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Lynn Hershman interviews Dr. Anthony Atala

Inventor of the Bio Printer

Wake Forest School of Regenerative Medicine

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LH: How did you and your team come up with the idea of using cells in printers?

A: Yeah, you know the use of printers actually for biological systems, has been around for many, many years. And I was actually still in Boston when we we're collaborating with scientists, who we're looking at using printers for use, with materials, with **BOW** materials. It just made sense to actually just add cells to it. We started doing that for possibly skin, a few years back and then of course, it progressed to many other things with a lot of help from our friends.

LH: What other things did it progress to?

A: So we've actually been able to print skin tissue and three dimensional organs, such as an ear for example. Or even more complex, three dimensional organs like two dimensional hearts or large kidneys.

LH: What happens to these things, once you leave them?

A: Now, it depends on the complexity of the structure. Usually for the similar structures of course, we have a lot of functionality. For the larger structures, like a two chamber heart or a larger kidney, of course, these are proto types. Just _____ organs right now that we are creating and trying to improve on how to make them so we can some day implant them into patients hopefully.

LH: You started out working with children?

A: Yes

LH: So when you we're building these new proto types, how long do you expect they will last and when do you think they _____?

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A: Yeah, I'm a pediatric surgeon actually. So, we did start working with children and we started implanting a lot of these structures that we created, in children first. And interestingly, we now have over a sixteen year follow up in some of these organs. Showing that of course, these structures, these organs do grow and get larger as the children grow. So these organs really get identified by the body, as being their own. And they act as if the organs we're just the patients' own organ.

LH: Did you expect that to happen?

A: You know, we knew early on that there was a simple concept in biology that stretch is equal to growth. So we kind of expected as the axial plan of patients that is growing when the patients we grow. That this would actually induce some growth in the organs themselves. Of course it was reassuring to know that it did happen.

LH: How long do you think the life span would be?

{Tech talk}

LH: Do you see this is a photographic process?

A: Well, one of the strategies that we have always used is how to best use what nature does and how we can reproduce that. And certainly when you talk about organ formation inside the body, it happens from a miniature size and it just keeps growing, as the baby grows. And it's the same thing with the printing technology; we are now creating miniature organs and basically, hoping to get those to be larger and larger over time. As we create larger organs and also we can implant smaller organs and let them grow in a patient.

LH: How did it feel to actually happen? To actually see that it was working?

A: Well, a lot of the organs that we have generated and that we have implanted into patients, we of course, do a lot of pre testing to make sure that they are going to work. So, by the time that we finally get these organs into patients, we pretty much have a high level of confidence that these organs will at least be safe. That's our number one concern, that they will be safe for our patients and of course, that hopefully they will be effective as well, as we follow them over their time course.

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LH: What do you foresee happening to some of the people that are using these organs?

A: You know, we of course realize that a lot of the technologies that we're developing today… that we plan to put into patients in the future, hold some sort of promise for patients and their disease. The question for us, which is more important today of course, is we've already implanted organs in patients and we know that they work for what we've put them on. But these are simpler organs. We are three levels of organs that we have implanted. We have not yet implanted solid organs so, for us, for the future, implanting solid organs is really one of the major goals that we have today.

LH: When are you going to start that?

A: You know, it's very hard to predict. We've learned not to predict because every time we predicted, we've been wrong {laughing} because it's so hard to tell when these technologies can actually get to patients. There are a lot of scientific challenges that need to be addressed but also regulatory challenges as well as making sure that these technologies get transferred effectively.

LH: We have the technology to regenerate limbs or fingers _____ can you talk a little bit about that?

A: Yes, well we know that right now, if you look at different biological systems, like a salamander for example. If a salamander injures its limb, it will regrow within three weeks or so. And that's an amazing feat. The question of course is, if a salamander can do it, why can't we? And so we're really studying a lot of these biological systems to see how we can best use our own body's ability to regenerate, to help us heal.

LH: Has this happened?

A: Well, we do have the potential to regenerate on our own, with our fingers and many parts of our bodies. For example, our own skin regenerates ever seven days. You get a brand new coating of skin every seven to fourteen days. For the intestines, every five to seven days of lining in your intestine turns over, every five to seven days. So it's the same thing when you get injured. Let's say you come in with a…you come into a hospital and you see a patient that presents with a car accident and they had liver trauma, they had an injury to their liver. Within, as a surgeon goes in to _____ that liver and the surgeon _____ fifty percent of that liver, within six months, you do an x-ray and that livers fully regrown. If a patient injures the tip of their finger, on its own, it will regrow. So, we as humans, do have the potential to

regenerate. The question is, when we have massive injury, very substantial injury, how can we make sure that we can in fact, allows that patient to regenerate its own tissues and organs.

LH: How do you do it?

A: Well, we know the body has the ability to regenerate so, what we're trying to do is using materials that the body can use as bridges for regeneration. And using small molecules' and proteins that will help the body regenerate better. And it's really not very much difference then when your mother used to tell you, you have to drink your soup to stay healthy. Well, we have to use the right soup to keep your organs healthy.

LH: What about the skin printer? What was the evolution of that and what's the use for?

A: Well, you know, one of the challenges that we had of course is, we're going to start generating these organs and we've implanted these organs into patients already in many different times. The question is, how can we scale this up? Currently we're doing this one organ at a time. For us, the challenge is well; we can do it one at a time by hand. It's like handmade organs, if you will. But to really scale it up, you need mechanisms which will allow you to do so and the printing technology, of course, appear to be an excellent resource for us. We're we could just print these organs automatically; program the printer to do what we can now do by hand.

LH: Does the skin printer _____?

A: So, we're working on the skin printing technology because one of the aims is to use these printing technologies right on the patient. Let's say that a patient receives an injury that affects their skin. Maybe we can just scan that area of the injury, like with a regular scanner. Just like you would scan a picture in a printer. But then you'd come back with a printer and actually print the cells right on the injured area. And this is work that we are doing specifically focused right now on patients with battle field injuries.

LH:

A: Yes, and it's really incredible to see all levels of technology of course _____. And as these levels of technology advance in different areas, like 3D bioprinting or nano technology or material sciences, all those areas help us as well. Because as we develop these organs, we

can utilize all the expertise necessary scientifically available to us that will allow us to accelerate the development of these technologies.

LH: What would be some milestones for reaching the goal of preventive care to maybe live to 120?

A: Well, it's interesting to note, at the turn of the century, the typical life expectancy was only about forty years of age for a male. So that was basically in the 1900s. And so now you… basically a hundred years later, just a hundred years later, life expectancy for a male is doubled to about eighty years of age. So that's just in a hundred years we've doubled our life expectancy. So, we are doing a lot more things now. We know more about our health. We now have nutrition components that allow us to really fulfill our potential better, in terms of living better, exercising better. So I really do think that increasing our life expectancy, we have not seen the end of it yet. Of course there are limits, currently on how long we can live but we have people living to a hundred and ten right now. So, going to a hundred and twenty is not that big of a stretch when you figure that some people are in fact reaching the age of a hundred and ten.

LH: Are there any ethical concerns when you chose which kind of projects that you are going to be focusing on?

A: Yeah, we have always been very thoughtful about the ethics behind the research that we do because we want to make sure that at the end of the day, we do not, we do not use one patient for the benefit of another. So, really, most of our technologies rely on using the patient's own cells. If a patient requires an organ because they have a diseased or injured organ, our strategy is to take the cells from the same patient, from that specific organ, to grow the cells outside the body, create the organ and then put it right back in. So, in reality, we are not dealing with any ethical issues at this point. But as our technologies advance, we always remain very attentive in making sure that we do not cross boundaries that make be unethical.

LH: And how do you make those decisions?

A: Well we have a lot of expertise in terms of our ethical committees. We actually have an ethicist, who is part of our institute. Who works _____ is actually part of her time is spent here with us and we really look at all these things very closely to make sure that we are creating technologies that will benefit patients by using their own cells. And therefore, there's no rejection and you're not using someone else's tissue and we're using their own organ tissue to regenerate their own organs.

LH: How long has this been going on?

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A: We've been working on this field now for over twenty years. Generating these organs and we…the first tissues that we implanted we're back in 1995, 1996, in terms of cell therapies for patients.

LH: If your able to have cells transfer a memory, could you transfer memories? Could you download memories?

A: You know, yeah, you know an interesting question may be, can you transfer memories if you transfer cells? You know, cells themselves have a memory, so every single cell in your body has all the genetic information to create a whole new you.

LH: Can you do that?

A: So, of course that's called cloning. You can actually take one cell and create a clone. But the one thing to remember is that that's a biological clone. Of course, that's considered unethical today, to clone a human being. But what you have to remember is that people, many times have a misconception of what a clone is. The fact is, that we see clones, human clones every day, there called identical twins. There basically biological clones. But as you know, twins are individuals with their own memories and their own history. So you can have a biological memory but the question is, can you have a mental memory and that gets created of course by the patients themselves.

LH: How far back does that go in our evolution?

A: Cell memory goes back to the very first stage of evolution because it is that memory of that one cell, which allowed the next cell to be _____ and build its own memory and the second cell could not have done it without the memory of the first. That genetic imprint that we have in every cell is like the key board in a piano. You can play many different pieces with it but the keys are the same.

LH: Can you recall all those early cellular experiences of development?

A: Well, the cells, in terms of their evolution, can certainly define what the cell is and what the cell needs to do but it's really the program, very much like a music sheet that you use for a piano player. The music sheet for the cell, drives with that specific cell will do. But every cell in

that body has the same keyboard. And that's what makes that patient unique. Each patient has a different keyboard; it's what cells of that keyboard you play. What is the music sheet, if you will.

{Tech talk}

LH: Do you think this kind of work is going to make a difference to stem cell research?

A: Yeah, it is really clear of course, that every cell that we use has a different program. Right, so a heart cell is programmed to be a heart cell, it's programmed to beat so many times per minute. Which is very different than a liver cell, which is programmed to do other kinds of things in the body. But the basic genetic makeup of both those cells are exactly the same. It just depends what keyboard, what keys you're playing on that keyboard. And so, we use the same technology for stem cells. We basically know what the keyboard is and we want to make sure that we deliver that cell, the right music sheets. So it becomes what it's supposed to become. Do you want that cell to play rock or classical music? Well it depends on the sheet that you give it. It's the same thing, when we create a cell and we want to drive it to become a hard cell, we're going to give it a different music sheet then if we are going to create a kidney cell or a liver cell.

LH: Do you think we will eventually be able _____ off the shelf organs?

A: Yes, you currently, the concept of course is your going to have readymade organs for the patient by using the patient's own cells. The question is, will we be able to have them just on the shelf, ready to put in. In fact, you could, you really could. If you had a bank of organs, which was large enough, you could actually do that. But its' not practical at this point to do so, maybe someday in the future as science evolves. That will become something that will be financially freezable. But certainly the hope is that someday, if someone presents, you can just pull a patient off the shelf and put it in. I may not see it in my life time but it's certainly a possibility.

LH: And that would come from DNA collecting when someone was born?

A: Well the concept of organs off the shelf is really no different than blood off the shelf. Where you have a blood bank and when the patient needs blood, you just go cross type and match that specific blood type and give it to the patient. So the concept would be very similar for organs off the shelf. If you had a donor bank, which was large enough to create these cells and you could create organs in a bank that would just be waiting there but its' really a financially challenging model currently with the methods that we have.

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LH: How do you get funding to do it?

A: Well they're currently; there are currently efforts to establish cell banks all over the world. And cell banks are being established now and cell banks would have a wide genetic variance. For example, if you we're to establish right here in the U.S., a bank of approximately 100,000 unique samples, you could supply over 90% of the U.S. population with a perfect genetic match for transplantation. But to obtain those 100,000 unique samples, you require a lot more samples to get there. So, the possibilities are there, it's just a matter of time and resources.

LH: In the future, what would you like to see happen?

A: You know, our mission here at the institute is really to advance regenerative medicine technology so we can bring this technologies to make patients lives better. Really everything we do at the institute is aimed at our patients. How can we improve their lives. How can we provide organs for them if they require them. Of course our goal is that any patient that requires an organ can have one readymade. So, for us, it's not just about the organs we've already implanted, it's how can we increase the number of organs that we're working on. And how can we make those, more widely available, so that many patients can benefit from them.

LH: Is there a downside?

A: Well, you know, no technology is perfect. And certainly, we do not expect regenerative medicine to be perfect either. The most important thing for us is to make sure that these technologies are able to be sustained long term. And that these organs are able to work long term. But even if there not, if you can replace an organ function for just ten years, if you can keep a patient off dialysis, a patient with kidney failure, off a machine, for just ten years, that may be an advance. That may be worth taking.

LH: What's next for you?

A: So we are currently working on about thirty different tissues and organs. Our goal really, is to be able to expand the number of indications of patients that can receive these organs and to expand the number of organs that can be implanted.

LH: Do you have a goal?

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A: Well, nothing would of course make us happier to have a day in the future, probably in the very distant future, where a patient presents to the emergency room, with a motor vehicle accident and who had trauma, that induced tissue organ loss, that the family can we reassured the moment that patient walks in, that they have options. They have options that will make their loved ones better.

LH: If you can transfer the memory of cells, can you suppress a part of that memory?

A: Yes, you can actually, you can modify cells genetically. You do not have to go by the memory of the cell itself. You can give the hard cell a music sheet and alter how that heart cell will behave. Genetic engineering though, has a lot of areas which are still very unknown. What we don't know is that if we affect the genetics of the cell, how will that cell function long term. It may start forming tumors, it may start doing things that you don't want those cells to do. So, affecting the memory of the cell is indeed possible. We're just going to have to work very carefully to make sure that we can do it safely.

LH: How many other institutions are using the techniques that you are developing here?

A: There's probably not a single institution today that is not working on some aspect of cell therapy, stem cells and cell biology.

LH: And that's worldwide?

A: And it's worldwide. So there's probably not a single institution, nationwide and worldwide, that is currently not working in some aspect of stem cell development and biology. So this field is advancing, very rapidly. We expect to see many more advances over the _____ decade.

LH: There has been some criticism of the downside potential of a genetically modified _____ we don't know about long term. Do you see anything happening with what you're doing?

A: Well we now have, you know, we now have organs that we have implanted into patients and these patients are, you know, fifteen years out. And the organs are still doing well and the patients are still doing well. So we know that using the patient's own cells for that specific organ has a good effect. Because by now, they don't have any more cells that we put in. These are

new cells that we're generated since we put those cells in. Right, so these are new organs for all practical purposes.

LH: What about _____? Does that include transfer?

A: Yes, so, when you use a patient's own cells and you put those cells back into the patient, those cells genetically, identical, of course to the patient. Which is important because it avoids rejection. These organs will not reject. The question for the future is, can we take cells from a patient and genetically modify them so you can make a super organ. Let's say, an organ that is, that can perform better than what the patient had. I think that you can certainly modify these organs genetically but there's a lot of danger involved at this moment because we really do not understand a lot of the genetics behind these tissues, especially, as you modify them artificially.

LH: Even if they perform better in the short term, would you do it?

A: You know, I think…for us replacing the patient's own organ to the way that they we're supposed to be, is already something that will make that patient better. So, we have no reason at this moment to try to make organs, better than they are. In other words, we are not looking for someone to have more strength just because they have our muscle cells implanted. Or someone who can generate, let's say in the future, that can actually, you know, run faster and have to be less stressed because they have a better heart. I think nature gave us what we need. At this point, that's our only goal. If we can just get to the point where we can give patients what they need today, we would be satisfied.

LH: How do you choose your patients?

A: So, once these technologies are developed of course, they have to go into patients and we really do go after patients that have the worse conditions. Because these patients usually have very few options left. There's not much else that can be done and when you reach that end of the medical therapy and you need to basically go into a surgical approach, a surgical approach that will hopefully make that patient better, we'd like to target that patient. Because really, there options are, at that point, limited. So it's better to start with those patients.

LH: If foreseeing anything unattended and what they are going to do next?

A: Yes…

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LH: Do you have any specific goals?

A: Yeah, a lot of what we're working on right now is to really try to induce a regeneration of the patient's own tissues and organs inside the body. So, our current strategy, that we already have in patients is you take a piece of tissue from the patient and you grow the cell _____, create the organ or the tissue or the cells for therapy and put them right back into the patient. What we're currently working on, is how can we actually induce the body's own ability to regenerate inside the organ and so a lot of our efforts right now are aimed towards using the body's own ability to regenerate and to improve that ability. So we don't even have to go outside the body to do so.

LH: How do you do it?

A: There mechanisms where we can inject small molecules and proteins inside the body and allow those to recruit cells to the area for regeneration. And that's the analogy where, you know when our mothers' used to tell us, you know, drink your chicken soup. Well if you provide the right soup inside the body, you can also induce those cells to grow. You may be able to do so to the point where you can help that organ along.

LH: Why now? Why are you able to do this now?

A: Well, so many advances that have occurred in just the last decade. I mean it's hard to believe that it was just 1998, when cloning was announced for mammals. It was just in the late 1990's when stem cells we're discovered that would give rise to many cell types. So this field is very new. We are talking about science that dates back only a couple of decades at most. And so, as these sciences advance, it is interesting to note, that more advances have been made in science and there is more knowledge in science in the last ten years then there was in the last century. So, it's an exponential growth of knowledge. And as these bits of information end up _____ the scientific community, I believe that the scientific advances will increase at a much faster pace than we have seen.

LH: Because you can program DNA now, right?

A: Yes, we can now program DNA. We can change the cells pathway. We can change the cells fate. We can direct cells from any different directions. The things that we can do with cells today, we're thought to be entirely science fiction, just a few decades ago.

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LH: Do you see anything that could be science fiction in the future? Something you're working towards now?

A: You know, it's interesting to think about the future and it's interesting, certainly to think about where things will lead. I've learned now, for many years, never to think that things are impossible, not in science. What people thought impossible just a few decades ago, was totally possible today. So, who knows what the future will hold.

LH: What about these trans genetics, crossing species?

A: Yeah, you know, we are doing transgenics everyday in the scientific world. Every single day, I mean, imagine the thousands of new flowers that you see today. That are all a result of mixing genes, you know. All these new colors you look at, orchids, right. All these new orchids that come out all the time. Different colors, different shapes, different sizes. All the different fruits that are being genetically engineered. I mean, now you can have your personal size watermelon. Right, it's totally genetically engineered. So, the question is, can you do that with biological systems, which are like mammals for example. I think that certainly, when it comes to healing these disease, this is a very wide open area. If a patient is born with cystic fibrosis or muscular dystrophy and they have a genetic disease, why not correct that genetic defect. So, it's not a new concept. People have been working on it for a long time, decades really. I really do think it's just a matter of time until you can use the information you have today, to provide treatments for these single gene defects. Which are so devastating today. So the possibilities are out there, we just need to be sure, like any other technology, that we always use these scientific tools in the right manner.

LH: If you're using them, can you wipe out disease in the future?

A: Yeah, you know it's interesting because people say, we'll will there be a time when we're disease free. Will there be a time when we are virus free or bacterial free. Evolution continues but we always have to remember is that, the evolution that we experience is not unique to us humans. The evolution we experience is also unique to the bacteria and the viruses around us. So as we change, so does our environment. So it's a constant game of change between how we evolve and how our surrounding evolves. So, having a day when we are entirely disease free, certainly for the next millennium, would be unlikely. To do so, we would really have to isolate the human species. And isolate it from everything else around it. Because bacteria needs something to live on too and so do viruses. So as we evolve, they will evolve too.

End of Recorded Material

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