

From the campus of Harvard Medical School, this is *Think Research*, a podcast devoted to the stories behind clinical research. I'm Oby.

And I'm Brendan. And we are your hosts. *Think Research* is brought to you by Harvard Catalyst, Harvard University's Clinical and Translational Science Center.

And by NCATS, the National Center for Advancing Translational Sciences.

How do you approach problem solving? Do collaboration and brainstorming spark solutions quickly? Or do you identify a goal and work backward? Oftentimes, we can't be sure what the answer is that we're looking for.

In a translational domain, researchers must develop processes to advance their technologies to patients quickly. But they don't always know how. Dr. Jeff Karp and his lab approach new opportunities by defining the problem before anything else. They call this radical simplicity.

Dr. Jeff Karp is a professor of medicine at Harvard Medical School and Brigham and Women's Hospital and a principal faculty member at the Harvard Stem Cell Institute. Dr. Karp, thank you for coming back. It's a pleasure to have you here.

Thank you.

So we want to talk about a story from your career about when an idea that you had didn't turn out the way you thought it would. In 2008, your lab was working on a targeted approach to stem cell therapy. But you were met with some obstacles. Could you tell us about that and what the story behind that was?

Sure. So the first project in my laboratory, what we were aiming to do was to develop a new approach so that we could engineer the surface of cells. So these would be in the context of stem cell therapy where you take cells out of the body, manipulate them, and then put them back in the body. And one of the great needs is if we could have the ability to inject these cells intravenously, for example, and then have them to target any place in the body.

That would be huge because there's a lot of places you want to get to. But it's just very invasive to put a needle deep into the tissue. And you can only really do that a small number of times. And so if we could develop the ability to have a stem cell therapy where you could program those cells to go anywhere they needed to go, to the bones, for example, to treat osteoporosis or to the joints to treat arthritis or to the heart or the liver, the lung, that could be very powerful.

And most of the time, when you inject the cells into the bloodstream, they just get filtered. And they don't really get to the location that you want them to go to. And so we figured out a way to engineer the surface of cells that could target various sites in the bloodstream. And we had advanced a project to a point where we had some very promising data. In preclinical models, we showed that it was possible to do this.

And so I was really excited at that time. I had just started my laboratory in July of '07. So this was around 2008 or 2009 time frame. And I approached a local investor. And really, I went in with the hope that this potentially could be a new company. And we'd be able to use this technology to bring new therapies to patients.

And I went through the data and shared all the results. And the investor essentially turned to me and started asking questions about the number of steps involved in the process that we had developed. And it turned out, we had a five step process. And the more and more that I described, the more I started thinking, wonder what he's thinking.

And then he turned to me and said, this is just way too complicated. He said, there's so many cases where we've tried to bring new technology to patients, but it just can't be manufactured. We have to be able to do quality control at every single step. And sometimes, you can't even do it for a single step it's so challenging. And let alone you have five steps in your process. And so he turned to me and he said, if you want to help patients, you're really going to need to simplify your approach.

And so I went back to my lab kind of tail between the legs kind of thing, not very happy. But I just knew I had to take that advice to heart. And so I started thinking from that moment onward, how can we really simplify what we're doing at every possible stage?

And that really got me into the habit of thinking not just about the academic problems that we were working on and publishing papers but really thinking about, what are the steps that come after we demonstrate a proof of concept, for example, in a preclinical model? And the more I thought about it, the more I realized that I really needed to understand what happened after the publication. After you have a technology, that's now you got to a proof of concept, how do you then bring that to patients? And there's so many steps involved and so many different types of people with different expertise that are required to bring a new technology, convert it into a product that can actually help patients. And that just changed my whole mindset.

You've talked before on the show about your mentor, who instilled in you this idea of taking discoveries and bringing them to market. Like this should be the goal. And what you just said about the goal being to publish a paper and then from beyond there is sort of somebody else's responsibility. And in the Ted talk that you gave last year where you talked about this, you talked about, it was, oh, it's somebody, like they'll figure it out. The entrepreneurs, they'll figure it out. But it sounds like what you're saying is to really be effective, you have to think about that entire process from the get go.

Yeah. I think I'd certainly been exposed to a number of different entrepreneurial academic mindsets. But I had never done it myself. And so I really didn't know what was involved. It was more I just kind of watching from afar a number of my mentors create companies and try and move things out of the lab. But I really didn't know what was involved.

And so I think that what I used to think was that you'd move a project to a certain point and then you'd hand it off to an entrepreneur or you'd license it to a company and they would just bring it to market. And so I used to think what we did in academia was really a big, big part of it. It was majority of once we could demonstrate a proof of concept and have a significant advance.

But now what I've realized through really being engaged in this translational process is that it's almost like what we do in the lab is just a few percentage, it's just like 2% or 3% of the way. And the other 90 whatever percent is what happens after something leaves the lab. And that includes trying to figure out how to do the manufacturing and the patent strategy and reimbursement, the whole regulatory process.

You need super creative people at every single step in this process who are putting as much thought and effort as you did to get to that proof of concept in the laboratory. And that's when I realized that I really need to understand this process better. And I can't just wait.

I think the typical thing to do is you go through. You may have like a two, three, four, or five, maybe even 10 year project. And then once you get to a proof of concept and let's say a preclinical model, then you go and find an entrepreneur to partner with.

But I think the problem with that is, often, the technologies when you get to that point are not translatable. They're too complicated. Or you've missed a lot of critical things that would have led to a better patent strategy. You'd have stronger patents had you been thinking about patents from the first step.

Maybe the technology, you picked the wrong first application to go after. There's a lot of considerations. We develop a lot of platform technologies in the lab, which means that you can use them for multiple applications.

But often, there's a lot of things you could do but very few things you should do. And it really is dictated by, what are some of the other products that are currently available? What are really some of the holes? Where is the most gravity? Where are clinicians really looking for change and willing to adopt new technologies? I mean, there's so many considerations like this that you need to think about right from the beginning. And that's when I realized that I really needed to change my strategy.

So when you went back to the lab, tail between your legs, what was your next step? How did you try and simplify this stem cell therapy process?

Well, what I did is I made a commitment to meet people in the entrepreneurial ecosystem and really form relationships because it's this understanding that I don't have any basic training in the business world. And it's a completely new world for me. And so what I did is literally, every couple weeks or so, I would meet somebody. And that person would be a patent lawyer, a corporate lawyer, an entrepreneur, someone from industry, reimbursement, regulatory experts, and develop relationships with these people.

How do you find those people? How do you get like searching LinkedIn, asking colleagues? How do you do that?

Everything, all the above. There's all kinds of networking events that are happening constantly in town. Law firms are putting them on. They're happening at academic institutions. There's always such a vibrant community here. There's always talks by local startups happening. And so it's really just kind of keeping my ear to the ground for all of these different networking events that were happening and then going to those events and making a point to just introduce myself to people and trying to figure out if there would be a hook for them to want to talk to me again. And so actively engaging in that process and making it a priority was really important.

And what kind of reception did you get from people when you introduce yourself and say, hi, I'm Jeff Karp. I'm working on this project. I would love to pick your brain about the business side of translation.

Yeah. Well, I think a big part of it for me was, early on, the reception really wasn't that great. I mean, you'd meet people. But they'd be looking around the room for someone to talk to that they were there at the event to speak to kind of thing. And so it took a while to figure out how to get people's attention and how to get enough time where they'd actually listen.

And for me, it was a little bit daunting but also exciting because you're taking a risk doing something that you hadn't really done before. But you almost have nothing to lose. And there's lots of potentially gain.

And so you know what, I really just looked at it like an experiment. So I would just try different things. I tried to tell them about projects I was working on. I try and change how I would tell those stories. And eventually, people started to listen.

And as we generated more data in the lab, I had more to talk about. And people wanted to hear what happened next. And so that started leading to multiple conversations and development of really some critical relationships that I still have to this day.

Great. And so you're meeting people. You're gaining perspectives on areas that you don't have a lot of experience in. And how does-- so take me through the next steps and how you changed your approach in your lab or just how you changed your approach to thinking about these problems.

Absolutely. So I think by starting to engage the groups that I was referring to, the patent lawyers and reimbursement regulatory experts and manufacturing experts, as we started to generate new ideas in the lab, I would then use this as a filter. And I think, in many ways, academia is a safe place where you can do almost anything. And there's just so many ideas. And there's so many decisions to make about what to do next.

I think, often, you might be working on something. You go to a conference or you read a paper and you see something. You say, oh, I could add that to what I'm doing, or I could combine it with what I'm doing. But I think the challenge there is that what often happens is you get led down this incremental path. And it may be exciting at the time, but it's incremental in the sense that it's not necessarily going to provide significant value to society.

So for me, changing just how I thought about approaching problems. And I started to realize that we really have the importance of making decisions and all of the decisions that we had. And so what I did is as we were brainstorming as a group and people were approaching us about various problems to work on, I would start thinking about right from the beginning, what's the patent landscape in this space look like? So I'd go to Google Patents and start looking at some of the patents.

I'd start thinking about, well, if we were successful, could this be manufactured? What would that look like? Do we have manufacturing strategies that would work right now? Or would we have to invent new ones?

What would the clinical trial look like? What would we compare to? What would the positive control be? Because then we'd probably want to have that in a bunch of our experiments. We want to compare to what's the gold standard that's being used right now in the clinic.

And so it really was this shift from doing more exploratory type science to really focusing on the application. And the application in the sense that if we were successful, we'd have the greatest chance to bring these technologies to patients.

No one thing I think important to mention is we need basic science. We need exploration in science and in academia. And a lot of incredible mechanisms have been discovered that have led to breakthroughs that have helped humanity. And we need plenty of that to continue and persist.

But I think that we also have an opportunity. And actually, I'll say one more thing is that we can't translate anything unless we have the basic science already there. We need to have a certain level of understanding of the biology. And there's many problems that we can't solve today because the biology is not well enough established. And so we really need to push basic science and exploration more.

What I'm saying is that I love basic science. And I love doing exploration. And we do do that in some of our projects. But at this point in my career, I'm most excited about trying to find ways to develop new technologies and bring them to patients as quickly as possible. And I think that's one of the decisions that I made is that I want to focus my efforts more on that translation. And that's really where my efforts have been for several years.

OK. Yeah, I think that's a great point that there's room and need for both sides. There's tremendous need for the basic science but also the understanding of how to bring new advances to market. So you eventually were successful in developing this stem cell therapy. Where is that technology now?

So the original stem cell technology that we were working on, we continued to advance that. We had developed a number of strategies to engineer cells to enhance their homing. And we continue to work on some related projects.

But what happened was that actually took us into an interesting direction. Because often what we do in projects is we'll dive in. And I always feel like when we start projects, most of time, we don't have very good ideas. But the goal is really to dive in and conduct experiments to gain some critical insights that can then shine the light on new possibilities that may enable us to make advances and move the needle beyond where the field is currently at.

And so I feel like that was almost one of those projects where we were really interested in stem cell therapy. We had identified some challenges in terms of engineering cells to control their homing and where they go in the body. I think we're not quite at the point yet where we're able to achieve a high enough efficiency where that can really be enabled for multiple applications. Although, I think we're getting there. And so we're continuing to think about it.

But what happened was, along the way, we had this other idea, which was when you put cells into the body, you lose control over the cells. They're entirely at the mercy of the biology. And the biology is different in different parts of the body. So the stem cells are going to behave differently. I mean, this is very different than a small molecule drug. We're talking about living therapeutics with when you take stem cells out of the body and then inject them back into the body.

And so we started to think, maybe there's better ways of controlling cells not just for homing but also for controlling what the cells secrete. Because there's a lot of really interesting cells that we can deliver that could secrete anti-inflammatories or could reduce fibrosis. And we can use cells for production of all kinds of interesting therapeutics.

But the challenge is that you lose complete control. You have control in the laboratory. In the culture dish, you can get the cells to do whatever you want. But when you implant them, you lose that control. And so we applied this concept of radical simplicity to stem cell therapy. And we came up with a very simple way to modify cells, so that we could control them following transplantation.

And what we did is we took standard materials that had been in the clinic in a variety of products, so like degradable suture material. And we made them into particles. And we put molecules into those particles that could activate certain signaling pathways in cells.

And what happened was so if you envision you have like a cell outside the body, it internalizes this particle that has a molecule in it. And that particle slowly degrades. So it releases the molecule inside the cell. And if you transplant that cell, the molecule is going to continuously be released inside the cell.

And so we can choose molecules that can activate specific pathways to control what the cells secrete or potentially control their survival or control their homing. And so it's a way of controlling cells from the inside out. And we show we can deliver these molecules to cells for weeks and potentially months. And so that was the kind of next technology that we worked on based on a number of lessons that we learned along the way. And then that technology was licensed by a biotech company that's in the process of bringing this technology to the clinic.

There's a couple of things that I wanted to follow up on. You said most of your ideas are bad ideas.

When we start, yeah.

Right.

Yeah.

Could you talk more about that?

Sure. When I say bad idea, I think it's more when we start, we have an interest in a particular area. But we don't necessarily have all the pieces in place. We don't really have a deep understanding of the problem. And I think that actually is a problem. Because if you believe that you understand the problem, majority of the time, you'll fail in trying to solve it.

And so it's really this sense of we try to understand the problem as best as possible by going into the literature and then going and talking to experts and seeing if there's nuances that you can't find in the literature, things, insights that we can gain. And then we start conducting experiments. We might conceive of a solution or we might conceive of a technology. But I think when we start, none of us really believe that that's what we're going to end up with.

And I think it's this understanding that what we really need to do is think about the best possible experiments to perform in the laboratory or in animal models where we're going to learn something new. Or we're going to gain some insights. Or we're going to be able to deconstruct that problem and figure out what should really be our guiding path forward because there's so many decisions to be made about how to approach a problem.

And I think what we want is we really want to understand the problem as deeply as possible. And often, you can't do that unless you start conducting experiments and really confirming what others have believed about the problem or figuring out things that others have missed. And I think it's critical to spend time.

I think there's a tendency to just jump to a solution. And so you look and you say, here's this problem of arthritis. And here's what people have tried. And we think this is going to be the next best thing. And we're going to now have this linear path moving forward. And it really never works that way.

And I think what we found is that you want to conduct experiments in a way that you maximize what you've learned to confirm or to refute what others have been describing as the problem. And so I think that's where the bad ideas come from is that, initially, I don't think we have good ideas because we don't understand the problem. But we have to take a leap of faith. You've got to start from somewhere.

And I think so you come up with the best idea you can and then you test it. But you have to keep a super open mind. And the goal is not to push the agenda that you started with but rather to look at it as an education process on understanding the problem.

What advice would you have for researchers who are either in the translational space or not? How do they take this idea of simplifying and understanding the problem? How can they put that into practice?

I think there's a number of things. To me, the problem is it has many different components to it. The problem often is not just getting a specific result in a specific model. But it's also understanding the regulatory path, the manufacturing. It's understanding the patent landscape. You really have to define the problem in the context of the societal problem and then not only how are you going to get a specific result in a model but how are you then going to bring that to patients.

And to me, that's a big part of it is looking beyond the problem that you see with what you're just looking at in that moment and actually need to think of the entire translational process of what's the commercialization process. And that is actually part of the problem. So I think that's a big, big part of it and needs to be considered right from the beginning if the goal is, indeed, to advance translation and not just-- so that's why I think the approach differs between exploratory basic science and translation is that you're essentially it's fine in basic science to have a five or 10 or 15 step process to do something if it's going to allow you to uncover a new mechanism or if it's going to allow you to elucidate new biology and answer specific questions.

But if you start thinking about it from a translational perspective, you want to be able to do it in one step. And so the approach is completely different. We also have to consider here that there is room for more complex technologies. And there are a number that have helped tons of patients. I think what I'm referring to is anytime you have a technology or an approach that has more complexity to it, it's just going to be harder to bring that to patients.

It's going to take more time. It's going to take more resources, more money that's going to need to be raised, which means you'll have less potential groups that you can go to because you have to raise even more money. But that's still a possibility.

I think if you have a complex process and you really think that there's a lot of promise, one thing you can do is start talking to manufacturing experts early on and ask them, is this possible? How long would this take? And what kind of resources would be required to advance this?

And I think that's a big part of the process of radical simplicity is engaging the types of people who are going to be essential to bring that technology and make it a product. And you want to be asking these questions early to the experts. And there's lots of engineering firms that you can bring in. These are contract groups that will provide quotes and give you better understanding of how long and whether it's possible and how much it's going to cost to really bring this forward.

And maybe even they have ideas on how to simplify the process. And I think you don't want to wait till the end. You want to do that right in the beginning. And to me, that's just a big part of radical simplicity is just constantly really thinking about the problem in terms of the whole spectrum of translation not just what you're doing in the laboratory but what comes afterwards and then engaging people in the community, so that your simplifying at every possible step and that you really have a deep understanding of some of the nuances that you need to be thinking of today to maximize the potential for that to help patients tomorrow.

Thank you, Dr. Karp, for joining us. It was great to have this conversation with you.

Thank you so much.

Next time on *Think Research*--

To us, it seems like one of the only ways to capture that complexity in a way that does it justice is to actually take the network perspective and actually rise above just the way of looking at health care as just kind of a list of doctors who are seeing a patient at a given time.

--Dr. Michael Barnett explains the impact of networks of care on health outcomes and spending. Thank you for listening. If you've enjoyed this podcast, please read us on iTunes and help us spread the word about the amazing research taking place across the Harvard community.

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