which we can really regulate how long it lasts once it's placed in the body. We've also developed a variety of technologies that allow us to control how strongly the drug or the cell holds onto the gel so it controls how rapidly it leaves or how slowly it ends up leaving from that network. Those are two general areas that we've been focusing on. A couple of things more recently that are more specific in recent advances, one is that we've been making - and you alluded to this before - these shape memory hydrogels.

We can make a gel that we predefine its shape and structure outside the body, and we've created these in such a means that they have the ability to be deformed very dramatically, including being put through a needle. Once they're released from

confinement, they can then rehydrate and go back to their original size and shape. This now allows us to deliver an exact volume, an exact dose of a drug, for example, where we would like it in the body because we can actually know exactly what the volume is of that device.

We can control its structure and its architecture so that we can control how readily, let's say, cells in the body can interface with this device that's releasing these drugs. We also know - unlike if we just inject a gel and allow it to form in the body, it may move from that site and maybe dissipate, but here, if we're introducing a discreet unit, we know exactly where it is and it stays where we placed it.

[24:28]

McNally:

That notion of being able to deform it and shrink it and then small enough that it could be injected, and then, once inside the body, pop up, not only to its original size, but its original shape. How is that done?

Mooney:

When you have these polymers, these long molecules that create the hydrogel, they have to be linked to each other in order to form a stable hydrogel. The process that we use to form what we call the shape memory cryo-gels is we partially freeze the solution while this chemical reaction is happening. We let ice crystals start to form within this volume. Then the polymer gets excluded from the regions where the ice crystals are. It then crosslinks and forms a network around these ice crystals.

After the reaction is done, we warm up the whole system and the ice crystals just melt. Now we have, in essence, holes wherever those ice crystals were.

We have a very high empty space that allows us now to take what maybe is a very large overall structure, and we can, with the relatively low amount of force, compress it or squish it so it becomes a much smaller volume than it was originally. We're in essence compacting all the solids into the space that was empty before.

The reason that it actually wants to spring back to its original dimensions is that after we release the force...it's kinda like a rubber band in that it wants to go back to its original size and shape if there's a not a large force being applied to it. So, after it's made it through the needle and into the tissue, it then will just elastically return to its original size and shape.

[26:25]

McNally:

You're making them out of a material that is readily available, but one that you can precisely tune so that you know exactly how long certain processes take? Can you talk about how you do that?

Mooney:

One way that we try to tune these is by controlling how we crosslink or how we attach the polymer chains to each other, and then we also can control the number of these

attachment points to control things like the physical properties and how slowly or how rapidly they will degrade. We use a wide variety of different chemistries.

We can also put in bridges between the polymer chains that are permanent if we want this hydrogel to last a very long time, or we can put in bridges that are initially very stable but that have some type of functionality where the presence of water makes it degrade or maybe some molecule cells in the area will make it degrade so it will disappear in response to the local cell activity. There's a lot of flexibility in how you put these structures together so you can control how and when they go away.

[27:30]

McNally:

So you've got flexibility on the one hand and precision on the other.

Mooney:

Yes.

[27:35]

McNally:

What is click chemistry? Where does that come into play?

Mooney:

Click chemistry is a broad term for a wide variety of different types of chemistries that we have been exploring in the context of making these types of gels recently. We did not invent click chemistry, that's been invented by others, but we're now exploring whether or not they could be useful to do the kinds of things that we want to do with these hydrogels for delivery.

People call them click chemistries because they're chemistries where you have two different agents that more or less will spontaneously click together when they come in contact. The idea here is that we have one type of polymer that has one of the click partners and another polymer that has the second partner, and when you simply mix these together, when the two components find each other, they will spontaneously react without needing to add energy, heat, light, or any type of other molecule. They'll spontaneously react just with each other.

I should say another key feature to these is that they typically have selectivity or specificity such that they only want to react with each other and nothing else. A lot of the chemistries that we've used in the past, when we form these gels, if we have cells or we have drugs also mixed in, we always have the danger that the chemistry that's causing the gel to form might also react with the cell or the drug and harm it. Here, with these click chemistries, since they are so specific, we can encapsulate cells or we can have proteins or other drug molecules present and they are not affected at all by this click chemistry. It's completely distinct and separate from the proteins or cells.

McNally:

Again, more precision.

Mooney:

Yes, very precise here in terms of being able to independently regulate the formation of the gel and its properties separately from the biological cargo that these gels will be carrying.

[29:41]

McNally:

So where are you now? What stage of research are you in? What's next?

Mooney:

Actually, we're exploring a wide range of different potential applications. Going back to the cancer immunotherapy, some of these cryo-gels we've actually been using in a similar manner as the implantable device I described earlier in the interview, where we are using these to promote an immune response, in essence a therapeutic vaccine, but one that is now injectable instead of implantable.

We have been using these to deliver different types of protein cargoes that promote regeneration of things like muscle or bone or blood vessels. Exploring using these in wound healing. We're also exploring using these to deliver - going back to something we started with - chemotherapy drugs, which will still be used for a very long time. Whether or not we can use these to deliver chemotherapeutic agents much more precisely to desired sites, for example, at the tumor.

[30:42]

McNally:

And you've been using ultrasound to turn chemotherapy delivery on and off rather than simply the sustained release that's the norm...

Mooney:

Often times, drugs are delivered just by injecting a solution into the body. They go everywhere and we can't really control where they go and how long they're around. If we take the controlled drug delivery process that we've been discussing, we can put them in a material and we can have them release in a sustained manner, but most of those systems are what I would call 'pre-programmed' - that when we put the device in the body, we actually already know how that drug or that cell will come out of the device as a function of time. That's highly desirable in many, many situations.

But sometimes, you might, for example, at a patient specific manner, want to modulate that in real time. You might say, this particular patient isn't really responding to this dose, so we really need it to release more rapidly. Or we may say there's a particular time when we want a lot of drug to be released and the rest of the time, just some low level is fine. We've been exploring the idea of having real time control where we trigger from outside the body the release, and one of the approaches we've been exploring with this is to use ultrasound.

Ultrasound is a very widely used technique in instrumentation and medicine. We're all pretty familiar with it, but you can apply ultrasound from outside the body, and the concept here is that when you apply ultrasound to a particular location where we've

placed one of our gels, the energy from the ultrasound can cause a disruption in the structure. In essence, it transiently opens up the structure of the gel and makes it have relatively large pores within it.

That allows drugs or cells to then come out very quickly, and once we turn the ultrasound off and stop inputting the ultrasound energy into the gel, then the gel will self-heal. It will go back to its original dimensions in its original structure. The drug release will go back to the original baseline level. We can turn on and then turn back down drug release using things like ultrasound from these systems.

[32:48] McNally:
Would that work in terms of pain relief?

Mooney:
That's one of the areas that we think this could have great potential. Patients will periodically have times when there's much greater pain, where they may want temporarily a higher dose of drug to be released. One of the visions for how this may be applied is that you put one of these gels into a patient who have a need for pain relief and they would have the capability themselves of periodically turning up the release rate if they needed more relief at a particular time.

[32:10]
One challenge that we're addressing now as well that I'm really excited about also, is - all of these systems that we've been describing to this point in time for delivery have a finite lifetime, that eventually their cargo is exhausted. The drug is released and they're done. At that point in time, if we still need to have more drug being delivered, we would be faced with the situation where we'd have to put in another device. That certainly is feasible in many situations, but in certain cases, that would not be desirable.

We've been exploring the idea of reloading drug delivery devices. The idea here is really simple, but I think potentially quite profound, which is that if you have a depot some place in the body, that you could introduce - either intravenously or orally just by taking a tablet - the drug molecule. The drug molecule, once it gets into the body, would have the potential - perhaps we put these click chemistries that we were describing earlier - to specifically bind to that depot and become concentrated at that depot. In essence, to reload that depot with drug.

[34:24]
McNally:
David, you just introduced the term 'depot.' What do you mean by depot?

Mooney:
When I utilize the term depot, I'm really referring to the use of one of these hydrogels or materials as location where put a large quantity of drug. In essence store the drug or store the cells for ultimate release into the body. This will slowly be released either in a preprogrammed manner or in a manner which we define in real time.

[34:50]

McNally:

Finally, David, as you look at your work, how do these two fields that we talked about fit together and how do they make sense for you going forward?

Mooney:

Ultimately how these two really relate to each other is that we're trying to use materials and bio materials to control biology in the human body. We like to be able to design materials that plug in to specific pathways and regulate biology in really precise manner to treat and hopefully cure disease in many situations.

[35:19]

Thank you, David...

Now we're going take a closer look at the process of translation of hydrogel technology into products and therapies with Chris Gemmiti, a business development lead at Wyss.

CHRIS GEMMITI joined the Wyss Institute early in 2015 to guide translation strategy and technology development in the areas of programmable nano-materials and regenerative medicine. Chris holds a B.S. in Biomedical Engineering from Johns Hopkins and a Ph.D. in Biomedical Engineering jointly conferred by the Georgia Institute of Technology's College of Engineering and Emory University's School of Medicine.

Chris Gemmiti, welcome to Disruptive. Can you share just a bit about your path, what you've been working on, and why you chose to move to the Wyss?

[36:00]

Gemmiti :

Sure. As you mentioned in the intro, my background is predominantly in regenerative medicine. Having spent a fair bit of time in industry, I have seen the process firsthand of bringing a new therapy through multiple clinical trials, through the FDA, and then launching it, bringing on sales and marketing. I very much love that process of bench-to-bedside. I loved it so much that I wanted to do it all over again, and what better place than the Wyss, which is an embarrassment of technological riches where we can really pull through some amazing new technologies.

[36:40]

McNally:

So let's focus on the hydrogels. What do you see as your role in helping this technology to achieve the impact it can have in the real world?

Gemmiti :

I see my role as divided in two synergistic but slightly different halves. The first is working with the internal technical teams and giving them some guidance from the market's perspective - what are the unmet medical needs, what are the business opportunities, what are some of the competitor or IP hurdles that we'll need to clear?

The other half of my position is more externally focused where I'm having conversations on a frequent level with potential partner companies, investment groups, VCs or angel

investors, and trying to get a sense from them where these technologies could go, if this represents a potential partnering possibility, or even a spin-out company. In a very cyclic fashion, I can bring that feedback back into the internal team, have the conversation, and it keeps iterating from there so that we can create the most valuable technology that we can.

[37:52]

McNally:

So you function as a translator in the translation process...?

Gemmiti :

Yeah. I tend to think I'm bilingual, if you will, and my background being ...

McNally:

You speak both industry and science?

Gemmiti :

I do. I speak business and science.

Where we are at the Wyss, a lot of the technologies are very early stage where, frankly, it's a really cool technology. We recognize it's really powerful and has a lot of different applications, but the question is what do we do with it? What is that ideal indication? What is the killer app, if you will?

It's my role to, as I mentioned earlier, really understand from the internal team what this technology is good at and what it is not so good at. Through market research and just understanding the industry, defining what indication we should go after in oncology or in orthopedics. and that kind of thing.

Hopefully, that is the spark that really helps focus the team and obviously we have a tremendous number of very brilliant scientists here that can - once we have that target - really push it forward and add a lot of value and experiments such that, as I mentioned, that an industry partner or a VC sees this as something that we should bring out.

[39:13]

McNally:

Can you give us a specific example of that process in action?

Gemmiti :

Sure. I think this refillable hydrogel system that came out of Dr. Mooney's lab is an example where it was an undefined avenue. What do we do with this? Where do we go? And in close conjunction with Dr. Mooney and Yevgeny Brudno, who's really the lead on this, we were able to whittle it down and say that oncology is really where we need to be going with this. And we're starting to move forward with that translational process, and finding clinical champions that are literally right across the street from us in the wonderful Longwood Medical area. We're really starting to put some momentum behind that.

[40:03]

McNally:

Where do you stand at this moment and what's right in front of you in terms of decisions that have to be made, pathways you're going to take, that sort of thing?

Gemmiti :

I'd say that a lot of it is defining what that killer app is, and once you're there, it really becomes a mix of business factors and technical factors that the team has to really agree upon. Do we have the IP? Do we have IP security that we need? Is there sufficient market opportunity? Is this at a technological maturity point where we're really ready to push it out and try to spin it off into a company, or do we need to perform multiple other experiments before we can really say that this is a real proof of concept and is sufficiently mature to go out and get additional funding?

[40:59]

McNally:

You mentioned the word de-risking... In some of our previous conversations with folks at Wyss. It's become clear that a lot of academic institutions, academic research centers, will de-risk academically, theoretically, scientifically. At Wyss, you de-risk along that but you also de-risk commercially. Can you talk a bit about that?

Gemmiti :

Having been in industry and interacting on a fairly frequent basis with industry, I really have to understand what their pain points are. By way of example, one of the most frequent and earlier hurdles to get over is the notion of safety. A lot of times in academia, the early development work or some of the pre-clinical work is showing proof of concept in some particular indication - whether that's oncology or orthopedics or ophthalmology - but we don't oftentimes look in a rigorous fashion at the safety, the bio-distribution, those types of things that is really one of the first bars that industry and, more pointedly, the regulatory authority, such as the FDA, will be looking for prior to proceeding into a human clinical trial, for example.

[42:23]

McNally:

With the hydrogels, what are the challenges that you're looking at right now and some of your thoughts of how to overcome them?

Gemmiti :

There are a fair number of them out there, whether it's hyaluronic acid, alginate, or synthetic polymers. There is a need to really differentiate that - what's different. Alginates have been used widely for a great number of years and, that's a good thing in a number of scenarios. But what we have to do is add that wrinkle, add that whatever it is, a biologic or some sort of releasing mechanism that is truly novel, that people can look at it and say, "Wow. They've taken this very robust, very well-known, very safe technology, and added this new twist on it that can really close some gaps."

[43:21]

McNally:

In terms of your work right now at the Wyss with the hydrogels, with the cryogels, what are some of those secret sauces, unique pieces, that excite you and fit the criteria you're just describing?

Gemmiti :

Cryogels that I mentioned earlier from Yevgeny Brudno and Dave Mooney's lab is that of a refillable therapeutic depot. Here we have an alginate that we load with a drug. It elutes that drug over time. That and in of itself isn't novel. There are plenty of drug-eluting devices. Drug-eluting stents is a common analog. The problem with a lot of those technologies right now is once that drug elutes, that's it. There's no way to refill that stent or some other eluting mechanism.

What Yevgeny and his teammates in Dave's lab have been able to do is engineer a new chemistry into that hydrogel such that you, through an IV or oral refilling, can deposit or load more drug into that depot. You can almost infinitely elute drug from these depots just by refilling it, by taking a pill, or an IV.

McNally:

You mentioned alginates. You're talking there about the substance from which these gels are constructed?

Gemmiti :

Yes. Alginate is one of the more popular hydrogels that's been around for a number of years. It's been tested in humans. It's generally recognized as safe. It's been used in medicine and the food industry for a great number of years.

McNally:

Is that, the one that comes from brown seaweed?

Gemmiti :

That's the one.

[45:10]

McNally:

What are some of the next steps to accelerate translation? What are some of the things you're working on right now?

Gemmiti :

I think at the core of a lot of these development efforts is intellectual property. Be that trade secret, but usually patent. We spend a fair amount of time on really understanding the patent landscape, the competition, and making sure that we have that locked up or, at least, feel very good about moving forward and investing in these technologies. That is a foundational developmental effort.

Past that is, as I mentioned before, an element of safety, and that can be either organic in that we've added some safety through animal experiments or in vitro experiments in the lab, or just by having a better understanding of what sits at the FDA or what other groups are doing.

Then after that, it's really understanding, showing the efficacy in a high value clinical indication with oncology, for example.

Once I think we have that, we have a really robust technology, something that's marketable, something that's translatable. Is it best to bring it into the clinic? We have great capabilities in the Harvard network to bring things into the clinic or is it best fit for a more vertically integrated company, a big pharma that has clinical infrastructure, that has the regulatory infrastructure, that might be better to shepherd this product along through the clinic.

[46:45]

McNally:

In terms of, let's say, a bigger or a long-term vision, if all goes well, how does the work, the project you're working on with the hydrogels, the cryogels, how will it change drug delivery? Lay out a timeline in 5 years, in 10 years. What can you imagine you've changed or improved?

Gemmiti:

I'd like to think that in 10 years you have these drugs approved or these therapeutic oftentimes combination products approved. It's a pretty laborious pathway. Most of these technologies are going to take at least three clinical trials that oftentimes last at least a year, if not, longer. It is a rigorous pathway to bring something to market both in terms of time, the number of people involved, and the cost.

I do think that if we really have a good understanding of how these things work and what it's going to take to get there, we can set these projects on their course now and in some amount of time, we'll be really treating patients and, whether that is curing a disease, alleviating a disease, or the symptoms associated with it, or oftentimes just the course of therapies can be really onerous on patients. Sort of reducing that overall morbidity and mortality in our population is something that we aim to do in the next 10 years.

[48:16]

McNally:

What sorts of applications do you see?

Gemmiti :

Part of the beauty of hydrogels is that they are very biocompatible and they're very tunable so we can engineer them to last for a long time, we can engineer them to last for a very short amount of time. They can elute drugs or they can bind things. They're very flexible. Because of that, they can be used in a wide variety of clinical indications, whether it's oncology, ophthalmology, orthopedics, general surgery, cardiovascular.

[48:53]

McNally:

You mentioned that it might take three clinical trials to establish efficacy and safety. Is that where you need to probably partner, license, or launch a start up to come up with the kind of finances that are able to afford those steps in the process?

Gemmiti :

Yes, absolutely. I think whereas the Wyss is absolutely critical to bringing something that is ready for a clinical trial and, in some instances, actually into a clinical trial. That is tremendous. Having that first-in-man clinical data is a real value inflection point for the project.

That said, to continue taking something all the way through registration where the FDA eventually approves it requires a tremendous amount of resources and expertise as well. A more vertically integrated company like a big pharma or a big biotech, that has clinical operations units, that have medical regulatory, so on and so forth, that can really not only have the expertise to efficiently shepherd those projects through, but frankly have the money to do it as well.

[50:08]

McNally:

Finally, Chris, you took a leap less than a year ago to come to the Wyss Institute...What's working for you?

Gemmiti :

I think one of the unique features of the Wyss is the focus or the imperative to bring on staff scientists and associates that have a wealth of industry experience. It's a community that has logged a number of years in big pharma or big biotech and medtech, so it's not just one person that says, "Well, I've spent some time in industry and I think this is how we should be approaching things." It's really the team. They've been there. Teams have brought other projects through clinical trials or through the FDA. So I can really appreciate that it is a translational center where the academic engine of innovation is still humming along and the Wyss putting industry veterans onto these projects really adds a tremendous amount of value as they continue to mature.

[51:20]

McNally:

You've been listening to DISRUPTIVE: CANCER VACCINE AND HYDROGELS. I'm Terrence McNally and my guests have been DAVE MOONEY and CHRIS GEMMITI. You can learn more about cancer vaccines, hydrogels and 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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My thanks to Seth Kroll and Mary Tolikas of the Wyss Institute and to JC Swiatek in production, and to you, our listeners. I look forward to being with you again soon.

[52:02]

