What's New Podcast Transcript
Season 2: Episode 23: The Regeneration of Body Parts
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Host: Dan Cohen, Dean of Libraries and Vice Provost for Information Collaboration at Northeastern University.

Guests: Anastasiya Yandulskaya, Brian Ruliffson, and Alex Lovely winners of the 3 Minute Thesis competition at Northeastern University.

Dan Cohen: 00:00 Every year, thousands of graduate students write theses on topics at the frontiers of research. Many of those topics remain obscure. But there’s a new movement to have students explain their complex and exciting research in plain spoken, succinct ways. Today on What’s New, we’ve got the winners of the Three Minute Thesis competition, in the studio to talk about their cutting edge work. And all of them are working on regeneration of body parts.

Dan Cohen: 00:30 Welcome back to What's New. I'm your host Dan Cohen. And I have to admit that I, too, was once a graduate student. One who like many others had trouble going home for the holidays and explaining to my family exactly what I was studying and writing about. The Three Minute Thesis competition began at the University of Queensland in Australia to push graduate students to describe their research briefly to a non-specialist audience. Students have just three minutes to explain what they are doing and are also allowed just one Power Point slide which, I have to say, is my favorite restriction.

Dan Cohen: 01:03 Today I'll talking with three of the winners of that competition. All of whom work at The vanguard of biology and medicine. They participated in the Three Minute Thesis competition here at Northeastern which was sponsored by graduate women in science and engineering. And in the spirit of the competition I’m not going to tell you about them or their work up front. But will let them introduce themselves and guide you through their research.

Anastasia: 01:27 Hi my name is Anastasia Yandulskaya. I am a third year PhD student at the biology department here at Northeastern. I work in the laboratory of James Monaghan. Our lab focuses on studying regeneration. How our regeneration of complex biological tissues occurs and we use as a model we use the Mexican axolotl salamander. The salamander is well known in the field as a really amazing animal model that is capable of regenerating lots of its body parts and organs. For instance, they
can regenerate limbs, spinal cords, tails, lungs, hearts, and even the brain. As for my particular project, I focus on studying regeneration of the retina. The retina is a very thin neural structure in the back of the eyeball that focuses on visual input from the environment which allows us to see. This input is light and color. In humans, as in other mammals, the retina lacks the ability to recover from damage. As a result, be it injury from physical impact or chemical impact or neural regeneration, retina in humans can not regenerate and as a result humans are left with deficient vision. However in other animals, such as lower vertebrates, the neural retina has the ability to recover from damage. My doctoral work focuses on studying how and to what extent the retina can recover from damage in the Mexican axolotl.

Dan Cohen: 03:09 Great, thank you for that introduction Anastasia. I have to say, how did you get interested in this particular topic and I think for our audience, I certainly didn't know what an axolotl was, I had to google it, and maybe you could describe a little more what they look like in your lab and how you got interested in working with them as your animal model for this regeneration?

Anastasia: 03:32 Absolutely. To describe an axolotl, just visualize a small to medium sized pink fish with red gills and bigish eyes that look at you. This fish also has four legs and it is capable of walking. This image will-

Dan Cohen: 03:56 Literally walking out of water, it can walk up on land?

Anastasia: 04:00 That's actually a really good question. The axolotls are salamanders which implies that they exist in two forms, some would say. One form is aquatic and the other form is land. Aquatic salamanders live in water and they use gills to breathe and land salamanders use lungs and walk on their legs or paws, some could say. Most salamanders transition from the aquatic form to the land form at some point during their life. This process is called metamorphosis. In most salamander species it occurs naturally. However the axolotl does not naturally undergo metamorphosis and they typically stay aquatic throughout their life, but they could be induced to become land salamanders under certain conditions.

Dan Cohen: 05:02 Is it your impression that this kind of hybrid and very interesting creature, not the prettiest creature, I have to say, when I googled it.

Anastasia: 05:09 It has its charm.
Dan Cohen: 05:12 This ability to move from land to sea, is this part of how this as a creature that has more flexibility than other species that we see to generate limbs, and like you said, even the brain, it seems to be a very flexible species in that it changes from a sea form to a land form and can also regrow a leg if need be?

Anastasia: 05:39 The adaptability of the salamanders to their environments certainly is, good probably be a factor behind their incredible ability to regenerate their organs. It is a really interesting question because it is not entirely well researched how metamorphosis affects their regenerative abilities and actually really few studies have addressed this question. But it appears that the regenerative ability of the axolotl and perhaps some other salamander species is not affected by metamorphosis, although of course this could probably vary by species and particular organs.

Dan Cohen: 06:21 What got you interested in the retina in particular? It does seem like a really important application to help people who might have a damage to, as you said, in human beings, the retina is so fragile and it doesn’t take much to really hurt it permanently. I’m sure there would be millions of people who would benefit from this research. Is that your motivation, what are you trying to get out of this research for your thesis?

Anastasia: 06:50 It is a certainly a very good point that in humans retinas cannot regenerate and research that focuses on studying how other animals can regenerate their retinas could possibly, potentially, in the future benefit lots and lots of people, which of course is one of the leading motivations of mine. I would like to contribute to laying the foundation to discovering how exactly we could develop treatments for helping people who have suffered some sort of damage to the retina and that of course is a major reason why I got interested in retinal regeneration.

Anastasia: 07:36 The other reason is that my undergraduate degree is in neuroscience. I have been interested in neural structures for a long time. The retina is a relatively simple neural structure compared to such incredible organs as the brain. In the axolotls, regeneration of the retina remains understudied and I would like to contribute to our understanding of regeneration of the retina in the axolotl so that we can know how exactly this animal model can be used to furthering our knowledge of retinal regeneration.

Dan Cohen: 08:18 You are a young scholar and you have decades of research ahead of you, do you see in your lifetime a solution to retinal
Anastasia: 08:33 I would like to say that yes, I do foresee that there is a lot of potential for better and more efficient treatments to be developed within our life spans. Because I read a lot of scientific literature to better understand what is going on in the field of retinal regeneration. And I have seen so many amazing studies that have really contributed to understanding how and why mammals cannot regenerate the retinas. And what could possibly be done to not necessarily induce retinal regeneration in mammals, but to give this process a little shove and each study that uncovers one or another mechanism of retinal regeneration contributes even more to this grand goal of ours, and as those studies further our knowledge, I can definitely foresee this cumulative understanding of this regenerative process being synthesized into something that could possible be developed into a cure for retinal degeneration in humans.

Dan Cohen: 09:55 Anastasia Yandulskaya, thanks for being on the program.

Anastasia: 09:59 It is my pleasure. Thank you for having me.

Brian: 10:02 Hey I'm Brian Rollifson, I am a master's in bioengineering at Northeastern. And I'm doing my project in directed chondrogenesis of human mesenchymal stem cells. I'll explain what that means.

Dan Cohen: 10:14 Please do.

Brian: 10:16 Stem cells are cells in the body that have the ability to turn into other cells. And mesenchymal stem cells are the ones that are found in your bone marrow. So these are the ones that can turn into blood cells or bone or fat tissue. It's sort of more limited but they are better at turning into those specific ones. We're using those cells and we're trying to make cartilage. Cartilage is a little bit tricky because when you tell a stem cell to become bone, what they do, the halfway point is cartilage. So if I'm telling a stem cell to become cartilage it's really tricky to make them stop that progression. If I take a bunch of stem cells, tell them to become cartilage and then I implant that in the body and then they continue to become bone, that's a big problem, when you have bone in your joints. That's worse than no cartilage right?

Brian: 11:06 So what we're doing specifically is that we found there's a specific gene, I won't go into that, but this gene has been shown to, if you down regulate it, it will promote bone growth. So
we're saying, what happens if we up regulate it? It that going to prevent the bone growth? We're putting this gene, we're doing some genetic editing, and up regulating this gene in some cells and then testing and seeing whether or not this helps these cells become the type of cartilage that will not become bone. We call it articular cartilage. As opposed to hypertrophic cartilage which is what's going to become bone.

Brian: 11:52  
We're testing this in a bunch of different ways and we actually have within the genetic editing system that we're using, we have a way to turn off and turn on this up regulation of this gene. Which is actually kind of important because if you have a gene that's always on, it's always telling the cell to make protein. And that can makes the cells tired. It uses up their resources. And this is a problem for, if you want to grow a bunch of cells, they're always using their resources that's going to limit their ability to grow, and so on and so forth, there's a lot of downsides to that. The ability to turn off this gene regulation, or gene up regulation is really important. We have this huge gene sequence that we're adding these cells and testing the viability of this kind of gene editing within these cells is essentially the basis of my project.

Dan Cohen: 12:47  
If I went into your lab, what is gene editing actually look like, I think we've all heard about gene editing and it seems like the hot new thing and the 21st century will be completely changed by gene editing. Is it a computer system, is a wet lab kind of a thing, where' you're working with petri dishes, what does it actually look like?

Brian: 13:08  
It depends on what side of gene editing you're doing, right? So there are the companies that are producing these genes that you are using to edit with.

Dan Cohen: 13:18  
Like mail order genes?

Brian: 13:19  
Right, yeah so what we've done is we've corresponded with this company, we said we want these different things in a gene, can you put that all on one gene for us to use? And then the way you get genes into a cell, we hijack nature's mechanisms to do that, we use viruses. The virus that we're using is a lentivirus. Another famous lentivirus is HIV. These viruses don't have any pathological DNA so they're not dangerous. They're still viruses so you don't want to let them escape. You have to have certain, be careful in certain ways. But instead of the harmful part that the virus would normally inject into the cells' DNA, you have your gene that you want to be injected into the DNA.
Brian: 14:06  It’s like a wet lab. It’s in a petri dish. You put some cells in a dish and then you also put a certain amount of virus in that dish and then you put it in a centrifuge to make sure that everything is down at the bottom in the same level. Hopefully that virus infects a certain amount of those cells. In that infection, in that gene, you add a resistance to an antibiotic. That means that all of the cells that are infected with your gene are also resistant to a specific antibiotic. So then after a set amount of time you introduce that antibiotic, it kills off all the cells that have not been infected and you keep the ones that have been infected.

Dan Cohen: 14:46  I see. Your research seems to really pinpoint a potential medical treatment for arthritis in that the cartilage, you talked about this mid point, I didn’t realize that, that cartilage if it keeps going it becomes hard bone but before that calcification you need these things in your knees, in your joints, it’s this more flexible cartilage that’s there. How far along are we in some sort of new treatment for arthritis? Because it seems like reading your work, the current medical regimen is more like maintenance right? Or joint replacement which only lasts a certain number of years. How close do you think we are, as a young researcher who’s in this field?

Brian: 15:33  I’m actually really excited about tissue engineering as a whole. I think just based on a lot of the talks that we heard, especially the axolotl talks, I’m sure the listeners[crosstalk 00:15:45]

Dan Cohen: 15:45  I just heard about the axolotl. [crosstalk 00:15:47]

Brian: 15:47  There’s a lot of very exciting regenerative medicine that’s up and coming. Science does move very slowly so there is that. It’s within my lifetime that we will have really good tissue engineering techniques that will be able to. I think I’m being a little bit generous here. It’s like 10 years to fully develop this technology. Okay let’s give it 20 years. And then you go through the regulatory process, that takes another 10 or 20 years. Maximum that’s like 40, 50 years, if I’m being even more generous. That’s within my lifetime. That’s certainly within my career time. So it’s very exciting for me being in tissue engineering and studying these techniques. That’s why I’m excited.

Brian: 16:33  Specifically with cartilage there are a lot of techniques that reduce patient pain and stuff like that. But like you said none of it is curative. The goal is to develop cartilage, not just cartilage but cartilage bone interfaces. It’s called an osteochondral junction. With my off/on gene technique, that means that if I
have some cells and I turn the gene on one side and I turn the gene off on one side, maybe I can get a gradient of bone cells on one side and cartilage cells on the other side. And that can mimic the junction between bone and cartilage, which is actually a very difficult junction to recreate in the lab and has not been done before. The way that people normally do it, is they’ll make some bone cells over here and some cartilage cells over here and then put them together. But then you have an artificial interface between the two. What you would like to have is a smooth transition between the two. That’s one of the applications of this research, down the line, like a few years down the line.

Dan Cohen: 17:43 Sounds like in your lab and in the field in general, we’re getting a lot better about fine tuning this really amazing process of stem cell to tissue growth and gene editing that has to go on with it to, in a sense, modify and morph these cells.

Brian: 18:02 Yeah. The difficulty with stem cells, stem cells are already amazing. They can do all the different things that you want them to do. The difficulty is figuring out how to tell them how to do those things. I think one of the most amazing things that we’ve discovered about stem cells, when I say we, I mean the general scientific community, not my lab, or me or whatever, but one of the most amazing things that we’ve figured out about stem cells is that they respond to many different things. It’s not just bio cues that you give them. They also respond to this stiffness of the material that they’re growing on. Cells that are grown in a stiff environment are much more likely to become bone cells. And cells that are grown in soft environments are much more likely to become like smooth muscle or fat cells and stuff like that. There’s so many variables in the equation, which is why it makes things so slow but it’s also amazing that these cells are able to take in all this information and deduce what the right thing is to do.

Dan Cohen: 18:57 Well Brian Roliffson, thanks so much for letting us know about your research.

Brian: 19:01 My pleasure.

Alex: 19:02 Hi, my name is Alex Lovely. I’m a third year at Northeastern University in the biology PhD program. My work mostly focuses on studying limb regeneration in the axolotl. My specific focus is on the skin of the regenerating limb. It plays a very important role during regeneration. We know that if that skin is removed or damaged in some way, regeneration will halt until it’s allowed
to regrow over the injury site. We know one, that if it's not present, regeneration doesn't occur. We know that the particular structure as well has a lot of nerves within it. That's something that's been shown in staining for decades now. It's been a very well characterized thing. But what we don't know is any actual specifics to the role or function that this skin plays in regeneration, as well as what cell types or the identities of the cells within the structure are.

Alex: 19:55

Where my work gets into all of that is that I study gene expression, specifically mRNA, or the functional molecule that is the building block of proteins or what proteins are translated from in biology. I look at where the mRNA of the specific genes of interest that have been shown to be important in regeneration, are located within the skin. And through doing multiple rounds of staining of these different genes I can kind of make what's called a transcriptional map or an overlay of all the different genes that are important, where they're expressed and then from that information kind of boil it down to cell types or cells within that structure that show similar patterns of expression. Let's say, we know that a lot of genes related to cell proliferation or telling cells to grow more, are all located in a specific region of the epithelium or hypothetically if we saw this it would allow us to infer some kind of functional information from these cells that was previously unknown.

Dan Cohen: 20:58

First of all, it's amazing to have a second contestant talking about the axolotl. We heard from Anastasia a bit about how sort of remarkable and unusual these creatures are. But can you explain to our audience, what if we had an axolotl with us here in the studio and damaged its skin in some way, what would happen and what's your research show happening at the surface of this creature? Can you explain that a little bit and where the skin starts to regenerate from?

Alex: 21:37

If it's, let's say not a whole limb amputation, more of just a nick in the skin, very similar to how we regenerate the skin on the edges will start to proliferate and push the cells closer to the middle. Whereas in humans that's generally taking the form of scar tissue or cartilaginous build up. The axolotl doesn't actually have that, it's just the same normal skin that you'd find on either side that just closes over and then eventually just becomes a normal layer of skin.

Dan Cohen: 22:04

Really?
Alex: 22:05 What’s really interesting is that specifically in regeneration of a limb, the very first stages are the closure of the wound. So the skin will creep over and cover the wound site. And then once that takes place some kind of change occurs very shortly after the closure is complete which shifts it from what you’d say gene expression wise, the normal skin would look like to this more functionalized, what we call regenerating wound, epithelium. Which then supports the growth of the limb.

Dan Cohen: 22:37 So the epithelium is this sort of new, more active skin. So we cut off a leg, these poor axolotls, the wound first closes as you mentioned, but then that skin, and say that little circular area, changes its nature and that's what you're seeing when you dye it?

Alex: 22:55 Yeah.

Dan Cohen: 22:57 And how does it go from there? This seems like a remarkable property, I wish we could translate this, in fact I’d love to ask you in second how you translate this into some potential medical application but how does it then end up with toes and joints and things like that?

Alex: 23:15 So the way that works is during regeneration, once the wound’s closed over, the skin over the wound site is more of this pro regenerative state. All of the cells were on the cut plane, there are endogenous stem cell populations present within the different tissue types. For example, muscle has stem cells present throughout it. Other cells will de-differentiate to a more primitive state, not primitive, but multi potent state. So for example...

Dan Cohen: 23:47 They become flexible again to...We just heard a little about this from Brian.

Alex: 23:52 They’re a little less lineage restricted then they were previously. Your connective tissue can be cartilage, it can turn into bone, things like that. You get a mass of these progenitor like cells, that’s what the main bulk of the structure we call the blastema is. And that is where the new limb will be formed from. And so gradually over time, generally on a small animal, let’s say about five centimeters long, that blastema will be in the early stages by about day five, where it’s just a very small cone over the structure. By two weeks it’s a much larger, protruding cone, kind of getting more grown out, more sub proliferation is occurring, that’s probably around the time where some of the patterning programs might start kicking in. And then what we call the late...
cone or early palate stage is when proliferation kind of starts to slow down and it's less the differentiation genes and the proliferation genes that are on but then instead ones related to patterning, so determining what cells need to become what. And then that's where more of the digit formation will actually start to kick in.

Dan Cohen: 25:00 Really remarkable that this creature can do it. How about the potential applications long term, what are you learning yourself in the lab that makes you hopeful about potential skin regeneration for humans?

Alex: 25:15 So what I've seen a lot of is the fact that the skin over the injury site has such a dramatic expressional change from let's say, normal skin. What we're learning about are the mechanisms that can either drive the shift in gene expression and so if we know what these particular mechanisms are, be it certain genes that are activated then send off cascade of other genes there's epigenetic programs in place so modifications and alterations that change what genes are active and available to be expressed, those change a lot during regeneration. And one of the thoughts of why axolotl is able to regenerate and other organisms like us can't, is that our epigenetic programming turns off during development and then once we're an adult organism we don't have access to those developmental programs anymore. Where as the axolotl, we think that those programs are never completely turned off and they're more easily accessible for them to go back, turn it on and then that's how the new structure will be generated.

Dan Cohen: 26:19 So they're remaining in this sort of juvenile state or developmental state, these creatures?

Alex: 26:25 Yeah the axolotl is pretty cool in the fact that unlike most salamander species that actually go through a metamorphosis, the axolotl is in its juvenile state throughout it's entire lifespan. So that's why they're constantly aquatic throughout their life. Most salamanders go through an aquatic stage in the very early life metamorphose and then they're either semi aquatic or mostly terrestrial. Where the axolotl just stays in that little niche.

Dan Cohen: 26:50 Right, Anastasia brought this up and I didn't know that, nor did I know much about axolotls before today's show. It's been great learning about this. Just one final question. How did you get interested in skin regeneration as a topic for your dissertation?
Alex: 27:07 It really came about with the method I started working on so the technique I used to stain gene expression. I was looking at a few kind of test genes to get the protocols to actually work. A few that we knew that were highly expressed and had very specific expression patterns. And a lot of those happened to be in the epithelium or the skin. Just because it’s a very easy structure to see staining patterns within. And then through seeing that, talking to my advisor and looking at other interesting genes that are up regulated or expressed more highly in regeneration, we saw a huge subset that are in the epithelium. And then I did a little bit more reading into seeing wow, this structure needs to be there for regeneration to occur. Nobody knows how it does this, so that would be a pretty interesting thing to figure out. Because if we ever want to actually bring this kind of regeneration to humans from these animals it’s key to understand every aspect of that process. If this is one of those key first steps that really starts the regenerative process in the axolotl, if we don't understand how that works, bringing it to a human would be near impossible.

Dan Cohen: 28:13 Alex Lovely, thank you so much for explaining your research and it's exciting to think about that future.

Alex: 28:18 Thank you very much for having me.

Dan Cohen: 28:20 And thanks to Brian and Anastasia as well for joining us on What's New. And this wraps up our fall season at What's New. For all of us at the podcast I want to wish you and yours a wonderful holiday season. And we'll be back in early January with a new slate of new ideas and discoveries. It's been great to see the audience for this podcast grow over the last year. If you've enjoyed What's New, help us spread the word and give us some stars on iTunes. Which helps surface the podcast for others to see. I'm Dan Cohen, take care for now.

Dan Cohen: 28:53 What’s New is a production of the Northeastern University Library. With engineering by Jon Reed and production assistance by Evan Simpson, Debra Mandel, Jonathon Iannone, Debra Smith, Sarah Sweeney, and Brooke Williams. You can catch all of our episodes, show notes, and transcripts at whatsnnewPodcast.org. And we're available on iTunes, Google Play, and anywhere else you get your podcasts. You can follow us on Twitter @ podcastwhatsnew. We’ll love to hear your thoughts and feedback. I’m Dan Cohen, see you next time on What’s New.