WYSS INSTITUTE
for Biologically Inspired Engineering

Disrutpive: Mechanotherapeutics - From Drugs to Wearables

Host Terrence McNally interviews Don Ingber, Dave Mooney, and Conor Walsh. Podcast published on September 30, 2016.

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

Recently the Wyss held its 7th annual international symposium, this one called Mechanotherapeutics: From Drugs to Wearables. I hadn't heard the term prior to seeing an announcement for the symposium, so I looked it up on Google. I found a British medical article from 1904 and a book, Mechano-Therapeutics in General Practice that Amazon tells me was originally published prior to 1923. That's it. That's the extent of my findings.

In fact, one of today's guests came up with the term, and the symposium focused on advances in what till now has been called Mechanobiology. Researchers are evolving our understanding of health by revealing new insights into how the body's physical forces and mechanics impact development, physiological health, and prevention and treatment of disease. This work has resulted in the development of new types of pharmaceuticals, drug delivery systems, engineered tissues, and wearable therapeutic devices.

Why mechanotherapeutics? Because these advances leverage physical forces or target mechanical signaling pathways as a core part of their mechanism of action. At the September 20th symposium, speakers provided a day's worth of examples of how mechanics is being harnessed in ways that can transform the future of medicine.

I'll talk with the two organizers of the event, DON INGBER, Founding Director of the Wyss Institute, and Wyss core-faculty member, DAVE MOONEY, as well as with one of the other presenters, core-faculty member, CONOR WALSH.

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

Our bodies — and all living systems — accomplish tasks far more sophisticated and dynamic than any entity yet designed by humans. By emulating nature's principles for self-organizing and self-regulating, Wyss researchers develop innovative engineering solutions for healthcare, energy, architecture, robotics, and manufacturing. [02:08]

In addition to his role as director of the Wyss, Don Ingber leads the Biomimetic Microsystems platform in which micro-fabrication techniques from the computer industry are used to build functional circuits with living

cells as components. He's authored more than 400 publications and over 100 patents.

McNally:
I ask him how he defines the term mechanotherapeutics. [02:31]

Ingber:
I think you defined it beautifully in terms of these are therapies that leverage insights into the important role that mechanical forces in terms of regulating cell and tissue formation function, healing, regeneration, as well as drug targeting.

McNally:
Ingber is actually pleased that I was only able to find two references in my Google search.

Ingber:
I often tell students that you really want to do a literature search, or a web search when you're getting into a new field, and they do that, and they get upset that they only found a couple of references, and that's to me the most exciting thing you could do. That's what you're looking for because that means that people have thought about it, but it's not yet blossomed or pursued.

McNally: [03:18]
He's reminded of when he first started publishing on mechanobiology forty years ago, asserting that mechanical forces are as important as chemicals and genes in regulating biological function in living systems.

Ingber:
I basically got to it by rediscovering 100 years before that - the end of the late 1800's, and early 1900's - mechanics was all they had in physics, and it was really how they approached biology so they described everything in mechanical terms, but then basically it died away when chemistry came in, genetics came in. But they sort of threw the baby out with the bath water, and they just said nothing is mechanical. I remember writing an article that there's a need for a renaissance in terms of mechanicalism. So that's happened, especially in the last 10 to 20 years, but for me, personally, the last 40 years.

McNally: [04:11]
He recalls a textbook example of how we stopped paying attention to mechanical forces

Ingber:
I always feel that the way you have a glimpse of the future is by feeling the progression of things over time, so understanding how fields evolve over

time, it's like a mathematical progression. You kind of know what's coming next, and I've been very lucky and successful in doing that in my career.

I started that with learning about development and biology in the late 1800's. I went to the libraries, and I was looking, and in every field I would read on what people talked about at that time. There was a biochemistry textbook, where it basically was about thermodynamics.

In the first textbook they had pressure and volume in the equations. In the next book it was left out. They basically said - this is for teaching students - we'll assume that all these biochemical reactions occur in a test tube. That's like looking for the keys under the lamplight. That's how they'd be doing their experiment.

They said to simplify this, we're going to take pressure and volume out. However, beware reader that nature is not as structural as chemistry, and that mechanics is undoubtedly important, but nobody reads the preface, and all subsequent editions... that's the way it's taught to the average medical students and graduate students.

Now more sophisticated students learn about the pressure and volume in graduate courses on thermodynamics, but most people don't. That's one reason I used to get incredible push-back from the community, who just said mechanics can't be important; it's all chemistry. Whereas, to me, it was obvious that it had to be a key part of bio-regulation.

McNally: [05:50]
Don, can you talk a little bit of your evolution in terms of how mechanics and the forces, especially say the forces within cells, and so on, have played a role in how you've seen things, and what you've developed along the way?

Ingber:
I think early on I recognized that mechanical forces in biology aren't only gravity, and the effects of gravity on your bones and blood flows, but that all living cells generate a tension themselves inside their internal molecular framework that's known as the cytoskeleton. This is the actomyosin filaments that people hear about in terms of how muscle generates tension. All cells basically have those actomyosin filaments and they're all generating tension from within.

I realized that, if you think of a blood vessel, which has these incredibly high flow rates, and shear stresses, dragging forces, on the surfaces of the lining cells, and the blood vessel. The fact is that the same cells are holding onto the wall of the blood vessel by binding to receptors and pulling against them with their internal tension.

What that meant to me was that the forces that the cells are kind of grabbing the walls with have to be stronger than the forces flowing by, or the cells would be torn off all the time.

The way cells take on their shapes is really a balance of forces between cells generating a tension, and it being resisted by a substrate or neighboring cells. So I started to say, you have to think of cells like a bow and a bowstring. You can look at a bow and a bowstring, and you don't know there's force there, but if you pull on it, that's what you harness to shoot an arrow because it's isometric tension. Everything is in balance.

Well, cells are under isometric tension. We call it pre-stress, so this is what led me to come up with the insight that cells use a particular building system known as tensegrity. It's an architectural system first described by Buckminster Fuller, but the important point is that there are underlying forces that govern how cells control their shape.

You could think of a tent with tent-poles like a pup-tent that has tent-poles and a membrane and then tethers, anchors in the ground, and then you kind of winch in on the ropes to stabilize it.

I realized that cells are anchored, not glued equally at all points on their surface, but they have similar sort of tent pegs in the ground that are called receptors that cross from this actomyosin contractile cytoskeleton on the inside to the extracellular matrix that they adhere to. They're called integrins. [08:31]

McNally:
It was such realizations that led Don Ingber on the path that eventually led him to the Wyss Institute and the recent symposium –

Ingber:
I was a cell biologist. I have an MD and PhD in biology, but because I was thinking about mechanics I had to get into engineering because I had to think, how could I apply forces to specific receptors on cells? So this got me into collaborating with engineers, and thinking about things like using magnetic forces, and magnetic particles that were on the scale of receptors.

That helped kind of birth this field of mechanobiology and mechano-transduction, that it wasn't phenomenology... that it wasn't just, "Oh, somehow forces do things," but that actually it was transmitting force to changes in molecular biochemistry, and binding kinetics, and opening and closing rate of ion channels, deformation of molecules.

Many other people have joined in that field, and made major seminal contributions, but that has really grown over the past 20 years.

I explored methodologies from engineering that may be able to control the substrate geometry... like the pattern of anchors for your tent, and that got me into microchip manufacturing which controls features at the same size scale, the nanometer to micrometer scale, that living cells live at. [09:56]

Which eventually led to the whole organs-on-chip technology we've developed, where we control not only adhesion and positioning, but tissue-tissue interfaces, flow, and we incorporate physicality.

We use microchip manufacturing, to make essentially molds that have surface features where we can now pour a polymer on top of it, and we could peel it off, and we could make little hollow channels, and we could make channels separated by porous membranes.

What we do is, we line those channels with living human cells, so we can recapitulate a lung, for example, by having the cells that line your air sac on one side of a membrane in a little hollow channel, and you could have the capillary blood vessel from the lung on the other, or we could use your gut lining cells on one side, and the gut capillary on the other. We could then start integrating things like immune cells, or microbiome in the gut which we've done.

One of the amazing things we've found is that the key to recapitulate functionality that you see *in vivo* is to give them the right mechanical microenvironment. You have to have the right flow, and you have to have the right breathing motions in the lung, and the peristalsis in the gut, or even the cyclic one-pulse-a-second deformation in the kidney. When you do that, all of a sudden you see functionalities that you never see in a dish.

That has allowed us to really develop potential replacements for animal testing as well as ways to do personalized medicine with capabilities far beyond anything in the past.

And also we can link them together by their vascular channels, their blood vessel channels, and begin to even build human body-on-chips for drug testing toxicity, and so forth. Key to the success was designing them based on my belief and my group’s belief that mechanical forces are absolutely critical for control of function, and that absolutely turned out to be true.

McNally:
To some extent that is the raison d'être of the organs-on-chips. Without that design you're not getting the physical forces?

Ingber:
...and you're not getting the functionality, exactly. [12:03]

It also led me to develop combining the microfabricated systems, and microfluidic systems which are using the microchip manufacturing to make

hollow channels that you put cells in and flow medium through, that mimic micro-vascular blood vessel networks.

We started to combine that with the magnetic beads we used earlier, and we're able to now bind cells, and move them around, and capture them and, for example, remove pathogens from blood. That was the birth of our biospleen technology that's now being commercialized in a company called Opsonics. The organs-on-chips has moved to a company called Emulate. So it all came out of mechanical thinking. [12:42]

McNally:
Don, is there value in coining a new term and inviting people to an event about a field they've perhaps never heard of?

Ingber:
It allows people who work in entirely different fields, but have a common perspective or vantage point or interest to begin to come together under the same canopy and start meeting and start talking, and basically spend a higher percentage of their time in those groups talking about what's relevant for them rather than going to their specialty meetings, and hearing things that they've heard for years.

It does help create a new identity, and a new culture, and basically gel an emerging field. If you do it too early, it's meaningless. If there are really people there that all of a sudden see their own work, and that they can gain by meeting with people they would have never thought of meeting because they didn't realize they were working with aspects of it that were similar, but they were in different disciplines, then it can gel and actually help catalyze an advance. [13:44]

I had published the term mechanotherapeutics in 2003 in a review article on mechanobiology and medicine. I actually have a table of things that people never thought of as mechanotherapeutics, but are mechanotherapeutics.

So an example is stents that people know save lives. When there's occlusion of a blood vessel, they put in this little tube. It's a piece of metal. They expand it with a balloon, and it holds the blood vessel open. The only thing they're doing is mechanical there.

McNally:
That's right. It's pretty simple. [14:23]

Ingber:
There are people who if they have a car accident, and they have a major defect in their skin like a large area of skin, they'll have to do a skin graft. But if they're doing it from the same patient... If it's a big enough loss of skin, if they were to make a skin graft, they would have a defect at the site where they took the other skin from, the healthy skin.

So what they do is, they actually implant a silicone bag under the skin almost like a breast implant, and they fill it with saline until it hurts. Then they come back a week later, and the skin grows. It's like when a woman gets pregnant, just the expansion of the uterus causes the skin to grow. A week later they put more saline in until it hurts. Then they come back a week later...

And after about a month they actually can double the size of the skin. Then they can take a piece off, do a skin graft, and they're fine at both sites. Purely mechanical stimulation. [15:10]

The first papers I ever saw had come out around the late 1990's or early 2000's time-frame of how acupuncture appears to work. Acupuncture has been around for thousands of years in China, people are now using it in the United States a lot. And the paper quoted all my work on mechano-transduction, because they basically found that the twisting of the needles on the skin pulled on the extracellular matrix. They could almost see whirls around the needle as they twirled it, and that pulled on these integrin receptors on cells, and that changed mechanical signaling.

The range of this is huge. And then at the larger level, obviously, physical therapy is mechanical. And anyone who's had any problems, including myself, where I've had back surgery in the past...Without physical therapy, I couldn't function. [15:55]

McNally:
At this point, it's pretty clear what you mean by "Mechano" – but how are you defining therapeutics?

Ingber:
Some people think a therapeutic is a drug. David Paydarfar talked about the mattress his group at the Wyss created to prevent apnea of prematurity. That's a prevention therapy, but it uses mechanical vibration to either remove or prevent premature infants from stopping breathing, so that's a therapy. It's not a therapeutic drug, but it's a therapy that prevents or treats disease, so that's the context we were trying to present here. [16:30]

McNally:
I'm curious...How did those you invited to present at the symposium respond?

Ingber:
100% accepted. There were some that literally cancelled other meetings to come because I think maybe it helped them realize that maybe what they're doing is even more exciting by thinking of it as a mechano-therapeutic.

All those people may not have ever thought of using the term mechanotherapeutics for what they are doing. For example, the apnea

mattress, he would never call that mechanotherapeutics. Devices...that use stochastic residence and physics, but if you ask him to look at it from our perspective, he would say, “Oh yeah, it's a mechanotherapeutic

McNally:
Oh yeah, that fits in that bucket, sure.

Ingber:
Exactly. [17:11]

McNally:
In this evolution question, where it was all thought of as - we're talking 100, 120, 150 years ago - mechanics and forces, and then it all becomes chemistry, and then now we see this return to the recognition of forces, and the utility of forces, and so on. Is it partially that the tools and our observational abilities, and so on, have allowed us to see and work at a level - as you talked about, where you're working at the nano scale on many of these things, the micron scale, and those sorts of things - that that has been part of what has led to this rebirth?

Ingber:
I always would tell my grad students, “When you're trying to bring new ideas in, you have to learn how to play by the rules of those that have control, that have a paradigm.”

You have to show that you can use their tools, and get their results, and then you have to develop new tools to be able to in a rigorous way manipulate the variable that you think’s important that they don't even see, and then you have to be able to explain things they can't explain. I think that's what has gotten mechanobiology on the map.

Yes, the tools were a key part of that, and a lot of my career has been - even though I'm a biologist by training - has been having to develop tools to convince people that there are things there they can't even see, and that they're equally important at times.

The other thing was that the field of bioengineering birthed during the last twenty to thirty years, so that the young people coming in learn some biology and some engineering, and mechanics is a big part of engineering, so they were much more open to that thinking. And in fact, it provided them a handle to get into biology by pursuing the physical side of it. I think that really also opened up the field. [19:10]

But to this day mechanobiology is still a small corner, and most people are happy doing what they've always done for fifty years - the same chemical genetic biochemical stuff. That said, I've had many people come to me at meetings who worked in genetics and development, for example, saying, “I hate it...but I'm a geneticist, but now I do mechanobiology because I cloned

this gene that was so important for development, and it regulates physicality via mechanics, so now I have to get into this." People are getting into it because they've uncovered so much about the biochemistry and genetics, and then it's leading them to physicality.

Just to be clear, it's not like mechanical forces work in a mystical way. They work by having impact on biochemistry and gene expression. It's all through the fact that that textbook said that mechanics, chemistry, and physics and electrical changes are all intertwined. If you have an ion channel that conducts ions based on its shape, that's biochemistry. Those ions change electrical fields. That's electronics. The change in shape is through changes in forces. That's mechanics.

I can apply a force to that same channel, and change the chemistry and electronics. If I change the electronics, it changes the mechanics, so they're all one. My argument early on is that, if that's the case then we can't explain things just in terms of genetics or chemistry. [20:43]

McNally:
That really makes so much sense to me. I think it was Buckminster Fuller who made the point that there are no divisions or departments in nature. What you're pointing out now is that even in events, in physical events or organic events in a body, there are no departments or divisions. All of that is going on.

Ingber:
Yeah, and there are physical constraints that we have to work with. Wherever you are in the universe, you have to deal with the physical environment.

McNally:
So what they are in some sense are just different perspectives that you're looking at a phenomenon.

Ingber:
It's like the classic elephant. There are different ways of looking at it. There are different handles on it. With mechanobiology, you kind of have to put it in the perspective of not just apply mechanics, measure mechanics, you have to be able to apply mechanics, measure chemistry, genetics, and all these other things, and that's why I think it's finally gotten traction.

McNally:
Because we're able to do all of these things fairly well at this point.

Ingber:
Yes, because the methodologies are now there. [21:42]

McNally:
So what did you talk about at the symposium?

Ingber:
I presented some of the work I just mentioned, but also other technologies where I had people, post-docs come into my lab, and to start to think, “Well, how can we harness this understanding that mechanics is so important?”

For example, for drug targeting... The biggest killers in man are heart attack, stroke, often due to blood clots blocking a blood vessel...The clots are made of fibrin, and there are clot busting drugs out there that degrade fibrin, and can save lives. I know most of your listeners probably know some family member or friend who had a stroke and, if they were brought to the hospital within three hours, they give him this clot buster and the blood clot is removed, and they're fine.

The problem is that only four percent of patients who have an occlusion of a blood vessel - heart attack, stroke, pulmonary embolism - are eligible to get that kind of drug because it can induce hemorrhage at other points in the body including in the brain. Great drugs, otherwise.

We thought ~~like~~ “What if we could just get the drug to target only to the clot site?” and we thought, “Well, there's a difference in mechanics at that site because there's an occlusion to the flow.” It's like you put your thumb over the end of a hose, and all of a sudden the water moves differently. It's an increase in shear stress.

Then we realized that the body already targets those narrowing of the blood vessels, like if you have an atherosclerotic plaque, they can become vulnerable, and cause a clot to form, because the high shear stress where they occlude the flow activates platelets to stick, and that's what causes a clot.

We thought, can we take this bad thing, and make it into a good thing. We said, can we design something that would carry drug around the blood, that would be the size of a platelet, that would sense the shear stress like a platelet, but instead of forming a clot, would deliver a clot-busting drug? And we did that. We basically created a nano-therapeutic that's shear activated, [23:52]

We use a technique that the pharmaceutical company uses to create aerosol-based drug delivery systems that basically spray dries these little particles into a big aggregate, which is big relative to a nanoparticle, but it's the size of a platelet - like three to four microns. We put the clot buster on that.

You inject them into a peripheral blood vessel. They flow around your body like a platelet, but wherever there is a narrowing, they deploy into many

small particles that, because they're smaller, there's less drag force, so they settle out quickly. They bind the clot, and they start degrading. If bits of clot break off - that can happen sometimes - they travel with it and keep degrading it, sort of like an onion skin unpeeling.

We showed that we could save the lives of animals that had a pulmonary embolism, a clot of the pulmonary artery, but we could do it with one hundredth the dose. That's something we're trying to commercialize now as well. That's an example of a true mechanotherapeutic, in that it wouldn't have a therapeutic effect without this sort of mechanical concentration, mechanical activation. [25:00]

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

And how does he define mechanotherapeutics?

Mooney:
The way I would define this term is that it involves efforts to use the intrinsic mechanical properties of tissues and organisms, as well as externally applied forces to regulate the biology of the individual cells in the system to drive therapeutic outcomes. For example, tissue regeneration, restoration of function in patients suffering from disease or trauma or perhaps congenital defects.

McNally:
How do you see the death and rebirth of interest in the mechanics of biology?
Mooney:
These things tend to go in cycles. We ended up with this really incredible tool set that allowed us to understand the chemistry of living systems, and then to exploit the chemistry of living systems, for example, with the modern pharmaceutical industry being a fantastic example. The importance of the mechanical side was overshadowed, largely because we simply didn't have an understanding, nor the tool set to enable us to really drive processes from a physical perspective.

But now that we're beginning to understand that over the last couple of decades, it opens up the possibility that - similar to the way we used everything we understood about chemistry to develop a pharmaceutical industry - now perhaps we can, in parallel, exploit what we know about the role of mechanics and physical forces to create a whole new range of

therapeutic approaches that will parallel the chemistry-based approaches that dominate medicine today.

I remember when I was a PhD student. and reading this book by D'Arcy Thompson and it was incredibly influential for me and opened up my eyes, that even though I was a chemical engineer at the time, that maybe I was only seeing half the story by not thinking more about the physical side of things.

But there also was a number of really significant advances where one could start to look at forces at the cellular level, one could start to look at subcellular structures, and understand that cells weren't just empty bags, or bags filled with a fluid, but they were actually filled with structures.

McNally: [27:26]
What were the topics that you presented on at the symposium, Dave?

Mooney:
We've been developing materials that we can carefully control the mechanical properties, and there's two elements of this.

One is that we can control the stiffness of the material, and we've studied how it impacts the ability of stem cells to become specialized cells that can form different types of tissue. We demonstrated that, as one varies the stiffness, one can control back in the body, how transplanted stem cells participate in formation of bone tissue. This opens up the possibility that we can now start to design materials that direct stem cell fate decisions back in the body, and control, regenerative processes.

McNally:
With the addition of the physical intervention, does it work better? Is it an improvement, or is it just an alternative?

Mooney:
Yes. It's both. It certainly is an alternative, and that may be advantageous by itself, because we may not want to use drugs. We may just want to use physical cues at times. One can more readily localize a physical cue than one can localize the effects of a chemical cue. It may just provide an alternative, but at times a better alternative, and then, in concert, then they also can be tremendously effective where if you now start to combine these cues, you start to get a more robust and stronger response.

McNally:
What's the current status and what's the potential that this opens up for us?

Mooney:
The current status is, we've developed an understanding and shown proof of

principle that we can regulate stem cell fate by mechanical properties of materials.

We found some surprising things that, for example, materials that are really squishy and act like liquids in some ways work much better at, for example, inducing bone regeneration than materials that are purely elastic. The kinds of materials that we focus on in orthopedics and dentistry today when we're trying to repair hard tissues like bone, we typically try to make materials that have matched the properties of the adult fully formed tissue, which means they're really, really hard, and highly elastic.

This kind of data suggests that what we might want at the interface when we're driving regeneration, instead is something that actually is softer, and more giving, or more liquid-like, and that may actually work better during the early stages of regeneration. It has the potential to dramatically change the way we look at what kinds of materials and what kind of devices we should be making. [29:56]

I should also mention that on the other arm to all of this is that, in addition to understanding how the intrinsic mechanical properties of the materials around cells impact behavior, we've also been looking at how, if you apply physical loads from the outside world onto a cell, and onto a tissue, how does that regulate behavior? And we have some very provocative findings that application of purely mechanical cues can drive really extensive regeneration in animal models and pre-clinical studies.

We found that simply applying cyclic deformation can lead to dramatic changes in skeletal muscle regeneration, following quite significant injury or damage. This opens up the possibility that maybe you can start to have simple devices that don't deliver drugs, but instead you wear a device, and it applies the right kind of mechanical stimulation or force to the tissue to enhance its regeneration.
There's been a long standing procedure that's done, called distraction osteogenesis, where you apply a physical force to bone tissue and get it to lengthen. Here we're seeing now, really quite dramatically, that we can enhance skeletal muscle regeneration by direct application of mechanical forces. The field doesn't understand in a detailed manner yet why these are effective, but they clearly are; and it really opens up some new possibilities for new types of therapies. [31:26]

McNally:
We turn to the work in which he is collaborating with fellow Wyss faculty member Conor Walsh.

In humans up to half of our body mass is made up of skeletal muscle, which plays a key role in locomotion, posture, breathing, and although skeletal muscles can overcome minor tears and bruising without intervention, major injuries, motor vehicle accidents, other traumas, nerve damage, can lead to

extensive scarring, fibrous tissue, and loss of muscle function. Mooney's approach is to use direct mechanical stimulation, and the results have been surprising even to him.

Mooney:
To be completely honest with this one, the PhD student who was doing these studies...We had actually made these materials for a very different reason, but we made these materials that we could basically externally actuate, which means we could use a signal from outside the body to allow them to generate forces. And we wanted to use these for something completely separate, but then we decided, well, we should really do the control experiment where we just use the material by itself and demonstrate that it doesn't do anything, so we can move on to what we thought would be the really interesting experiment. Lo and behold, the control experiment worked pretty darn well.

McNally:
...and you were working on mice?

Mooney:
Yes. Yep, that work was all on rodent models.

McNally:
Explain what you did and what you found.

Mooney:
What we originally did was we took a hydrogel, which is a polymer network that's filled with water. You can think of jelly as a hydrogel. *Jello* gelatin is a hydrogel. But we had one that we put little particles in that would respond to a magnetic field, so they would, in essence, lead to generation of a force when we applied a magnet so they'd squish the device, and then apply a force to whatever it was in contact with. We implanted these next to muscles that had been severely damaged.

Once a day we'd come in with a magnet and cycle these little sponges and just make them basically compress and expand, compress and expand, a number of cycles.

What was really shocking was when we looked a couple weeks later at the muscle tissue, it had regenerated as well as any other therapy that we'd ever explored. We've developed some very sophisticated stem cell and drug approaches that we were very proud of, and this thing worked just as well.

So we started with that, then we said, "Well, if it really is just purely mechanical, then if we apply the same kind of mechanical loads some other way it should also work."

Conor Walsh and I actually co-mentored a PhD student who was working on something separate, but we brought her into this, and we said, "Why don't you make one of these little soft robotic devices that we can have the mouse wear and do the same kind of thing, just supply this cyclic load periodically."

The two PhD students got together and did those studies and found that it worked equally well. It really did validate this idea that it was really just the mechanical cue that we're providing, that was driving this really robust response. [34:16]

McNally:
I always ask, where does this go? It seems to me, this has enormous potential. What do you foresee down the road?

Mooney:
This work has two really important directions. One from a basic side is, we'd really like to understand why this works so well. That's one arm of this, is to really go at it from a scientific perspective and really try to understand, what are the cells that are involved? What are the signaling pathways involved? To really put a firm basic scientific learning underneath this. But the other is to say, “Here’s something that really seems to be profoundly important, and we've got a responsibility to try to push this forward therapeutically as well.”

We're actually optimizing the system now in collaboration with Conor's group. So we figure out, what is the right duration of treatment, cycle of treatment? We need to look at different types of injuries, then begin to look at large animal models, and say, "Does this work just as well in a larger animal and ultimately a human as it does in a mouse?"

The attractive feature is this is a very minimally, or I should say, non-invasive approach to treatment. It's something that could translate quite quickly to human therapy.

McNally:
Everything that you're doing is building on the body's own, or any body's - mice or humans - ability to do this already? Correct?

Mooney:
Yes. That's really, I think, a crucial part because really we're trying to hitchhike on what the body already is set up to do, and maybe turn the levers a little bit to make the body's ability to regenerate a little bit stronger and maybe turn down some of the levers that inhibit the process.

McNally: [35:55]
Conor Walsh is John L. Loeb Associate Professor of Engineering and Applied Sciences at the Harvard John A. Paulson School of Engineering and Applied Sciences. A core faculty member at the Wyss, he founded the Harvard Bio Design Lab, which brings together researchers from the engineering,

industrial design, apparel, clinical, and business communities to develop new disruptive robotic technologies for augmenting and restoring human performance.

Conor received his BAI and BA degrees in Mechanical and Manufacturing Engineering from Trinity College in Dublin, Ireland and his Master of Science and PhD degrees in Mechanical Engineering from MIT. He's the winner of multiple awards including the MIT Technology Review Innovator Under 35 Award and National Science Foundation Career Award.

What is his perspective on this newly named field? [36:44]

Walsh:
I come at things from a human scale or more of a macro level when we think about devices to help people from a healthcare point of view. We really look at it that, you can build devices that apply mechanical forces to people, to their limbs, to their soft tissue from the outside of the body that can actually have a significant therapeutic and healthcare benefit for them.

For us, it's really about, how do we develop technologies that can be worn by people potentially throughout their everyday life, that at the same time could be delivering some type of mechanical stimulation with these software robotic devices that would help tissue heal or recover better and help people who have neurological injuries. That's really how we look at this area of mechanotherapeutics. [37:34]

I don't think I would be thinking about mechanotherapeutics in quite as much detail as I am at the moment as a field or a topic or as an area that my lab might continue to focus on in the future, unless I was in an environment like this at the Wyss, where you're interacting with other faculty members who have a chemical or a medicine or a biological background.

For us, it really started out by, we're a robotics research group. Being able to ask colleagues and say, "Hey, this is what we're building. Do you think this could be useful from a therapeutic effect?" That's really where a lot of the synergies or collisions have happened that are starting to make us think more about that direction. [38:21]

One example of that is myself and Dave Mooney co-advised a graduate student, Ellen Roach. She really worked across our labs, where some of her time was spent building soft robots and other times she was building tissue-engineered scaffolds or implanting these into mice and running studies as well. I think having an environment like this where people get to work on very diverse and different disciplines is what's opening up my eyes anyway to the possibilities of where we might take some of the technologies we're developing next.

McNally:
Do you see therapeutic potential down the road in this device, or again, ~~will~~ this be, do you see this always being assistive?

Walsh:
For the exosuit and the soft robotic glove, I think there's significant potential to really understand the therapeutic benefit for these devices, in particular, I think, in the post-stroke population. We've had a lot of interest from the clinical community both on the exosuit and thinking about how you can run studies to demonstrate that there is a therapeutic benefit in wearing this type of device.

One of the collaborators who's now an associate faculty member at the Wyss Institute is Lou Awad. One thing that he's interested in doing is really saying, if stroke patients are wearing the exosuit as part of a training program, are they going to see a therapeutic benefit from doing that?

Then we've had a similar amount of interest from people all around the world really on the soft robotic glove to say, if someone has suffered a stroke and they are undergoing rehabilitation, could they be wearing this glove as part of their rehabilitation, where maybe it's being programmed to execute certain routines, or maybe they're wearing it during therapy and it's helping them to train how to move their hand in a more natural way. I think both of those are avenues that we're going to be exploring more in the future. [40:12]

McNally:
Can we talk a bit about your collaboration with Dave Mooney?

Walsh:
The project with Dave Mooney is really a very first basic step to say, we believe that physical therapy and we believe that massage really do have benefit, but can we actually quantify that and study that?

What we actually ended up doing was deciding to build a very small and very simple soft robotic cuff that we could put on an injured limb for a small animal, a mouse, and be able to show that by delivering external mechanical stimulation that this actually does have a therapeutic benefit and can help the muscle heal better compared to a control.

That's, I believe, one of the first of its kind where people have actually demonstrated that with skeletal muscle, to show that giving this external mechanical stimulation at a particular frequency over a number of different days actually does help the muscle regenerate to levels that are pretty significant. The exciting thing there is that this is a noninvasive external and simple approach to actually encouraging at the cellular and molecular level certain signals to happen that helps this tissue actually regenerate.

McNally: [41:29]
So, Conor, how do you and Dave Mooney complement each other?

Walsh:
I would claim to know little to nothing about tissue engineering and biochemistry. I think Dave maybe feels the same when it comes to robotics and soft robotics in particular. You really have very complimentary disciplines where it's the sum of the parts is much greater then each on their own.

I think that's been one of the key things is that, I can show Dave a soft wearable robot and he starts to think about all these different possibilities of how it could be used as a platform to perform more controlled or better animal experiments.

Then I look at the work that he's doing and I think about, oh my God, they can really measure all of these different things that are going on inside the body, and can develop different materials that have different mechanical properties. How could we use that? How could we understand that? I think it’s really, you learn more from people outside of your domain than people who have a more similar background to yourself. [42:27]]

McNally:
That makes sense to me. What stage are you at? In other words, we said you found that this discovery that it had a measurable positive effect. Where do you stand, what other potential applications, and where are you going next with this research?

Walsh:
I think the initial work really was in collaboration with Dave and Georg Duda as well, who's another associate faculty member at the Wyss Institute. Now that we've demonstrated and shown that external mechanical stimulation can have a therapeutic effect on injured muscles in a mouse model, the question is, how should we use that platform that we’ve developed to really perform more experiments so we can actually really understand why we are seeing that effect, what the reasons for that are.

Can we actually make that effect even larger by optimizing some of the mechanical stimulation parameters? We picked a particular frequency and a particular time course for delivering that frequency over multiple days and weeks. What if we increase the frequency? What if we increase the amplitude and provided higher forces? What if we provided forces in different directions?

The nice thing about it is that, by building a soft robotic device, we can actually control and program all of those different conditions in a very repeatable way versus if you were to try and do that with just the person's hands delivering that mechanical stimulation themselves, that would be very

challenging to do in a repeatable way. I think one of the exciting things is now to think about - from a basic science point of view - how do we use these soft robotic technologies as a platform to really perform controlled studies to better understand the biological mechanisms that are leading to these interesting findings? [44:04]

McNally:
I can see that. Just for a picture for a listener, what you do is you have a mouse with an injured limb and you create a little cuff that sits on a little mouse limb and you wrap it around, and you program it to deliver, as you said, a certain amount of stimulation for a length of time, a number of times a day and so on. That really is the picture, isn't it, of what you've done so far? What you're talking about now is what if we tweak it this way or that way? Will we get better results?

Walsh:
Exactly, yeah. [44:36]

McNally:
I return to Don Ingber and we talk again about the big picture.

What is the value of calling a symposium, of having a symposium, of particularly pulling together people from diverse specialties? What's the magic there? What's the secret sause?

Ingber:
First of all, all the interesting things happen at the interface. This is where crystals form. This is where biochemical reactions happen. This is where revolutions happen, whether it's a social revolution, or a technological revolution.

McNally:
Yeah...

Ingber:
When you cross boundaries, and at the interface. So by bringing people from different disciplines, this may evolve in even new directions. It also may catalyze and accelerate things because ideas from one group...

Great example is Dave Mooney and Conor Walsh. Dave is in the programmable nano materials platform, works on materials, bio materials, and tissue regeneration. Conor is in sort of the bio-inspired robotics platform, and he's working on wearables and fabrics. He has people with sewing machines, but he also has engineers analyzing biomechanics.

The fact that they're at the Wyss, where we connect people in these totally disparate ways, and they listen to each other speak at symposia internally, leads to new collaborations, and things... just disruptive innovation. So by

having a symposium, the goal is to kind of expand that to bring in people around the world, who, without realizing it, may be working in potentially synergistic areas, and maybe develop new collaborations.

And also for the public. There are going to be people from around the world, people from companies that come to these symposia because they're international, and they're free. So that may allow companies to realize, “Hey, maybe there's new therapeutic areas here that as a drug company we should think about, or as a device company we should think about...,” where they don't think of it that way now. So it's really to catalyze, to ignite, to open new pathways for pursuing both basic science and translational applied science. [46:43]

McNally:
You mentioned it there, but expand a little bit on how the Wyss model is particularly supportive of these interactions and these overlapping specialties and so on -

Ingber:
The Wyss model has some unique facets. One is that we do medical and non-medical work. The basic idea is emulating how nature builds, to leverage biological principles to develop new engineering innovations. Most places would focus on medicine because it's biological principles, but we felt that non-medical areas like architecture, manufacturing, robotics could actually benefit from insights we have into how nature does things, and vice versa. Techniques and materials that have been used in the industrial world may be useful for medicine, and that's panned out in many ways. [47:34]

McNally:
How do you think having labeled this field with the term, kind of carved out a little territory... How do you think this will affect development going forward?

Ingber:
You will see a lot of other people using our term, that's the one thing. And all of a sudden, boom, it's like ours never happened - that's classic. I've watched that many times.

McNally:
That's the good news almost, right?

Ingber:
That's the good news. Yeah, that's great. Others will emulate our emulation. It will make people think that, “Hey, I never really thought about it that way,” which is good.

I hope that it will stimulate companies to start thinking, “Should we be having groups that think about therapeutics from a different perspective?” I

think it will, hopefully, also influence more fundamental scientists who are looking for new areas to pursue, to think about could my phenomena, or response, or behavior have a physical component, if they're trying to do things that could lead towards therapies. [48:34]

McNally:
One thing that I learned in speaking with Dave and Conor was that, when you begin to do that cyclic pressure cuff that they're working on, you now can get precision. You know exactly how much force, and at what cycle, whereas, massage, physical therapy is a little less precise. Is that a goal? Is that something that we should see over the next few years?

Ingber:
It's a goal of people in those fields without a doubt. I've had many physical therapists, dance therapists, massage therapists contact me over the years based on my work on tensegrity. It's referenced all the time to provide a generic scientific basis for what they do, but there's a subset of them that have been developing instrumentation and devices to quantify the forces they apply, and how they're distributed over long distances, and how they impact biochemistry.

Helene Langevin spoke at the meeting, and she is at Harvard, actually, in the Brigham and Women's Hospital in their sort of alternative medicine division. I think exactly that's their goal ~~is~~ - trying to develop a more quantitative basis for this.

McNally:
Obviously, we're dealing with an aging population. These things are going to be, you know, more and more in everyone's life.

Ingber:
They also can be less expensive because they're outside the body, so they don't have to go through the same sort of FDA... I mean they would go through the FDA, but they wouldn't require the cost of development, and so forth, and it's a much lower hurdle. [50:06]

McNally:
I want to know how they each of them imagine the future of mechano-therapeutics. First Conor Walsh –

Where would you see this field in 5 or 10 or 25 years?

Walsh:
I think that robotic technology in particular... It won't be just soft robotic technology. There are other groups who are working on very elegant and nice devices that are more based on traditional rigid robotics. I think you're going to start to see more evidence and studies that will be demonstrating the value of people using these types of devices. Wearable robotics as a

field at the moment is really growing quite a lot. I think we've only begun as a field to scratch the surface of what is the therapeutic benefit associated with wearing these types of devices.

Both our group and many other groups, I think over the next five years will release studies that will actually demonstrate that these devices do have a real benefit for people when wearing them and walking around with them. We're already starting to see that happening. A lot of work has been done on the upper extremity in that area and from a neural rehabilitation point of view, but I think more and more work is going to be done on the lower extremity as well.

McNally:
So, we'd be talking about this very, very differently in five years, wouldn't we?

Walsh:
I think so. I think it'll be more taken as standard that this makes sense rather than, hey, we think this could be cool, should we do it?

McNally:
Very good. Thank you Conor, it's been great speaking with you again. My pleasure.

Walsh:
Thank you. [51:31]

McNally:
I turn to Dave Mooney – In talking about the future, he reflects a bit on what holds this new field together -

Mooney:
It's a new field, so it's a field that actually is, in essence, being birthed now. I would say most of the people at the meeting would not probably label themselves as being this is their discipline, but what we expect is that in a few years, that will be true. What holds all the people together and why they all were excited to come and participate is, that they all recognize that physical forces may play a very important role in biology, one that not just has been under-appreciated, but that's really been under-exploited therapeutically. And that there's a big open space in front of us that we can try to help people by exploring these ideas.

McNally:
You mentioned that the Wyss is a place where you can take risks. Can you talk a little bit more about how being at the Wyss has influenced or set the scene for what you're doing?

Mooney:
Yeah. In research, failure is not typically rewarded. Similar to what most people do for a living. You are always trying to succeed. You're always trying to show that whatever you're doing is successful. Really one of the wonderful features of a place like the Wyss is that it's okay to fail.

It's okay to take something on and to fail at it. If you're really going to pursue new ideas, you have to have that possibility of failure and not have something that, "Gee, if we fail it means the whole lab gets shuttered down because now it didn't work and that was our one shot." The Wyss gives the possibility of trying new things, daring ideas, and failing, and being able to get up and try again.

McNally:
Finally, Dave, the last time I talked to you we talked about immunotherapies, a cancer vaccine, we talked about hydrogel-based drug delivery, today we talked about mechanical stimulation, work with stem cells, and so on. How, for you, do all of these things overlap and fit together? What does this all look like to you?

Mooney:
We do a lot of different things that probably from the outside can look like it's kinda random. What they all have in common is what we are trying to do at the end of the day is use materials to control biology.

Whether the biology we're trying to control is the immune response against a tumor that a person has in their body, whether it's using materials to impose a physical force to promote regeneration of muscle stem cells. What we're doing is using materials as a convenient means, and hopefully a fairly effective means of conveying information to cells and tissues in the body, and controlling their behavior. [54:21]

McNally:
If you were to look ahead Dave Mooney, five, ten years, what kind of work do you hope to be doing, or what do you hope to have accomplished? Is there some vista over the horizon...?

Mooney:
Yeah. The accomplish is an easier one probably. What I hope to have accomplished is to do two things. One is to have opened up some new possibilities and inspired a lot of young, really brilliant people that are out there today to get engaged in these areas because science is a team sport. It's not an individual sport, and it really takes a team of people for things to move forward. I'm hoping that the work we do inspires this whole team to get engaged. That's one thing that I hope.

The other is that I hope some of the things we're working on right now actually have benefit to patients, so that some of these ideas go beyond

being ideas, or go beyond experiments that we might be doing in animals, or in people, and go on to actually be routinely used therapies.

In terms of what I'm thinking about doing, I don't know. I'm fortunate enough to work in an environment with some incredibly talented PhD students and post-docs, and there's always lots of exciting ideas, and we tend to follow what seems really exciting at the time.

McNally:
Thanks a lot Dave Mooney. It's been a pleasure.

Mooney:
My pleasure. [55:35]

McNally:
Finally I return to Don Ingber -

Now that the stake is in the ground, now that there's a term, and so on, where do you see development over the next five, 10, 15 years?

Ingber:
I think there's no doubt that some of these are more straightforward, and a smaller step forward in terms of transition for industry. For example, in the pharmaceutical area there are many drugs that affect ion channels. At the meeting Philip Gottlieb spoke about ion channels that regulate cardiac arrhythmias that are mechanically activated. So to develop a drug against that ion channel, the drug companies would say it's basically an ion channel blocking drug, but it's really blocking a mechanical signaling pathway.

The work that my group has done, which we presented also is related to an ion channel... the signal I mentioned through integrins that turns on cells. We have shown using our organs-on-chips that this ion channel is very important in pulmonary edema. This was pulmonary edema that was a drug side effect, a cancer drug side effect - Interleukin-2. But what was really interesting, is that without the breathing motions, the physicality of back and forth expansion and contraction of the lung, you had minimal pulmonary edema.

That's what led us to look at a mechanically activated ion channel, and a drug that inhibits that ion channel completely blocks that response. Now that drug, which is developed by a classic drug company path, to just generically inhibit ion channels, inhibits the opening to the channel, so it just blocks anything that goes through. But it turns out that we find that that ion channel can be activated by two signals. It can be activated by chemical signals, and it can be activated by this sort of mechanical stretching signals, so now you might be able to get a much more specific drug by being able to develop a drug that only inhibits the mechanical.

Now a drug company would really have to think about this as mechanical drug development, not just generic ion channel chemical drug development. That's a baby step, but you'll see things like that happening. [57:49]

Medical device area... I think that's an area which has much more engineering, where they know mechanics is important in what they call compliance matching, making sure the device can have the same flexibility as your natural tissues.

Same with regeneration and tissue engineering and implants. But that's an area where they know they need to know more about how it works. I think that's where there's more and more mechanobiology needed.

Simon Hoerstrup talked about heart valves that are bioengineered, but you have to have the opening and closing of the valve, the physical pre-training *in vitro* to get those valves to be structured in a way that basically function *in vivo*. Or if they're going to design valves to go right *in vivo*, they're designed so that they seamlessly mesh with the natural physical environment so that they undergo remodeling and regeneration in a way so that they can be integrated into the body and actually grow. If you put it in kids, the idea is that they grow over time.

With all these areas, I think what's going to happen is... The hope would be that they put more effort into understanding the mechanical side of things. Rather than being an add-on, actually begin to be a specific focus. [50:00]

McNally:
Thank you so much.

Ingber:
Thank you. [59:06]

McNally:
You've been listening to DISRUPTIVE: MECHANO-THERAPEUTICS, I'm Terrence McNally and my guests have been DON INGBER, DAVE MOONEY and CONOR WALSH.

You can learn more about MECHANO-THERAPEUTICS, as well an exciting range of other projects at the Wyss website - wyss.harvard.edu – that's W-Y-S-S dot Harvard dot edu – where you'll find articles, videos, animations, and additional podcasts. In fact, all three of today's guests have been featured in other podcasts, focused on specific aspects of their work. Give them a listen.

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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. [59:52]