

3 Takeaways Podcast Transcript

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Ep 35: A Unique Model of Innovation - Making Breakthrough Discoveries and Turning Them into Real World Products at an Unheard of Pace: Don Ingber

INTRO male voice: Welcome to the 3 Takeaways podcast, which features short memorable conversations with the world's best thinkers, business leaders, writers, politicians, scientists, and other newsmakers. Each episode ends with the three key takeaways that person has learned over their lives and their careers. And now your host and board member of schools at Harvard, Princeton and Columbia, Lynn Thoman.

Lynn Thoman: Hi, everyone, it's Lynn Thoman. Welcome to another episode. Today, I'm excited to be here with Don Ingber. Don is the founding Director of the Wyss Institute of Biologically Inspired Engineering at Harvard. The Wyss Institute is a new model, they make breakthrough discoveries and then bring their discoveries to market. Their products range from healthcare to energy, robotics, architecture and manufacturing. I'm excited to find out how the Wyss Institute is so successful in making breakthrough discoveries in so many different fields, and then turning the discoveries into commercial products and bringing them to market to solve real world problems. Welcome, Don and thanks so much for being here today.

Don Ingber: Oh, it's my pleasure. Thank you.

LT: Don, you have about 200 patents, you've founded about 5 companies and you've published about 500 articles, you've also spent several decades as a faculty member at Harvard. What are you proudest of?

DI: I have to say, certainly the most gratifying thing I've ever done is the founding of the Wyss Institute. It has been kind of a culmination of my career in terms of it's taken all sorts of creativity, and I'm someone who's crossed many disciplines, I tried comedy-writing and television at one point, I'd made films, I've written, I've done all sorts of things, and I had to use all of that experience, including past failures at start-ups, learning from your failure, had to use all of that experience to help pull together a vision and sort of shepherd the formation of the Institute and its development. So I am probably most proud of that at this point, although I've had scientific contributions, I'm extremely proud of as well.

LT: What is so special to you about the Wyss?

DI: I think it is truly a unique model for innovation and for crossing boundaries between institutions and disciplines. I've had people visit from all over the world, presidents of universities, senior leadership in government and at the end, though, after we give them a tour, walk them through, describe what we've been doing, ask, "Have you ever seen anything like this before?" And the answer's always been No. And so to create something that unique in a world where there's so much competition for creative efforts, and the word innovation is all over the place, but I find that most times I hear people talking about the process of innovation or applying

existing technology on steroids and industrializing innovative things, we literally create new innovations, new technologies, new capabilities on the fly, and then we have developed a structure for business development and translation so that we get it out the door at a pace that's really unheard of.

One of the things that is amazing, we have had between 11 to 18 core faculty, all of whom, almost all of whom have their home labs still intact in their home academic institutions, and we're part of Harvard, but we're also at 12 collaborating institutions, including MIT, Boston University, Tufts, UMass, all the Harvard hospitals, so most faculty, including myself, still have home labs, and they moved their entrepreneurial problem-focused and translation-focused part of their groups to the Institute, but with only 11 to 18 core faculty and maybe another 15 associates, again, who also only have a few people on-site, we're responsible for almost 25% of all of Harvard University's intellectual property start-ups at each year, and it's kind of unheard of.

DI: And we started in 2009, so we've done this really quite quickly. And so I am very proud of the fundamental science I've done, science is what fuels all of this, it's the beginning of the pipeline. But most people in science and in the government and in the funding agencies focus on how little we know. I think one of the things we did at the Institute is to admit that God, we've uncovered so much about how nature builds, controls and manufactures from the nano-scale up over the last 50 years, that we can now leverage that and we can leverage to develop new innovations and that's really what it's all been about.

LT: The Wyss full name is the Wyss Institute of Biologically Inspired Engineering. What exactly is Biologically Inspired Engineering?

DI: For Biologically Inspired Engineering, to be accurate, but I came up with that term. I remember... We were talking about names for the Institute, I was with the then Dean of Engineering walking down the street to a dinner, and I suggested this, and I remember him saying, "It's a little long, but it's exactly what you're talking about." I have not trained as an engineer, so what biologically Inspired Engineering comes down to, is essentially-engineering from 50 years took classic mechanical, electrical, engineering types of principles and applied it to problems, in particular medicine, where it was called bioengineering, or in other areas where they solved problems like industrial applications. By this idea of admitting that we've uncovered so much about biology in my lifetime that we can now leverage it, the idea is to flip this on its head, and now leverage biological design principles that we've all uncovered to develop new engineering innovations. That's what we call biologically inspired engineering.

DI: And it's not classic biomedical engineering or bioengineering. And therefore, people like Jim Collins, who was control theory engineer, became a leader in synthetic biology, and I am a cell biologist, but I'm now a member of the National Academy of Engineering, and have done all sorts of devices and patents that involved everything from organs on chips to computer algorithms. It's this idea of breaking down the disciplines, but looking to biology for inspiration in order to solve problems.

LT: What is so special about looking to biology, what is different about biology now?

DI: It's not that it's different now, it's really how life evolved on this planet is through processes of self-assembly, hierarchical self-organization, natural selection, evolution, using biocompatible, biodegradable materials, doing things with incredible efficiency, building as networks, not as bulk materials, all of these things is that nature and our physical world have selected for and have spontaneously emerged in our three-dimensional space with our physical conditions and gravity and sunlight and temperature. Most of what has been done industrially by man has been to try to control, to constrain, to restrict. We've all often got into trouble by that in terms of leading to over-growth, taking over of insects or pests, because we killed something that used to feed on them or plastics in the environment. So this whole idea of biomimicry or bio-inspiration, that maybe we can come up with ways of making materials that are... We had one paper on a biodegradable plastic that was inspired by the insect cuticle. And it's completely biodegradable, or being able to use synthetic biology. There's a project going on at the Wyss where they're trying to make foodstuffs synthetically using engineered bugs, or you're now hearing about artificial meats. There's good reasons to be inspired by biology.

And lastly, in medicine, rather than putting artificial materials in people, why not put materials that really are built the way our bodies that are... That match their compliance, their chemistry, or that we learn how to essentially, let's say, nurture, or foster or control our body's own regenerative properties. So there's just huge power in biology. And this really is the century of biology. This is where I think all fields are beginning to see the power of being able to control. The genetics is one that people know about in genomics, but we're beginning to get into the biomaterials, into the physical world as well, the brain. It's really just beginning to explode.

LT: I still vividly remember when I was a new member of the Harvard Medical School Board, meeting you, Don, and you gave me a tour of the Wyss Institute and you showed me the range of products being developed, it was extraordinary. Can you tell us about some of the inventions and products?

DI: They do range in all areas. One that I'm most involved in for the last 12 years are called human organs on chips. These are little microfluidic devices, the size of a computer memory stick or an old school eraser, they're optically clear, they have little hollow channels and they are lined by living human cells that can be layered to reconstitute the structures of our organs, and in the lung, for example, we have lung cells with air, we have lung blood vessel or capillary cells beneath them and it's flexible and it stretches and relaxes. When you breathe in, your lungs expand; these expand.

DI: And we've done this for 20 different organs, but the amazing thing is that little device demonstrates clinical mimicry of normal physiology and function, but disease stage, response to drugs, response to toxins, response to radiation. That went from concept to proof of principle with government funding and then industrial partners, validation to a startup, that is now being sold around the world. They have instruments at the FDA, they have instruments at most major pharma and biotech and it's spawned a whole field of organs on chips, it's also known as multi-physiological systems, but the idea of replacing animal testing, it really comes down to that, because animal testing is required by the FDA to be used to validate the safety and efficacy of drugs before you go to humans, but it turns out that something like 70% of the time, and in some

areas, 90% of the time they're wrong. [chuckle] They don't predict what you see when you get to humans. That's one small example.

DI: George Church's lab was involved with the CRISPR technology that has revolutionized the world. And so the patents that came out of the Wyss from George [Church] and at Harvard and the Wyss are now licensed to a company called Editas that is moving to the clinic. Another technology that I had developed in my team was a blood-cleansing device for sepsis, that essentially when a patient comes to the emergency room, you might suspect that they have a systemic infection, and this can go very quickly, very high death rate. But 70% of the time, you never are able to diagnose what the bug is, what the microbe is. So, we developed something that is inspired by the natural proteins in our blood that evolved before antibodies and bind to over 100 different types of pathogens, bacteria, viruses, fungus, protozoa. And long story short on that, we engineered a version that we could produce very easily using methods that came out of the biotech world, because we have over 40 people from industry with 10, 20, 30 years of product development experience in every area. And this guy came out of a biotech company. We then put it on a dialysis device that... You know, commercially available. And if the patient has sepsis, without knowing what it is, you can put their blood into this device, like a dialysis *ex vivo*, outside the body, it's a blood cleansing system, and remove the pathogens. That has entered clinical trials as well for general blood infections and for COVID-19 with military support.

Jim Collins has developed synthetic biology. This is engineered DNAs and other molecules that can read out quickly, recognize the presence of pathogen in a diagnostic mode. That was commercialized by a company called Sherlock, which I think had the first EUA (Emergency Use Authorization) for rapid diagnostics in COVID-19.

DI: On the non-medical side, Joanna Aizenberg is trying to come up with a way to restrict ice from sticking to airplane wings. She wanted something that was slippery. She looked to the pitcher plant in Africa, which is a plant that when it's dry, insects crawl over it, and when it's wet, they slide into it and are eaten like a Venus flytrap. She studied how does that work and turned out to be the nano-topography, the sheet on the nanometer scale of the surface and it had a liquid bi-capillary action that would fill that surface. She made artificial materials like that, and nothing sticks to it. It's all over the place. There's so many examples.

LT: Don, that's such an extraordinary range of products. You've brought together biology, engineering and material science. How do you see the convergence of these fields?

DI: I go to meetings on convergence and on how you get people to collaborate and crossing disciplines. And I think it's pretty simple. You find a problem that is really exciting to people. And we tend to look for really high-risk, high-impact types of problems. That was what we were tasked to do as when I founded the Wyss, with Hansjörg Wyss. But if you get the best people and they are interested in that problem, or you think they would be interested in that problem, and they can't solve it on their own, and you get the right complementary people in terms of talents surrounding them that are great people, you just got to get out of the way. Because if they really want to solve the problem and there are other people there that can fill the spaces that they can't, it will happen. It's all about people when you build an organization. And there are some people that just will never get along by personality. Sometimes it doesn't work, but if they can

get along and they really want to solve the problem and you got the right people and the right skills together, it will happen. And that's what we've found again and again.

LT: What discoveries do you see on the horizon?

DI: There's no doubt that artificial intelligence, curves like machine learning, network biology, all of these intersecting with the biological world is leading to an acceleration of everything. We are seeing that in applying machine learning and AI to drug discovery, to synthetic biology, designing systems to control artificial viruses for drug delivery or constructs to control bacterial resistance to antibiotics. The fact is that most drugs don't work the way we think they work. And we often say good drugs are dirty drugs.

DI: When I went to medical school, we learned that we knew how one drug worked, we were sure of that, it was aspirin, and it inhibited a particular enzyme. Twenty years later, we know it hits 14 different pathways, and it needs to do that to have its effect. How do you design drugs to hit multiple different things at once? Pharma doesn't do that. They think they know the target and they try to get it more and more specific. And with machine learning and artificial intelligence, you can start getting in things like that. And we've been doing that with COVID-19, but this is happening all over the world. People are using it to accelerate design and discovery of new materials also.

DI: I think areas that are growing, the whole robotics world and the man-machine interface... and that involves both miniaturization, but also materials. That's an area. 3D printing is one that's... I was involved with a start-up in 1998 to do 3D printing of devices because I could see this amazing technology used in the industrial world. They were using it to build airplane parts, and I thought like, "Wow, couldn't this be amazing for biology?" But it was too early, the company died, nothing ever happened. I see what is being done now. People like Jennifer Lewis and Chris Chen at the Wyss, we have a major initiative, and they're able to build in ways with living cells, with living materials and put blood vessels into the tissues while they're building it, that I think is going to revolutionize organ transplantation.

And one thing that I will say about the Wyss that was affected by my experience with this 3D printing in the '90s was that I realized that there are methods and approaches used in the industrial world that could be powerful in the medical world. But also when I was in medical school, and in medicine for all these years, there are methods and materials and approaches we use in medicine that could revolutionize the industrial world, and synthetic biology has shown that to be true. But think of things like dental adhesives. You go to the dentist, they flash a UV light, boom, you have this material that's incredibly strong. Well, that could be used in non-medical areas too. And so that's one reason at the Wyss why we're so broad. That was intentional from the beginning.

LT: Looking ahead five or ten years, what does the future of drug discovery, medicine and healthcare look like

DI: I think it's going to be more linked to the individual. What I see going on in our place, we have these human organ chips that you could make your liver on a chip, or your Crohn's disease model of your intestine on a chip. You can imagine linking it with your genetics, your genomics and artificial intelligence, and being able to predict what might work better for you and be less toxic for you, and then test it in the chips and then get more information and iterate. That's one example. Another example are home diagnostics, it's beginning to happen. We've seen that with COVID-19 where FDA's approving things to be done at home that are a little bit more complex. But imagine if you can have all the tests that you get in the hospital now, your blood counts, everything you go every year to the doctor, but you do it at home inexpensively and that data gets fed back, analyzed, and essentially it democratizes diagnosis. You deal with huge amounts of data to understand that, Oh, there are subpopulations of people and we need to develop drugs for them and not generically and fail all the time.

So I think the drug development, moving from animal models that are not predictive to more human-relevant models is going to speed things up. I think understanding that you can design drugs for subpopulations using things like... you can make stem cells from an individual, you could take your, cell out of your blood, give it a few genes and it becomes like an embryonic cell that can become any tissue. You can now build things like an organ chip of your different organs, and so you can begin to essentially personalize not only diagnostics but therapeutics development, or you could do this for clinical trials design where you might test 300 women who are Hispanic who have asthma and are ultra-sensitive to cigarette smoke, and develop drugs just for them and then use them for your clinical trial. This is the opposite of the way it's done now.

DI: Right now these companies spend tens of millions of dollars, they'll do a huge trial, they almost always fail, and then they come back and they statistically number crunch to find a genetic sub-population that might be more sensitive. If they're lucky they find it, they'll do a limited trial and they get approved for a narrow application. It would save huge amounts of money and time and increase the likelihood of success, that's one example. I do think you're going to see Amazon-type things in the future that are going to probably handling all of your diagnostic data and recommending, oh, here, this is the most cost-effective and highest personally rated and professionally rated physician to do this for you. It's going to be a different world.

LT: What will we see next from self-assembling materials?

DI: We have an effort at the Institute called molecular robotics, which are basically self-assembling molecules that can build into structures that are at the nanoscale or even microscale. People can now build from the nano to something you can see, but they can carry out desired functions. We've been using them in... There are groups developing at the Wyss that led to diagnostics, but they also are being used for analytics. For example, this is very scientific, but when they want to identify a target in a molecule, imagine you have a virus and you have some protein you want to target on its surface to develop a therapeutic, they'll crystallize it, they'll rigidify it, and then they'll use a high power microscope to get its three-dimensional structure, but it's rigidified, where in life everything is vibrating and flexible, and you don't really have its real look, plus it's very expensive and it's very hard to do with a lot of molecules.

DI: With lots of little self-assembling robots the idea is you could have them probe the molecule in solution and give you read out and tell you what it is. I think in vivo is where you're going to see more self-assembly, where you inject materials. And it's beginning to happen that we'll self-assemble into a structure that might be an optimal device depot for a vaccine, but other ones would be optimal to promote stem cell migration and growth to heal a muscle. Those are places where you're going to see self-assembly. The way your body builds is through self-assembly. Let's say you want to heal a bone. That is cells putting out molecules and they start coming together and building structures, which bring in other cells, which put out other molecules, which build more assembly. I think people are exploring ways to trigger that process with engineered trigger materials.

LT: Don, you've talked about an incredible range of discoveries. How do you turn these discoveries into products and market them to the world to solve problems?

DI: We have what we call an innovation funnel at the Wyss. In America, generally scientists are funded through grants, and you struggle to write a grant, it takes a year to get it, and if you're lucky, 5-10% of them are funded. If you get a second one or a third one, by the time you get it, you've done most of it. In fact, you have to have done most of it to get the funding. That's not the most exciting thing for scientists. It's already a year down the line. But if they have money for people and supplies, we always say we do the interesting stuff in the space between the grants, because you could just say, "Okay, do what we said we'd do in the grant, but pursue your vision, pursue your ideas." With the Wyss Institute, we turbo charge that by giving additional funding and free access to facilities, equipment, know-how to get that process started.

DI: We don't ask people to write proposals in that early phase of our funnel. They have their funding from government, we give them creative funding, say, "Anything you want to do in this space is fine, and it's enough for two students and fellows for core faculty." But there's so much creativity and ideas coming out that the key for us for translation is just harnessing that. The first thing we do that I think is really unusual is we have our own strategic intellectual property team, our own strategic attorneys. We teach our staff and our students and our fellows to do reports of invention, not your usual thing in academia.

And they'll get feedback from that strategic IP person that might say to a grad student, "Great idea, not patentable. However, if you did this and this, it could be really valuable." That student then is focused on the shortest path towards impact from the very beginning, not after they publish their paper five years down the line.

What happens at the Wyss is, I mentioned earlier that we've hired over 40 people from industry with enormous depth of experience. That's self-assembly of a team. It's a biologically inspired organizational system, where they don't have to ask for approval, their salaries are paid, we have what we call platforms that have funds that they could buy some supplies, or if they start building and they get the head of their platform or faculty member excited, they can hire a tech.

We have free access to machine shops, and our machine shops can do anything. They can just prototype and build and explore and build a team. We have our own business development

people, and we have Harvard's Office of Technology Development. They sit at our site, and they're 100% our people. They have worked at big companies and small.

They start getting involved when the project starts coming together a bit, because the team wants to know where the applications would be and who might be interested in this. We have two programs we call Validation Projects and Institute Projects. Validation projects, for the first time, is a short application. It needs to basically see that you're building a team of excited entrepreneurs. The faculty become less central at this point, it's more the team of young people that may take this out as a start-up, for example. They have a vision. They need to validate it technically, they need to get more input from business development, and this proposal will lay out a plan to do that validation and it will have a timeline and milestones, and those applications are reviewed by business development people, not by faculty. Some of those go out as start-ups because they've grown so quickly.

DI: We then have a program called Institute Projects that is now to complete the technical validation, but to validate it commercially as well. You can even request hiring someone as an entrepreneur-in-residence, who's not there as a mentor but is there possibly to take it out as a future CEO, and often these people have done this in the past. They now become part of Harvard, they join the team, IP that comes out of it is owned by Harvard, so it's academic, but they bring commercial expertise, and they start leading the group meetings, almost like it's a startup. People often ask, "Do you have incubator space?" We don't need incubator space, we're like 20 small start-ups. It's just the way we think and how we act. This is the funnel that we have, and we do de-risking that really brings us much closer to what I think current investors want to see.

LT: Don, before I ask for your three takeaways that you'd like to leave the audience with today, is there anything else you'd like to discuss that you haven't already touched upon?

DI: What I've learned is it's all about people. Those in the supervisory or administrative or in academia or funders, when they want to build something new and innovative, they think about just the structure of the organization or in business school analysis, they want to see the org chart. It all has to be structured. Nature doesn't work that way. Nature self-assembles, grows, culls back, grows out, branches. That is how creativity works, that's how good scientist's work. It's non-linear. We created an organization that harnesses that. It's all about how you assemble people in ways that you harness the creative process to be productive rather than destructive.

We drive our board members nuts because they always want to know what's the return investment on Project A. Well, Project A led to 32 projects, three start-ups, and five licensing deals, and four major grants. Just to look at this one start-up doesn't answer that, or the organizational chart, it's a matrix. Everybody interacts with everybody and different times, at different times it changes. So, it's all about how you assemble people in ways that you harness the creative process to be productive rather than destructive. And sometimes it doesn't work, like I said, 'cause personalities don't mesh, but if you get out of the way, you get challenges that are exciting enough, and you get the right people. It just happens.

LT: What are the three key takeaways you'd like to leave the audience with?

DI: I think that we really are at a point where the next 50 years are going to be dominated by biology in a way, but this is way beyond genomics. This really is being inspired by the principles that nature uses, not only for things, but for organizational systems. I'm most proud that the Institute itself is organized in a way inspired by the messiness of nature. Engineers often talk about natural systems are robust systems with sloppy parts. And that's really what you want for a resilient, strong, impactful network of interactions that bring about impact. The other is that to really bring about positive change through innovation and breakthroughs that really come out of nowhere, you have to break institutional and disciplinary boundaries. Academia is still set up the way it has been set up for hundreds of years. My work was inspired by Buckminster Fuller. He has a quote that says, "Nature has no separate departments of chemistry, biology, physics or art." It's absolutely true, yet that's the way young people are taught, people are channelized and compartmentalized. And that's not the way the world works, and that's not the way real impactful solutions work.

DI: Lastly, I do want to share the message that the world is changing and academia is changing and industry is changing, and that there are places like the Wyss Institute where we've explored and I think reduced to practice models that can break through these barriers and bring about transformative change in quite a rapid way.

LT: Thank you, Don. This has been terrific.

DI: Thank you so much for this chance to share with you my obvious enthusiasm and excitement about what we've accomplished over the last 12 years.

OUTRO male voice: If you enjoyed today's episode and would like to receive the show notes or get new fresh weekly episodes, be sure to sign up for our newsletter at 3takeaways.com or follow us on Instagram, Twitter and Facebook. Note that 3takeaways.com is with the number 3, 3 is not spelled out. See you soon at the 3takeaways.com.