Dr. Aaron Carroll:

Welcome back to the Healthcare Triage podcast. Today's guest is Chandan Sen. He's the Associate Vice President of Military and Applied Research at Indiana University. He's also the director of the Indiana Center for Regenerative Medicine and Engineering and Executive Director of the Comprehensive Wound Center at IU Methodist Hospital. Chandan, welcome.

Dr. Chandan Sen:

Thank you. Thank you, Aaron. Glad to be here.

Dr. Aaron Carroll:

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So we like to start out the podcast as always by asking people, how did you become interested in this? How did you get to where you are today? What is your educational biographical path to become what clearly is a number of fascinating jobs?

Dr. Chandan Sen:

So my master's degree and my bachelor's degree was in the area of human physiology. And when I did my PhD, it was also in human physiology and it had to do with a little bit of sports medicine and then injury repair, which as you know is integral to sports medicine. And as I went from my post-doctoral studies at the University of California at Berkeley, we were looking into fundamental processes that play in tissue repair. And at Berkeley, I ended up meeting a surgeon, Professor Thomas Hunt, who is one of the fathers of the wound healing field in this country who had a laboratory at UCSF, the University of California San Francisco. And he one day came into my office and said, "Chandan, I know you work into the fundamentals of tissue repair, but I'd like to really have you for one of my grants that I'm writing a grant that I'm writing on wound healing. Would you be interested in this?"

And then at that point, really I did not understand the overall public health burden caused by wound healing. He educated me on that. Sounded very interesting and that some of what I was learning could be easily applied to that field. Long story short, we wrote the grant together. It is in nice terminology, it's called a P50. The grant got funded. That was my first sort of program grant participation. Although, Dr. Hunt was the PI, I was a sub investigator. So that got me into the field. Now once we were in the field and we were trying to repair these chronic wounds that would not heal and would lead to amputation and stuff, gradually we started learning that when the adult body repairs itself, it repairs itself in a somewhat limited manner, in that after repair you do not have the tissue or the organ that you really lost.

So now you have a tissue that somewhat is close to what you lost, but is now scarred and somewhat inefficient. So that being the case, it became a scientific goal to see, can we improve the quality of repair? Now when you would like to improve the quality of repair, the ultimate goal is to really restore what you had. And that's the definition of regeneration because that's what we had and we would like to have back what we had. The aspirational goal is to regenerate your tissue, not just repair your tissue. So that's what got me into this field.

Dr. Aaron Carroll:

So when we talk about regenerative medicine, is it all about wound healing or is it about other topics or issues as well?

Dr. Chandan Sen:

No, it is not all about wound healing. It is about pretty much any part of the body you can think of. And I'm going to try to tell you a small story that actually excites all of us and got us practically excited because you see, there can be an aspirational goal, but there has been to be an observation that tells you that this is possible. And that observation happened when I was training at UC Berkeley, and I was also spending some time at UCSF, University of California San Francisco. And in the next door lab was Professor Mike Harrison, one of the fathers of the fetal surgery field. And there was now a friend at the time, a colleague Mike Longacre was working in that lab.

And what they found was if you went in utero, so if you went into a fetus and you caused injury, that you had perfect repair, you can't even tell what the injury was. So when the baby was born, of course not a human, in this case it was a sheep or so, but when the baby is born and this can be produced in mice and other animals, you can't even tell. You have to put an India ink spot to know where you injured. Perfect repair happening in the womb cannot be reproduced after you're born. So that became a very interesting goal for us because the apparatus is there, what happens at birth that it is gone, and then what happens as we mature and become adults and then adults with disease, it is really completely lost. So that observation told us that in this case this was a model of cleft palate. But coming back to your question, the ability to repair in originative fashion, any part of the human body would fall under originative medicine.

Dr. Aaron Carroll:

Why does the fetus repair itself entirely, but we as later developed creatures cannot, what happens?

Dr. Chandan Sen:

I guess your question directly asks for the mechanism and I'll tell you what we know today and where we are heading. So what we know today is the bottom line, the fact that you have on a robust basis, no matter who does the experiments, you get to see the same thing. You have this regenerative repair. Now with it, in the fetus what you see is a very blunted inflammation response. So when you have injury, injury is followed by, as we all know, hemostasis meaning the blood clot should form and the blood flow should be checked, but then the inflammatory cells leave the circulation and visit the injury site and that mounts the process of inflammation. And this process of inflammation in the fetal tissue is very blunted. Now today, as we know from all the sciences of wound healing that is available in the literature, inflammation is required for wound healing.

But if we have too much inflammation or lingering for too long or not resolving in a timely manner, inflammation becomes an enemy of wound healing. So that's in the adult scenario. Interestingly, the fetus does not even require much of an inflammatory process. It can do with very little inflammation. And by the way, other studies have shown a relationship, a direct relationship, but with inflammation and scarring. So to begin with, there is this inflammatory process. But then as we got our hands on some fetal tissue and we started looking at the molecular machineries responsible for wound healing, we ended up finding a couple of proteins that are present in feeders, very active in the repair process, but progressively lost in adults, completely sort of absent in adults with diabetes. So there seems to be a molecular missionary that is sort of hidden or locked once we are born.

Now some people have been asking, and we just published on this, so some people were asking me, "Why do you think it is locked?" And it is difficult to say, but what can think of such that nature has made the human body to be sort of immortal so it doesn't just spontaneously regenerate organs. Otherwise, that would be in conflict with this whole process of us ending our lives and new lives coming into play. This is just a story that I'm sort of making up to explain what we are seeing, but the fact is this missionary is there. And this missionary, a lot of people thought was lost, but we ended up finding it is not lost, that it is locked. So when we unlocked that we could substantially improve the repair process even in adults with diabetes.

Dr. Aaron Carroll:

How do you unlock it? I mean is it a medication, is it something else?

Dr. Chandan Sen:

No, very good point. So this is what we have currently achieved is in this case the example is again, the skin wound. It's a convenient example because when you're doing these types of experiments, you don't want to work on the brain or the heart on an exploratory basis because the damage you could cause to the individual or the organism could be really substantial. The skin or the bone or the cartilage allows a lot of degree of freedom, if you will, in taking risk. So we like to learn from the skin and if things work, we'll then approach the more complex organs. So in this case, we went through a gene delivery process. We first identified what was missing and we gave it back to the wound and we found that this was then expressed and as it expressed it had a substantial impact on the healing process.

So in this case there are two partner proteins, one of which now we have published, already remarkably improves the repair, the speed of repair. And if you add now the second one, which we did not yet publish, we also start seeing regeneration. So I'll just give you a quick example. Regeneration in the skin means now you are growing back hair follicles, you're growing back in a so-called appendages, the hair normally, otherwise the skin will heal sometimes without not good nerve supply, mostly with no appendages or hair follicles or hair. But now you can actually achieve these endpoints if both of these proteins were to be put back in through a process of gene delivery using a technology we have developed called tissue nanotransfection.

Dr. Aaron Carroll:

Can you talk more about that? I mean how does that actually happen? I mean can you walk us through the physical, how do you actually get this to the patient's wound?

Dr. Chandan Sen:

So for that I have to take a little bit of time explaining to you what is tissue nanotransfection, the technology itself.

Dr. Aaron Carroll:

Please.

Dr. Chandan Sen:

Most of those that take or work with a cell, as you know, unit of all tissues, the way we deliver genes to cells, there are many pathways of doing that. One is what is known as a viral vector. In our case we don't like it because accidentally we can end up delivering to places where we don't need. And therefore viral

vector is something that for this purpose that has to be limited to a given part of the tissue may not be the best choice. So we don't like it. There are many other delivery avenues, but one commonly known avenue is what is known as electroporation. Now electroporation is where you apply a certain amount of electric field and you open up certain pores in the cell and while you open up these pores, you deliver the so-called plasmids or genes and then they enter where the pores are open and then the pores close and the gene is delivered.

Now that's the big picture. A more detailed picture is that large amount of electricity is used for that. That ends up killing a lot of cells and those cells that are killed are lost because obviously they're dead. And this process that is commonly found in the laboratories today is called bulk electroporation where many cells die, some cells do not die, but end up opening holes through which gene passes. What we found was that if you end up using this type of a bulk electroporation, then you end up doing a lot of damage to the membrane. And if you damage the membrane, then the regenerative potential of the cell is dramatically blunted. So this is not an acceptable, especially in regenerative medicine, bulk electroporation is not very acceptable. So what would be very acceptable is what we now call nanoporation. So what is nanoporation? Nanoporation is where you take a cell and you open up no more than 2% of the cell surface area.

So the technology is such that it opens up a very tiny hole into the surface of the cell and through that hole, as we have videos to show, you deliver the gene and the hole is then closed in a matter of milliseconds. Okay? So this whole thing takes a hundred milliseconds and no more. So which is one tenth of a second. So how it looks is you have a silicone chip and the chip is nanofabricated. Why nanofabricated? Because the scale of structure within the chip is nanoscale, meaning a hundred nanometers thereabout scale. So once you nanofabricate this, what you have is an array of needles and then in the chip you have compartments where you load up the gene and then you apply a certain amount of electric field. And because of this electric field, electrophoretically the genes are delivered into where you want.

And we have computational modeling based on how much biophysical power needs to be given in order to deliver the gene where, how far from the surface of the [inaudible 00:13:19]. For example, if you wanted the epidermis of the skin or the dermis of the skin or the subcutaneous part of the skin, we can tackle that by changing certain physical parameters of the switchboard that we have in delivering those genes.

So anyway, so now you have one centimeter by one centimeter in a chip, which is actually made as a wafer and depending on how much area, you can pick 16 of those or eight of those or six of those or four of those. In a mouse, we typically use one of those. In a pig, we use four to six of those. In a monkey, we use about eight of those. So once you put the chip on the skin where the wound is, you then apply this electric current for 0.1 seconds, one 10th of a second once. Then the chip goes away from your body, the gene is now in your body and that's it. You don't do it twice, you only do it once. So that's the entire process.

Dr. Aaron Carroll:

So this is still in the experimental stage? I mean is this still being just used in animals for experiments or is this something that is being deployed to actually help heal human wounds?

Dr. Chandan Sen:

Safety testing in human is on the way, has been used successfully in rodents, in pigs, and very recently in 2022 in monkey, and safety studies in human underway.

Dr. Aaron Carroll:

How much does one of those chips cost to fabricate?

Dr. Chandan Sen:

So if you're talking about bulk fabrication, then the chip would cost less than a hundred dollars. If you fabricated one chip at a time in a homegrown manner, of course the scale, it is expensive because enormous amount of times. When a few years ago we were in Ohio State, the first version of the chip was made, but that was completely the homegrown version. Then here I'm fortunate to have a laboratory in Purdue University and at the Nanotechnology Center there, the Birck Center, we started developing the next generation. So between that facility and the nanotechnology facility in Chicago, we have now basically set up the large scale manufacturing of the chip. And we just published that in a journal called Nature Protocol because a lot of people were asking me for the chip and I was not able to make for every one of them. So I discussed with an editor of the journal, Nature Protocol widely read and they published a 52 page article on how to make the chip. So anybody interested and is aware of the art can now make it because of that paper that just came out.

Dr. Aaron Carroll:

Is there some way to describe what the difference in wound healing is with the use of this technology versus if you were not using it? Is it that it looks better, heals faster, less infection? What is better?

Dr. Chandan Sen:

Okay, so first let me clarify what the chip can do and then I'll come to your answer. So the chip not only improves wound healing, but does many other things. Such as say even without a wound, so the two things that we have already published, and I'll give you those examples first and then I'll go give you some examples of what we did not publish and is currently established in the laboratory.

So what is published now is say you have a damage in the brain and you need to have a lot of neural cells because neurogenesis in the brain after injury is very limited. And say you wanted to grow neural cells that you would like to transplant to the brain. So we have shown that you can actually use the chip and apply that on skin, a skin that does not have any wound by the way, just intact skin. And you can make thousands and thousands of neural cells that are electrophysiologically active in three weeks. Then we harvested those cells and we put it back into the damaged brain and we could recover brain function. And this was published in National Nanotechnology demonstrating a functional improvement and grafting of these cells.

So on one hand it can be used to generate cell types. So that's what we call neurogenic tissue reprogramming. Now related to that is neurotrophic tissue reprogramming. What that means is say I have diabetes, I have peripheral nerves that are on their way to die because of all the toxic biochemical reactions that are going on in the skin. So while I'm converting skin cells, not the nerve cells of the skin, we have demonstrated that we can convert skin cells into electrophysiologically active nerve cells. So while we are doing that, what happens is the rest of the skin that does not reprogram end up making very large quantities of neurotrophic substances such as neurotrophin, nerve growth factors.

And because of that, what happens is in the diabetic skin, the nerves that are at threat now are no longer in threat. And we should see those nerves also. So those nerves are not the ones that we made. They were preexisting. If we did not have, so that paper is now published showing that you can use neurotrophic reprogramming to rescue a preexisting nerve fibers that are at risk of withering away because of the toxic reactions caused by diabetes. Those are two examples that are published. Another published example is when we went into the leg, as you know, one of the major suppliers of blood flow

to the leg is called the femoral artery. And now you cut away one centimeter of the femoral artery from the leg of a mouse and then what happens is the affected leg gets so ischemic that it necrotizes, it basically falls apart, the leg. And you can tell that visually. You don't need scientific measurements.

What we were able to show is that if you take away that one centimeter femoral and in a distal part of the leg, you go and do this vascular genetic reprogramming using TNT, we show the appearance of thousands of new blood vessels within seven days, complete rescue of the leg, an animal without femoral supply running around, already published, [inaudible 00:19:03] running around and poor pressure or types of blood flow details because these little journals are pretty demanding. So plenty supplemental data to show that you can actually convert skin cells into functioning blood cells, which then rescues the functionality of the limb as a whole. So that's vascular genetic reprogramming. Something that we are currently working on and was quickly advanced by NIH with some funding in the monkey is now we are seeing that we have come up with, so the chip remains the same by the way in each of these application, the cocktail that we deliver is different and proprietary. Proprietary meaning belongs to IU.

The third example, and then I'll sort of pause and see what you have to say, is that we now have insulinogenic cocktail, which if you again touch the skin for one tenth of a second, we are demonstrating that the insulin precursor proteins and insulin itself, and they reside in pockets in the skin and deliver insulin for the next eight or so weeks, eight to 10 weeks, and brings down your hyperglycemia and with only that one TNT done. So that is insulinogenic reprogramming.

So the examples I'm giving, just to make sure, that with this chip and different cocktail for different application, you could actually end up having a variety of problems that could be addressed by TNT. Now coming back to your question of wound itself, wound heals anyway sooner or later, but the problem is when you are in a diabetic organism, then the wound really does not heal. And in this case TNT made a difference where the diabetic wound was healing with a trajectory of healing that would be comparable to the trajectory of healing in a non-diabetic animal. So that's already a very important advancement. Now is this particular repair a hundred percent regenerative in the work we published? Not yet, but now I was talking about the second protein that we did not yet report, with that we are seeing also clear signs of regeneration. So the overall situation is very hopeful.

Dr. Aaron Carroll:

I mean this sounds borderline miraculous. Am I misreading it or is this a huge potential area of where you could do good where we're not doing anything else? I mean, how close are we to getting to where this is being able to be used in human beings?

Dr. Chandan Sen:

So the first time this was reported was just five years ago and my postdoctoral fellow who was the first author of the paper, then won NIH Director's Award. And so we have two NIH director award on this, which is sort of a recognition of the importance attached. And Dr. Collins also did a blog on this technology. And if you go to Google and write about tissue nanotransfection, there is a lot of buzz. So a lot of people getting interested. So yes, so this is the concept of not cell reprogramming, but tissue reprogramming achieved without a laboratory, where your body is the laboratory that grows the tissue that you would like to have for therapeutic purposes. And sure enough, we recognize the need to take this to human. So therefore the FDA process, we have hired a consulting agency and this human safety study planning, so on and so forth, is currently underway.

Dr. Aaron Carroll:

Are there downsides? Are there potential risks of this or have you seen... Again, does messing with the genes have any issues or is there ways that this can go wrong or has it been pretty safe?

Dr. Chandan Sen:

So far safe, but for a scientist it's never fully safe until so proven. So I think it is too early to call, but we have had six month follow of studies in animals. The beauty is because this is a physical way of delivering genes, it stays where it is. And the other good news is that you are making this manipulation in the skin and the skin turns over within so many weeks. So for example, this insulinogenic unit after 12 week disappears, so you'll have to redo because it keeps rising and then goes to the top layer of the skin and falls off. So there is this natural process by doing it in the skin that it automatically will fall off in a few weeks, like three months or so depending on which animal you're doing. And so it does not propagate within. So we have done six month follow up studies, whole body safety monitoring because obviously those questions were also raised by the reviewers. So far nothing has been observed that would be a major concern.

Dr. Aaron Carroll:

So then is this at the moment isolated to skin wounds or can it be theoretically used to do regeneration of deeper tissues?

Dr. Chandan Sen:

So very good questions. So we just published, actually one sponsor that has shown a lot of interest in this is the Department of Defense, the US Department of Defense. And one of the problems that they had that they wanted us to work on was what is known as volumetric muscle loss. So a significant chunk of muscle missing, say from one of your limbs, which happens in a trauma situation. And they asked us whether we could come up with a myogenic TNT. And long story short, the myogenic TNT paper just came out in [inaudible 00:23:58] regenerative medicine demonstrating that you can actually go into the skeletal muscle of the leg and make it to regenerate by doing a myogenic TNT.

So the point is that yes, other tissues, tissues other than skin can also be lending themselves to this type of a... But so far bulk of our work has been on the skin. The skeletal muscle work is the only one that has been where we have gone into the body. But theoretically speaking, if we talk about our intellectual property, we have TNT mounted on the top of a catheter that reaches any part of your body they could internally and you can trigger the TNT in one tenth of a second and come back. So access wise you don't need to open the body, you can actually send catheters and do it sort of on endoscopy basis.

Dr. Aaron Carroll:

So I mean is this the kind of thing where someday you could envision you could repair heart tissue through a catheter or if it was damaged by an infarction or I mean, how far can this go?

Dr. Chandan Sen:

So again, we so far have not worked on the heart, but you see the basis of what we see, so I'm going to take a little bit time here to explain. You see regenerative medicine, if you talk in general, people talk about stem cells. Now I have a different view of the stem cell. So you see, when I went to school, I was taught something called terminal differentiation. An organ has been made and it stays that way. That skin can all of a sudden flip and become another tissue was beyond my imagination based on what I learned in school. So this concept of terminal differentiation was sort of a cornerstone of our understanding, but now at least in my head, that has fallen apart because what I am able to see is that

you see, terminal differentiation and if you now go to the extreme opposite end, you would find stem cells.

Why I say extreme opposite end is because you see in the earlier days, people had to work on embryonic tissue to show that indeed one tissue can be reprogrammed into some other, okay. But then when there was pushback from people, we started looking at adult body and adult tissue and sure enough, we found stem cell niches in the adult body. But what I'm saying is you don't even need stem cells to reprogram. Pretty much every fibroblast of your body, when we do what is known as single cell sequencing, we find typically in any tissue that the fibroblasts can be broken down into 10 or 11 subsets by single cell sequencing. Of these 10 or 11 subsets, three or four are dedicated to move around. The others are housekeeping. They do the job that they're supposed to do and functionally they do not move around. But then we find three or four subsets of fibroblast that can really move around and go towards being a neuron or go towards being a vasogenic cell.

And by the way, when I say that, I say go towards being is because in our terminology there are two important terms. One is a state change and the other is a fate change. When a cell stops being what it was and becomes something else, that's a fate change. Because I used to be a fibroblast, now I'm shedding my fibroblast properties and acquiring endothelial properties and now that is a fate change. But then that is very uncommon in the body. What is very common in the body that we see is a state change, meaning I'm a fibroblast, I will retain my fibroblast properties to some extent. I will not shed all of it, but I will acquire neural cell properties or I will acquire endothelial cell properties if it is to make a blood vessel, for example. And once I have made a pseudo sort of blood vessel where that lacking endothelial cells, I will recruit endothelial cells.

So in a few weeks when you do histology, you can't even tell that I was involved. You will see it is the same endothelial cells, smooth muscle cell and so on and so forth, arranged in the order. But actually when I triggered the formation of the vessel, there was no endothelial cell. So what I'm trying to tell you is that every organ has fibroblast and fibroblast has stemness and that stemness can be leveraged to make myocytes or anything else you want. So to that extent, yes, you can regenerate the myocardium by the right cocktail and the right approach to reprogram the fibroblast of the heart. So theoretically, yes. When will it be actually accomplished? I think the more grasp we have of the fundamental knowledge, the closer we are to doing it.

Dr. Aaron Carroll:

So where are we right now? What are the experiments that you're working on right now that you're most excited about?

Dr. Chandan Sen:

So first and foremost, we think that we can make blood vessels from cells that are not of vascular cells by nonvascular cells. So to bring blood supply be to the heart, be to the brain, be to the leg or whatever it is, is something very doable in our minds and very doable as opposed to the following. As opposed to the other approaches where you take a bunch of those cells and you tissue engineer a blood vessel in the laboratory. It all goes wonderful as long as all of the culture conditions are in your control. The moment you put it into the body, the immune system objects. So what we do is all our reprogramming is under immune surveillance. So either the immune system is rejecting it as we are doing it. So it's not like we did it perfectly, but when we planted it, the immune system threw it out.

So we don't have to deal with that. So we think that in vivo tissue reprogramming, our form or some other form, I will not claim because we are just scratching the surface of this topic. I'm not going to say that ours is the best possible form. Ours is one feasible form and maybe as we learn more, better ways of

doing it will come into being. But this whole approach of in vivo tissue reprogramming does not require a laboratory, can be scaled to pretty much any corner of the world, can be conducted under austere conditions. For example, a military setting provides a great hope for many applications.

Dr. Aaron Carroll:

Is it very, very expensive or is it reasonably cost effective to do?

Dr. Chandan Sen:

No, this is very cheap. I'll explain to you why. First of all, the chip when you scale it up will be in tens of dollars to make it. Now how much you sell it, I cannot comment on that. That is market force. That is something else. I'm telling you about manufacturing cost can be brought to below a hundred dollars and to tens of dollars, the chip itself. Of course, they will be disposable chips. What I see is something that you're stamping if it is the skin or otherwise it'll be a catheter based. Then the gene itself, the cocktail is our classmates in some cases. But for the blood vessel we have found one antisense oligo, one antisense oligo can make thousands of new blood vessels out of a skin tissue in a week to two weeks. Okay, so those are really cheap. You're talking about again, maximum tens of dollars. So you're talking about everything done. And some pulses of electricity, this can come from any source that you have. So this is very inexpensive to conduct.

Dr. Aaron Carroll:

And you say right now it's in safety testing for humans. I mean do you have thoughts or predictions on when this might actually move into actual clinical trials or further?

Dr. Chandan Sen:

So the concrete situation is we have an MTA with another country that was interested also to do human safety testing because there's a lot of interest in it. So we have a successful MTA and that particular country regulatory process is currently ongoing. And limited human testing on seven people have been already concluded. And now our more systematic testing is to take place. Here we are putting together the right type of dossier that would fly through the FDA.

So we are working with the consultants to do that. There are several people interested in the technology for commercialization at the table. So the university is in talks with those such investors. I have had many investors that have come and a very long story, very short few of those investors have really expressed interest in just getting everything lock stock barrel. And the university is hesitant to do that. They would like to license in pieces. So my role there is pretty much almost nothing. But that's a problem. Some investors would like to have all of it as one thing, but the university may want to license one thing at a time, but these things are all advancing in the right course.

Dr. Aaron Carroll:

Where do you think this goes next? Is it a new area, a new tissue, a new gene, a new method of delivery getting it actually out into everyday practice? What do you think is the big thing next?

Dr. Chandan Sen:

Yeah, so first and foremost at this time, the paper on tumor regression, a tumor that kills all animals in 14 to 16 days, and now more than two third of those animals living more than six months. That paper just got accepted in Molecular Therapy, which is a journal of the American Society of Gene Therapy, a

well respected journal. So the point I'm trying to make is that we already now have seven or eight different applications resolved within our group. At this point I'm looking forward to also collaboration with other groups that they could start generating their application. The reason we published the chip is because we want other groups to get involved. And I think when this goes to other laboratories, there'll be more fresh views of this and that will benefit the technology I think. That is the reasons we so quickly published the entire chip technology and making these genes, pretty much any lab can do that. So that limiting factor was accessibility to the chip.

So I think between us and other laboratories, there could be great progress, but as it relates to our own, I am now publishing more and more mechanistic data, so my peers can find this more believable, because a lot of people would say that is impossible to be making a blood vessel.

So right now, to your point, there is a paper which is now in the last cycle of revision where we have more than 200 panels of figures showing that a vessel can be made without endothelial cells. And that after the vessel is made that these cells, which are actually fibroblast in origin, recruits endothelial cells to give mature shape to that vessel. So these types of fundamental questions take an enormous amount of effort to really prove to somebody that this is fundamentally possible. So we are not so much keeping on expanding application and wowing people without really establishing the fundamental is not in our best interest. So right now we are going to stick to the six or seven applications that we already have and we are going to go vertically down and nail down the fundamental principles, how they happen and would like to collaborate with others or let others do on their own and see what they find. So that's our strategy right now.

Dr. Aaron Carroll:

Can you talk a bit more about just the field of regenerative medicine and how it got to be where it is now?

Dr. Chandan Sen:

Thank you for asking that. Let me start with the regulatory process because anything in the healthcare must go through the regulatory process to see so-called the light of the day. And if we talk about the FDA, the US FDA, it was founded essentially to regulate food and medical drugs way back when. Okay? And not so long ago came in medical devices. So now investigational new drug, investigational new devices. So at this point, thanks to the 21st Century Cures Act, FDA now has the RMAT designation, regenerative medicine advanced therapies. And through the RMAT designation, until last year, 2021, they had 67 approvals, and this year they have 12 more, 79 approvals. So what I'm trying to say is drug devices and then making bits and pieces of your body parts, plugging it back to you. In layman terms, the RMAT track is now in place. So I think the RMAT track is going to be growing tremendously in the near future.

And anybody interested in healthcare regardless of... So it's not an option like you know what? I work on cancer. I'm not interested in regenerative medicine. It's not an option because if you look at RMAT, many of the RMAT solutions are cancer directed. So what I would say is that RMAT is a cross-cutting platform that really touches each and every aspect of healthcare. And as RMAT grows, we need to be mindful of the underlying science and a new way of taking care of ourselves. Well, that does not necessarily depend on say, a pharmacological molecule or a particular device as we knew of the past. So now we are playing in a field that says that in the next five years there's going to be a 25 to 30 billion dollar industry. There's a rapid growth process going on and responsive to that, what we found at the Indiana Center for Regenerative Medicine and Engineering is when we spoke to a lot of the industry people, that they're

suffering from a dearth of supply of well-trained young professionals that would work in the laboratory regenerative medicine.

So to that end, we just got approved by the Indiana Council of Higher Education for our RMAT MS PhD program. So the MS PhD program is now in the process of implementation, and our primary focus is workforce development. We see this as a massive industry of the near future that regardless of when we work in a particular discipline, we think this is my discipline and that is their discipline. So we are called the Regenerative Medicine Center as opposed to the Musculoskeletal Center, as opposed to the Cancer Center. What I'm trying to say is that this is going to cut across all other centers and every other center would have an input into this. Otherwise, this field will just go... That is what is needed for this field to be developing. So I've been looking forward to 10 years from now, more than 500 FDA approvals that are basically touching the lives of hundreds of millions of people. We need to actively participate in that transformation of healthcare.

Dr. Aaron Carroll:

This is all fascinating and before 10 years from now, we would love to have you back to talk about where things stand and advances that have been made. Thank you so much for being here.

Dr. Chandan Sen:

Thank you, Aaron, for having me here. This was a pleasure to talk to you and hopefully people would be inspired and would like to participate in this. And we are always hungry for high quality talent. These disciplines all are dependent on the influx of high quality talents. So if somebody really finds this exciting, participate in this and then lead this and define the future.

Dr. Aaron Carroll:

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