

**Disruptive: Cancer Vaccine and Immuno-Materials**

Host Terrence McNally interviews Dave Mooney, Kai Wucherpennig and Aileen Li.

McNally:

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

What if I told you there are vaccines in the works that can target and destroy a tumor in your body, cure you of an addiction, or more safely and efficiently spay or neuter your pets? These are just some of the possibilities that led the Wyss Institute to introduce their new focus area, Immuno-Materials.

Immunotherapy – treatment that uses your body's own immune system to help fight disease – has groundbreaking and life-saving implications. In addition to cancers and addictions, Wyss believes this work could help develop new therapeutic strategies against infections such as TB and autoimmune diseases like type-1 diabetes.

In today's podcast, I'll be talking with Wyss core faculty member Dave Mooney, collaborator Kai Wucherpennig of the Dana-Farber Cancer Institute, and graduate researcher Aileen Li. We'll not only cover why the Wyss feels the time is right to create this new focus area and look into projects in progress, but we'll also explore the relationship of research in the lab with research in clinical settings.

Our bodies — and all living systems — accomplish tasks far more sophisticated and dynamic than any entity yet designed by humans. The mission of the Wyss Institute is to: Transform healthcare, industry, and the environment by emulating the way nature builds.

DAVE MOONEY, who leads Wyss's new Immuno-Materials focus area, is the Robert P. Pinkas Family Professor of Bioengineering at the John A. Paulson Harvard School of Engineering and Applied Sciences. He plays an active role in major biomedical and chemical engineering professional societies, serves as an editorial advisor to several journals and publishers, and participates on several industry advisory boards. Mooney is a member of the National Academy of Engineering and the National Academy of Medicine and a fellow of the National Academy of Inventors. [01:55]

McNally:

Dave Mooney, welcome again to Disruptive.

Mooney:

Oh, it's my pleasure.

McNally:

So we're talking on the occasion of the renaming and the redefining of one of the platforms within the Wyss Institute, what has been in the past Programmable Nanomaterials is becoming Immunomaterials. Now can you share with us the story, the evolution there? What have you been doing in Programmable Nanomaterials and what led you to rename and refocus as Immunomaterials? [02:26]

Mooney:

At the Wyss Institute, we believe that it's very important to continue to change with time. When we started the institute, we felt that if we were doing the same things five or 10 years later, that probably meant we weren't actually looking forward enough and moving forward enough.

So the goal from the beginning has been not to establish and then stay static, but instead to keep moving. To succeed or to fail, and to learn from that, and then to move on to the next challenges. So that's really what we're doing here. [02:56]

Programmable Nanomaterials - the concept was that we would design materials that would largely be used in medicine but also in other areas, and we would design these materials at the size scale of individual molecules, so the nano scale. And by doing that, we would be able to achieve a wide variety of functions - biologically, physically, medically - that were unavailable previously, and this would open up new possibilities for commercial products, for treatments for patients.

And we were quite successful with that over time. We've developed a number of different strategies, there's been a number of inventions, companies that have spun out. But also with time, we began to realize that over the last year or two, our focus was increasingly around the idea of manipulating the immune system.

Immunotherapy I think is one of the new frontiers for bioengineering and we decided to really just end the old platform and start this new platform with a focus specifically on manipulating the immune system. [03:54]

McNally:

Mm-hmm...And choosing to focus on immunomaterials, and immunotherapies ultimately, let me ask you this in terms of the criteria, how much of that is because you see that's where you're going to have the greatest impact or because you see that's where you're going to have the most likely or the most efficient translation? What kind of tipped the scales when you said, "You know what? We're going this way" ? [04:15]

Mooney:

It's been clear for quite a long time that dysfunctional immune system underlies many diseases, including cancer, autoimmune disease, things like type-one diabetes ... But also, over the last number of years, it's become clear that immune cells play very active roles in many other aspects of biology that we didn't appreciate previously, things such as tissue regeneration.

And immunologists have done a simply fantastic job of identifying the relevant cells, identifying the molecules that oftentimes mediate these effects of the cells.

And so we realized that this creates a really fantastic opportunity to now come in from the engineering side and to develop materials that can then manipulate immune cells in the body to try to drive therapeutic outcomes, and cures for disease, diagnosis of disease.

And so this really was kind of the starting point, this recognition that that field was at the point where it was making this transition from a lot of basic science knowledge to where we could really begin to apply that knowledge in a very targeted manner. [05:21]

McNally:

One of the things I sense that you're saying is you refocused not because you failed, but because you succeeded. And so what were some of the successes?

Mooney:

Yes. So there's a variety of different successes. The nano scale, let's start there. There's been a tremendous amount of advances, both scientifically as well as translationally, in the area of understanding how one can build materials out of DNA. And this is really exciting because a single molecule of DNA will associate with another strand in a very specific manner that we understand very readily and it was appreciated that beyond DNA serving as a means of storing information, which is how we normally think about it, it also could provide a really incredible approach to provide nano scale control over structure. [06:12]

McNally:

For listeners to whom that field is fairly new, one of the things that you're talking about there is DNA, and RNA as well, have this very limited set of rules. And that's actually what gives you so much control versus a protein, which is ...

Mooney:

Yes. Yeah, proteins have a lot of freedom in terms of how they form structures internally as well as then interact with other proteins, while DNA, as you said, has a much simpler rulebook. And so once you understand that rulebook, then it opens up the possibility of being able to design in a really precise manner. [06:46]

And so we've been exploring that through the activities of some of the faculty - Peng Yin, William Shih - in the platform, and they've just been spectacularly successful in really creating materials at the nano-scale with incredible precision. [07:02]

McNally:

By the way let me just say to listeners that there is an earlier Disruptive podcast with William Shih and Peng Yin about molecular robotics and programming DNA. So if you want to delve into that one in depth, check out that one.

Mooney:

We've been developing a wide variety of different materials that are useful for drug delivery. Examples include new types of a gel that we can inject via needle - so a minimally invasive introduction into the body - and these materials provide a depot for a drug.

And the drug slowly is released over time, so instead of having to take multiple pills spaced apart every four hours or twelve hours or go into the doctor's office to get an infusion, these open up the possibility of introducing the system once and then having days or weeks, even months of release of a drug. And the release may either be continuous or we may be able to actively regulate it by applying signals like ultrasound or electromagnetic fields from outside the body.

And so we've been exploring and using these in a variety of different contexts and currently have partnerships with several different companies to move these towards clinical translation in the delivery of specific drug molecules. [08:12]

And then also, at smaller size scales, we've also been formulating various types of nanoparticle-based drug delivery systems that can be injected in the bloodstream.

One of the great successes in the platform and the Institute was the development of technology coming out of Donald Ingber's lab, where one can inject nanoparticle-based particles into the bloodstream and they will specifically unload their drug at a site where a blood vessel would be blocked. So it allows you to then really specifically deliver drugs to those locations, cause the clot to dissolve, to allow blood to flow. And that went on to become an institute project at the Wyss Institute several years ago and is under active development right now. [08:55]

We also have a lot of biomaterials activities that we've done to develop new materials that enable various kinds of functionalities. And one set of these materials, we've realized over the last few years, are tremendously useful in creating immune responses against cancer.

And the first of these is a little piece of plastic about the size of a baby aspirin tablet that's currently being placed in patients at the Dana-Farber Cancer Institute, and these are patients that have stage four melanoma. And the intention of this little plastic disk is that it will generate an immune response against the patient's cancer to destroy those cancerous cells and those tumors. And at the end of the day the disc itself, after it's generated this immune response, will dissolve away. [09:41]

McNally:  
What do you do so that it triggers that immune response?

Mooney:  
So the material's designed so it first releases a drug that will cause accumulation of the target immune cells, literally inside the device.

McNally:  
Wow.

Mooney:  
And then once the cells are accumulated inside, we then have another drug molecule they pick up that activates those cells and simultaneously they see

fragments of cancer. So they then associate these fragments of cancer as being something dangerous and something that they should try to generate a response to seek out and then destroy any cells that have the same signature. [10:22]

McNally:

You're overcoming the fact that the body doesn't attack these cancer cells because they're its own and what you're doing there is you're ... not tricking perhaps but whatever word you would use, the body to now recognize those as something they need to attack.

Mooney:

Absolutely. So we're presenting fragments of the cancer in a context that the body would see it as being something dangerous and foreign. And so really trying to reprogram the immune response in that the patient's immune system, because - as you said - cancer's part of their body, the immune system tolerates it. And what we're trying to do is break that tolerance, and make the immune system respond to cancer cells the same way they would to some, foreign agent that invaded your body like a virus or a bacteria. [11:10]

McNally:

Mm-hmm.

Mooney:

...And so we have these different strands, to kind of go back to the starting question of how we ended up in Immunomaterials... We have these materials that we can control structure and function, we've shown that they can be very useful in a very broad sense for drug delivery in the body. And we've shown that we have a capacity to be able to concentrate and manipulate immune cells, and so these really came together and we began looking at where the real frontiers were going to be in medicine in the coming years.

And we realized that we had a really incredible tool set that we thought could allow us to broadly address immune dysfunction and a variety of different types of diseases that involved, one way or another, immune cells. [11:53]

McNally:

And so, if you are refocusing to narrow the range of projects ... And I often think of when one focuses it so there's many, many things worth doing and what you're saying is, "We've got to discipline ourselves here and put our resources in the most fruitful directions." Are things getting eliminated? [12:11]

Mooney:

So there's a ... Yes, basically. The short answer is yes. In academics, it's always hard to say that but the reality is yes. And being eliminated in a few ways.

Eliminated, one in a very good way, that some of these things have been very successful, so they've now gone out into the world and so, we don't need to keep them as our baby anymore 'cause they've grown up and they've left the house and we just need to let them go and do their own thing. So part of it is that.

Other things...When we set out to form this institute, we said, "We're going to take risks and we're going to fail," and we have done that. There's some projects that have failed, and so it's very important to be able to recognize failure and be able to stop when you recognize something is not going to work. And so some things we've said we're not going to do anymore.

And then others are in transition. Some of these pieces are ending up in the new platform. Others are actually very vibrant but maybe not quite ready to leave completely yet. But we have a lot of interest, let's say, from companies that we collaborate with, so some of the activities that are in essence self-supporting, we're keeping, and we're maintaining if we think that they have a real value and a potential synergy with Immunomaterials. [13:24]

McNally:

What's your vision for the next year?

Now, obviously when we talk in terms of just a year, I'm not asking so much what are you going to achieve in the lab, but how will the fact that you're refocusing change things over the next year? Where do you want to be in that process of the refocus, a year from now?

Mooney:

That's a great question. So, a year from now where I think we would really like to be and what we'd consider to be successful, is if one of the projects that we've started at this point in time, has transitioned to being in a phase one clinical trial. So if we've really been able to take one of the new projects and start to explore whether it can help people. So that's one criteria for success.

We'd also like to have signed an agreement with a company to commercialize at least one of our products or systems. And the reason why that's important is, at the end of the day we have resources internally, but they'll never be sufficient to take a medical product all the way through to FDA approval. That's multiyear, hundreds of millions of dollars, so at the end of the day we need to partner with somebody who can do that. So we'd like to have that kind of partner in place for at least one of our projects.

And we'd like to have three or four of the projects that we're just starting now at more the pipeline stage have transitioned to become platform or institute projects so we know, "Okay, we've got several different projects... They look really promising, they're on their way to being evaluated, at the end of the day, in humans."

And what underlies all this is, we obviously need to build the structure. We need to hire a few people that have the right expertise. We don't have a lot of expertise in immunology within the staff before, so we need to build that up.

[15:08]

McNally:

We return to the cancer vaccine, and Dave Mooney talks about the second generation, what they had engineered using the implantable plastic disc the size of a baby aspirin can now be injected into the body from a syringe. Listen closely. This is pretty remarkable.

Mooney:

We came up with the concept of injecting small micro-particles. So these are particles that individually are quite small and distinct, but the idea is that we would inject these and they would assemble to form a three-dimensional structure once they're in the body.

So we're in essence injecting discreet particles and then they coalesce and form a structure in the body, that can then achieve all of the same things that the implantable device, in terms of it creates a physical space, in essence a home, into which immune cells can be attracted, accumulated, and they will literally crawl in and interact with the material to get appropriately trained, but this in a much less invasive manner. [16:05]

McNally:

I let Dave know that I'm a bit impressed, and he quickly salutes his partners.

Mooney:

The collaboration with the Dana-Farber is really crucial to what we're doing here. We have tremendous expertise on the bioengineering side, the materials side, the chemistry side. What we don't have is the deep knowledge of immunology and the really thorough understanding of patient needs, patient biology, and the historical perspective of what types of strategies are both feasible and likely to succeed in the diverse people that have cancer.

And so it's really a marriage of synergistic knowledge bases and expertises. And I feel completely comfortable saying that neither we nor they alone could be nearly as successful as we are together. [16:54]

McNally:

Following Dave's lead, I turn to Kai Wucherpfennig, Professor, Microbiology and Immunobiology, Harvard Medical School; Professor of Neurology and Chair, Cancer Immunology and Virology, at Dana-Farber Cancer Institute.

Wucherpfennig:

I first came to the U.S. as a medical student, and I was very impressed by the interface of science and medicine, in particular at Harvard Medical School. I therefore returned as a postdoctoral fellow, initially for two years. My plans were, of course, to go back to Germany, but then I ended up staying because I just loved the science that I was doing, and the fantastic scientific environment at Harvard. [17:38]

McNally:

I talk a lot on this podcast to folks in the lab and in the translation end of things, and I realize Kai brings a clinical perspective. He's someone who

treats patients. I'm curious how he sees the intersecting paths of cancer research and treatment and how our approach has evolved over the years.

Wucherpennig:

Treating cancer has always been a very challenging problem, because cancer cells are normal cells that have acquired abnormal capabilities. For example, the ability to grow in an uncontrolled manner so that they don't follow the guidance cues of their environment to stop proliferating.

The problem essentially is how do you target the tumor cells while sparing all of the normal cells in the body. [18:27]

McNally:

He points out that traditional approaches to cancer therapy - radiation and chemotherapy - both target all cells that are rapidly proliferating. And that means a lot of collateral damage to healthy cells.

Wucherpennig:

- the cells in the hair follicles, with chemotherapy the hair falls out. Patients get very sick and get diarrhea because the cells in the intestines are rapidly replenished. And then, very importantly, the cells of the hematopoietic system that form the blood and all of the immune cells, meaning that cancer patients treated with chemotherapy have a much greater incidence of infections.

Where the story has started to turn is that we can now use the capabilities of the immune system to target cancer. We've learned that strengthening the ability of the immune system can result in durable responses in patients even with advanced disease. Right now this is in a subpopulation of patients. For example, in patients with advanced melanoma, which is a very rapidly progressive skin cancer, about 30% to 40% of patients benefit from immunotherapy, and some of these patients are actually long-term survivors. [19:51]

McNally:

When I ask how they trick the immune system into taking on cancer, Kai refers first to the evolution of our immune system

Wucherpennig:

The immune system actually developed to deal with infectious agents. If you think about our evolutionary history, infections were a much larger health problem than cancer.

Cancer most frequently develops in people who are past their reproductive age, while infections happen at any period of life, in particular in young people. So the immune system has an exquisite ability to mount a very potent response to infectious agents, but tumors are much less immunogenic. [20:36]

McNally:

He tells me we've now learned that the immune system can use the same principles of immune recognition to deal with cancers...Dave Mooney's lab has taken this on.

Wucherpfennig:

The conventional approach to develop a vaccine is to develop an antigen and then co-inject it with what immunologists call an adjuvant which is essentially a molecule or a group of molecules that will induce an immune response. And then these are drained into the local lymph nodes where they elicit an immune response by T-cells and B-cells.

The problem with this approach is that the antigen is only available for a relatively short period of time. It drains into the lymph nodes, it's taken up by cells there, it's probably around for a couple of days.

Now what Dr. Mooney has done is to create a local microenvironment at the injection site that slowly releases the antigen and the adjuvant over a period of weeks.

The second important aspect of this approach - and he calls this scaffolds - is that they actually recruit the right type of immune cells into this micro-environment where they're exposed to the antigen and the adjuvant, and then they migrate from there into the lymph nodes to elicit a T-cell and B-cell response. So you get a much stronger and more sustained immune response compared to the traditional approach. [22:14]

McNally:

What is the stage you're at right now in terms of your clinical trials? What's next?

Wucherpfennig:

The implantable version is actually being tested in a clinical trial at Dana-Farber at the moment. This is in patients with advanced melanoma. The Wyss and the Dana-Farber team have actually worked very closely together to take this very novel concept into a clinical trial without the involvement of a biotech or pharma company.

Basically, the way this worked is that the Wyss developed a scaffold and the process for making the scaffold in a reproducible manner, and then there is a clinical grade lab at the Dana-Farber that took this and then incorporated all of the other components, in particular, the tumor antigens from the patient's tumor, into the scaffold, and then these are implanted into patients, and the trial is ongoing. I've seen some of the data from the trial, I think I can say it looks encouraging.

We are now collaborating with David to use the injectable version as a second generation vaccine. Obviously, it has a lot of advantages because the manufacturing will be much more straightforward. Basically, you take

the rods and then you mix them with whatever antigen you want to immunize with. This is something that can be done in a very straightforward manner and doesn't require a very complex manufacturing process at the clinical side. [24:02]

McNally:

Kai reveals to me just how dynamic the interaction of medicine and research can be at the Dana Farber.

Wucherpfennig:

Most people think of biomedical research as doing something in the lab, which we call the bench, and then taking it into the clinic, which we call the bedside. So a traditional approach is sort of the bench to bedside.

But what actually happened here was that one of my colleagues at the Dana-Farber, Dr. Glenn Dranoff, developed a cancer vaccine in the lab, took it into the clinic, to the bedside, and then analyzed the immune responses in the patients and identified several interesting antigens, and then we've actually taken them back into the lab. So from the bedside back into the bench to develop the vaccine, and we're now going to take it back to the bedside. So it's bench, bedside, bedside, bench. Bench to bedside, right?

The point is to actually learn what is happening in a productive anti-tumor immune response in people and then to use those insights to formulate next generation vaccines. The reason this is important is that experimental animal models can be very informative, but, of course, they don't fully simulate the human biology. This is particularly important in an immune response, and so insights from the clinic as to what actually works in people are very important for developing the most effective immunotherapy agents. [25:42]

McNally:

Mm-hmm...So it sounds to me like not only is the technology cutting edge or experimental, but the process of collaboration between the Wyss and the Dana-Farber sounds like you're going a little bit outside the box there as well.

Wucherpfennig:

Yes, we definitely do. So I think what's happening in the cancer immunotherapy field is that we now see amazing responses to immunotherapy agents in people, and we're starting to examine that at a high cellular molecular resolution, really learning what's happening in people.

We're really taking that back into the lab and asking, "What does that teach us for the next generation of immunotherapies?" And I think that's actually an important paradigm because every experimental model, including the many different animal models of cancer, all have a lot of limitations. And so bringing in knowledge of what works in people and what doesn't work in people is actually very instructive. [26:54]

McNally

I mention to Kai what Dave Mooney had said about the contributions of the Wyss and Dana Farber being complementary...

-- that what you're very good at and what you bring to the game is different from what the Wyss brings, and so there's a kind of a magic that goes on there. Could you talk about that?

Wucherpfennig:

Yes. There's actually a lot of this type of magic ongoing at Harvard Medical School, this is actually why I came back-

McNally:

Very good.

Wucherpfennig:

-as a researcher. I saw that magic ongoing when I first came there.

The Wyss has tremendous expertise in bioengineering and developing novel concepts to address key problems in human biology. And then the Dana-Farber and the other hospitals have the ability to study human disease at a high resolution and to also do interventions in people, to perform clinical trials to test new ideas.

When you bring these two different sets of expertise together, new and exciting things can happen. Somebody develops a new approach for vaccination, it's being tested at the Dana-Farber, we analyze the immune response, develop a next generation vaccine. It's really a positive feedback loop -

McNally:

Mm-hmm...

Wucherpfennig:

- where you learn from what the other people are doing and I think both components are absolutely essential to rapidly make progress. [28:31]

McNally

Kai has a clear sense of what sorts of partners make the best collaborators.

Wucherpfennig:

What actually is impressive about Dave Mooney is that he not only has the bioengineering expertise but he's actually made the effort to learn a lot of immunology. I teach one of the major immunology courses to our graduate program, and I was actually very surprised to see him in the back row in one of these classes. He took an advanced graduate level immunology course to really immerse himself in the field.

People talk about collaborations between different fields but it can be really fantastic but there are also barriers because different fields have different language, for example. To develop a productive collaboration, people have to understand the other field sufficiently to be able to really communicate at an advanced level. So David really made the effort to learn immunology and so that really comes through in our collaboration. [29:54]

What a lot of people do is they have an idea, they get some collaborators involved, they publish a nice paper, they write a grant, and then they're done. What David and Aileen really had to do was to push the boundary of what they could actually do. He could have said at this point, "We have something that's in clinical trials, it looks like it's showing intended benefit," but he said, "Okay, let's take it to the next level. Let's develop an injectable version." He keeps pushing the boundary. [30:31]

McNally

I want to hear from Aileen Li, Like Kai, Aileen offers a novel perspective on the process of innovation at the Wyss. She'll be leaving the Wyss soon, but as a graduate researcher, her work on her PhD thesis has been integral to the development of the injectable cancer vaccine.

Li:

Yes. I actually just defended last week.

McNally:

And how did you feel?

Li:

I passed. It feels really good to put together all of the work that we've done in a finalized form to look at where it started, where it could potentially go. Yeah, I definitely feel a sense of relief.

McNally:

How many years you've been at it?

Li:

Seven.

McNally:

Oh god!

Li:

I know. I started in 2010.

McNally:

Do students realize that when they start on that process that it might be seven years.

Li:

I don't think so. Actually when I started, I remember going to interviews at different graduate school programs and I always asked the students, I'm like, "What's the average time to degree in your lab?" And if they say anything more than six years, I'm like, "No, I don't think so."

McNally:  
Okay.

Li:  
So when I interviewed at Dave's lab, they're like, "Yeah, five and a half years," like that's the reasonable amount. I think at my year four or five, I didn't think about wrapping up and just defending, but I was really interested in just doing more work so I stayed on. [31:57]

McNally  
Dave Mooney makes clear how remarkable her commitment was.

Mooney:  
She's a PhD student now. Most PhD students get to a certain point where they get eager to finish and move on to the next step of their lives. We're always, as a society, we're always in a hurry. And she had been working on this project and she'd been training actually a postdoctoral fellow and a little unusual that PhD students training postdoctoral fellow.

But she was training this postdoctoral fellow in these vaccines and how to utilize this, and I think the concept was that Aileen would finish and this postdoc would take over the project. Well this postdoc got very excited about taking a job in consulting and so ended up leaving the lab and, you know, so I'm wondering what's going to happen to the project.

And what's really striking to me is, Aileen came in for our next meeting and says to me is that, she'd been thinking that she would probably finish up her thesis and defend, in the next six months or a year. But she was really concerned that with this other individual leaving, that then the project might not really finish the way it should, it might kind of fall apart a little bit with her being gone and no one immediately there to take over. So she was going to put off her defense, the completion of her thesis, and stick around for another year or so, just to make sure this project got done.

And I was just really astounded because she has these wonderful papers she's published, she's gotten a tremendous amount out of her thesis, she could've moved on to a very prestigious postdoctoral fellowship at that point in time. But she more or less just said, "I'm going to put all that on hold because I want this to be done right. And I think it needs me." [33:29]

Li:  
I just really wanted to see where we could take the vaccine, what kind of responses we can generate. For example, if the vaccine can actually have an effect on controlling tumor growth in mice, that was partly the reason that I stayed, just

because I was very interested in understanding more, I was very curious about what can happen.

McNally:

Right. You've gotten hooked, right?

Li:

Yeah. I don't think I would've been very satisfied if I left. [34:03]

McNally

Li came to the Mooney lab just as they were moving from the implantable to the injectable form of the vaccine.

- And the advantage of the injectable over the implantable?

Li:

The advantage is simplicity. It's simple to manufacture, it's simple to utilize, it's a modular system that allows us to combine different immune-modulating drugs and assemble different types of vaccines.

So right now, we've evaluated the vaccine platform using a number of tumor-specific antigens of proteins and peptides, and we're seeing positive response in several of these contexts, and we've demonstrated that the vaccine could eradicate established tumors, control tumor growth, induce all sorts of powerful immune responses such as getting more T-cells into the tumor, and we've also shown that the vaccine plays in synergy with some of the existing immunotherapies.

So, we're very excited about what we have shown pre-clinically. [35:20]

McNally:

As you leave to move on in your life, there's been a lot of progress on this vaccine, and now we're moving to human clinical trials and you can see a future of this actually having impact, how does that feel to you in terms of pride or that sort of thing, in terms of what you've accomplished?

Li:

So when we started we were starting from scratch, from literally point zero of making a new material in the lab, and not knowing what that material will do. In the process of these six, seven years that we've been developing the vaccine, we've built all the way to a vaccine that where we've now seen tremendous preclinical results in a number of settings. I'm very grateful for being able to do all of this work and I'm very proud of how far we've come in developing this platform, and the broad applications that this will have. [36:26]

McNally:

At that point, as you said, five, five-and-a-half years into the process, when you decided, "Well, wait! I don't want to quit. I want to keep going," have you felt like that last year and a half or two was worth it?

Li:  
Totally. Absolutely.

McNally:  
Okay. Thank you very much.

Li:  
Thank you. [36:40]

McNally:  
I return to Kai Wucherpfennig. I want to know how he sees cancer treatment evolving over the next five to ten years?

Wucherpfennig:  
I think we're in an era of very rapid change in cancer therapy. What you can see is that in some cancers in which immunotherapies were evaluated first, immunotherapy is already front line therapy. For example, with patients with melanoma, immunotherapy is front line therapy, and chemotherapy is the backup.

McNally:  
Mm-hmm.

Wucherpfennig:  
I think we're going to see that trend continuing. That immunotherapies will be given earlier in patients and maybe ten years from now, immunotherapy will be given first rather than chemotherapy in many cancers. Because, for immunotherapy to work optimally, you want a fully functional immune system.

McNally  
You want the person the to be as healthy as possible, you don't want to have compromised it.

Wucherpfennig:  
My prediction is that immunotherapy will be much more efficacious in a front line setting where the immune system hasn't been beaten up yet, than in the late stage of disease where it needs to be first evaluated. [37:58]

The other trend that I think we're going to see is that immunotherapy will be combined with what we call targeted therapies, that target specific molecular lesions and tumors. I think those types of combinations will be effective because the mechanisms of resistance are very different.

The targeted therapy targets specific molecular pathways in tumor cells, while immunotherapy targets specific immune cell populations. The more distinct the resistance mechanisms are, the more likely a combination is going to work. Now, what will have to be taken into account as to what the

impact of a targeted therapy on the immune system is going to be. So I think in the future, drug development in cancer will have to very closely involve examination of the effects of drugs on the immune system.

When you think about the past, a lot of immunotherapy trials failed because they had to be done in patients with advanced disease, and in those patients, the immune system was already seriously compromised. I think this will have to change. I think we need to move towards therapeutic approaches that leave immune system function intact.

McNally:

And the reasons immunotherapies have usually been a last resort is because we hadn't yet proven that they were effective nor were we clear about their side effects, am I right?

Wucherpfennig:

Yes. This is the path for all therapeutics. They're first tested in patients with advanced disease who have exhausted other options, and then if there's a signal, then they can be tested in the earlier stages of disease.

I think with immunotherapies this is particularly important. There are even studies underway to ask, "What are the benefits if we give immunotherapy before any other therapeutic strategy?" For example, even before surgery.

There's an interesting idea, it's called neo adjuvant therapy, and it's an interesting idea because you leave the source of the antigens and the immune cells in the tumor in the patient while you give an initial dose or two of immunotherapy. We're not talking about a long period of time, maybe two to four weeks. But there would still be enough time to boost the existing immune response before you take the antigen and a lot of the immune cells out of the patient. People are starting to explore that, and I think that this will turn out to be extremely interesting.

McNally:

Thank you, Kai, that was wonderful. Thank you very much.

Wucherpfennig:

Thank you so much. [40:55]

McNally

I've got a good sense of the cancer vaccine and the team at work, but what about those other potential pathways for Immunomaterials? I turn back to Dave Mooney.

- Can it help fight infections?

Mooney:

We're not trying to, at this point, trying to treat kind of a routine garden variety infections that, you know, "Take this antibiotic and you're going to be fine." We're

thinking more along the lines of chronic infectious disease, where you have an infection that you simply can't get rid of, antibiotic resistant threats, situations where you don't even really know what the disease is, but it's clear the person has a debilitating disease that may be life threatening.

So we would like to develop a therapeutic vaccine. So again, the idea of treating patients who have the disease so we can be able to identify or at least extract some information about what the agent is that's causing the disease, and then have a very rapid generation or fabrication of a vaccine specific to that agent to induce a therapeutic response and either slow down the disease or clear the disease completely from those patients.

So we're really going to be targeting a wide variety of different types of infectious agents, but what they'll have in common is that they tend to be deadly, they tend to be chronic, they tend to be things that aren't treatable or are very difficult to treat with the classic approaches. [42:15]

McNally:  
Okay... What about autoimmune diseases?

Mooney:  
Yeah, so you know in autoimmune diseases, things like Type 1 diabetes, we have in many ways the opposite problem or challenges we do in something like cancer. In autoimmune disease, your immune system is now attacking agents in your body that are normal and not disease-causing. And by attacking and destroying these cells and tissues, they wreak very significant havoc in the body and can lead to a variety of side effects and death.

So here what we're trying to do is actually tune down an over-exuberant immune response instead of tuning one up.

McNally:  
Instead of making it go after cancer that it was ignoring, you want it to begin to be less aggressive against something that it doesn't need to be going after...

Mooney:  
Yes, that's correct.

And so the idea is similar in many ways - we have immune cells that are doing something we don't want them to do, we would like to reprogram their behavior, and so we're again using materials as a very convenient means of attracting and concentrating large numbers of immune cells. And once we have a large collection of them, we can manipulate those cells and in this case now, give them cues to turn down the immune response instead of turning it up. [43:30]

McNally:  
Mm-hmm... You're also doing some work with addiction. I know one of the things that you're talking about is of being able to use this technology, this approach, to deal with, for instance, a nicotine addiction.

Mooney:

Yes. So one of the really striking observations that have come out of work, for example of Aileen Li, who is really targeting cancer, but we realized that these systems are very potent and seem to have the capacity of breaking tolerance against many if not virtually all agents or molecules that are in the body.

And so this opens up the possibility that this approach could be a very effective means of generating immune response against addictive agents. And this is not a new idea by us, this is something that people have been exploring for some years, but it looks like our systems may be particularly potent in this regards.

And the general idea is, let's say, if somebody has an addiction to cigarettes, there's a particular chemical, nicotine, that gives them the "benefit" and provides the addiction to cigarettes ... Well, if we can generate immune response so when those chemicals get in the bloodstream, they're cleared virtually immediately before they have a chance to bind to their biological targets and give the individual the -

McNally:

The signal -

Mooney:

- the effect... Yeah, the signal. Yes. That then you would smoke and you would get nothing from it. You would take an addictive drug, you would get no benefit from it. So this could be a very effective means of breaking those types of addictive behaviors if the patient no longer can get any benefit or activity.

So a similar idea. We're vaccinating again, but now against a target simply trying to clear it and prevent it from binding and having any biological effect.

McNally:

And I had mentioned nicotine because I'd seen that mentioned in the writings, but obviously the big one in America right now is the opioids. Would this potentially be helpful in that regard as well?

Mooney:

Yes, it potentially would. We've not begun to explore that yet, but that clearly is just a tremendous need in our country today. And so I think that's a very clear and pressing target for us to explore. [45:33]

McNally:

I asked you what your vision for the Immuno-Materials focus and platform is within the next year. What is it within the next five or 10?

Mooney:

So the vision for the platform within the next five to 10 years is that we have both a very specific focused impact, in terms of having some of the devices and systems we develop, not only enter human clinical trials, but also be established as being

effective in terms of actually helping these patients.

So I would like to see us go to that level. That'll probably be more of a 10 year time scale, because clinical trials take a considerable period of time. But I would like to actually have validation that this concept of using materials to concentrate and manipulate immune cells can have a therapeutic effect in a reproducible manner in patients.

And then in a much broader impact... You know, we are in academics, we're not a company so it's not just about having a product, it's about changing perceptions, developing fields. And I'm hoping that with the successes that I'm planning on us having, we're able to train a lot of really talented people and influence a broad community and have many others follow the path that we're taking in similarly trying to develop new bioengineering strategies to manipulate the immune system. So over the long run, that impact can also be great and really magnify what we can do ourselves. [46:57]

McNally:

If you went back instead of forward, if you went back about 10 years, what have been the biggest surprises to you about what you've learned and what you're working on today?

Mooney:

I'd say the biggest surprises have been, one, that this strategy seems to be so potent in really changing the immune system. So it's not just initiate an immune response, we can dramatically change or alter the path and the type of immune response much more than I would have first guessed. And then, I was a complete neophyte in immunology, very unknowledgeable about it when we got started down this pathway. And so the other thing that's been really striking to me is the range of diseases and situations in which vaccination could be very, very useful as a therapy, well beyond my perspective 10 years ago.

McNally:

Yeah, I can see that. In other words, you stuck your head in a door and didn't realize what was possible there, partly because no one had pursued it in some of these areas. Isn't that right?

Mooney:

Absolutely. And you know, we went through the one door, as you just described it. I was going through a cancer door trying to develop a therapeutic vaccine for cancer, and once we got through that door, then you realize that once you went through that door, now there's a whole bunch of other doors with other possibilities in front of you that you can now go through that you didn't have available previously.

McNally:

- You didn't even know existed, right?

Mooney:

Yes.

McNally:

Yeah. Okay, thank you very much Dave Mooney, it's been a pleasure as always.

Mooney:

Oh, my pleasure. [48:23]

McNally:

You've been listening to DISRUPTIVE: Immuno-Materials. I'm Terrence McNally and my guests have been Dave Mooney, Kai Wucherpfennig and Aileen Li

You can learn more about their work as well a broad and exciting range of other projects at the Wyss website - [wyss.harvard.edu](http://wyss.harvard.edu) - that's W-Y-S-S dot Harvard dot edu - where you'll find articles, videos, animations, and additional podcasts. In fact, Dave Mooney has been featured in another episode of DISRUPTIVE.

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My thanks to Seth Kroll and Mary Tol-ee-kas of the Wyss Institute and to JC Swiatek in production, and to you, our listeners. I look forward to being with you again soon. [49:06]