Published on *Up Close* (http://www.upclose.unimelb.edu.au)

Episode 114: Growing bodily tissues: An engineering perspective

Growing bodily tissues: An engineering perspective

VOICEOVER
Welcome to Up Close, the research, opinion and analysis podcast from the University of Melbourne, Australia.

SHANE HUNTINGTON
I?m Shane Huntington. Thanks for joining us. The first successful kidney transplantation was performed over half a century ago and since then organ transplants of various types have come to be regarded as one of medical science?s more extraordinary achievements. Today organ transplants are performed in many hospitals with high rates of success yet the number of available organs for transplantation is still limited.
Many patients find themselves on long waiting lists with even greater numbers excluded from consideration due to a variety of factors. One alternative to donated organs is to artificially grow new organs in the laboratory using what is called tissue engineering, a relatively new research field.
To tell us more about tissue engineering and what it promises, we?re joined by Associate Professor Andrea O?Connor from the Department of Chemical and Biomolecular Engineering at the University of Melbourne Australia. Welcome to Up Close Andrea.

ANDREA O?CONNOR
Thanks Shane.

SHANE HUNTINGTON
Why don?t we start with what sort of issues would lead to a patient actually needing tissue regeneration or organ replacement?

ANDREA O?CONNOR
Sure. As you mentioned, organ failure is one of the areas where tissue engineering holds a lot of promise so people who might have a kidney failure, heart, lung, liver failure require replacement tissue and organs and these are very difficult to get from donors. There?s a shortage of donors and so a lot of patients miss out and may

actually die while they?re on the waiting list for that organ. As well as that there are patients who require new tissue after something like a car accident or cancer where they may have had surgery and so reconstructive surgery is something that we work on in particular with some plastic surgery colleagues at the O?Brien Institute at St Vincent?s Hospital here in Melbourne.

SHANE HUNTINGTON
Andrea, over the years the sort of knowledge surrounding organ replacements and the trust that that knowledge has also garnered in the community has enhanced, has there not been a corresponding increase in the number of donors that are available or is the number still way too low to deal with the needs of patients in hospitals?

ANDREA O?CONNOR
I think the numbers may have increased a little but the numbers are still much less than the demand. I think it?s something like a third of the patients on a waiting list may actually get a donor organ in time to meet their need. Then there are some organs for which donor tissue is not readily available. For example, if you want to treat diabetes, people with pancreas failure, the donation of tissue is just technically very difficult. So even if you have a donor organ that won?t necessarily treat that condition adequately from one donor to one patient.

SHANE HUNTINGTON
What are the remaining or lingering limitations in using donated body parts?

ANDREA O?CONNOR
The major issue is that it?s tissue from somebody else and so your body will recognise that that isn?t part of you and will try to reject that donated tissue. So patients with donated tissues typically have to take quite strong anti-rejection drugs and these have an impact on their life expectancy and can have fairly severe side effects. So they?re fantastic that it can work but tissue engineering holds out the hope that we may be able to actually make replacement tissue from your own cells and your own tissues and then you wouldn?t need the anti-rejection drugs so that would be fantastic.

SHANE HUNTINGTON
Before we get on to tissue engineering in your laboratory tell us how the body actually goes about building tissue itself and holding the individual cells together in the structures that form the various parts of our body.

ANDREA O?CONNOR
Well, it?s a fascinating process, the development of embryos, and there?s a lot of research around embryology and people trying to understand that process. Tissue basically comprises cells and there might be a few different kinds of cells in an organ or a piece of tissue and then lots of materials around that that hold those cells together and transmit the signals and keep them in the right environment.

SHANE HUNTINGTON

Outside of the body it?s a different scenario. The things that hold these cells together are not necessarily there. How do you go about that outside the body?

ANDREA O?CONNOR
It can be quite difficult to create the right environment outside the body. Traditionally a lot of cells have been cultured just on a plastic dish. So lots of cells will grow on a hard plastic dish like a Petri dish but that may not be the environment that suits their normal tissue growth comparable to what you would get inside the body. So one of the big areas for research and development is making materials that will help to mimic or copy the environment that cells would feel inside the body and that?s one of the things that we?re interested in developing as well.

SHANE HUNTINGTON
Do you need to generate some kind of scaffolding, some kind of super structure for the cells to grow into?

ANDREA O?CONNOR
That?s certainly one hypothesis and a lot of people are working on developing scaffolds and materials that will provide a ladder or a structure that cells can stick onto and grow and that works well for some cell types but not all cell types. Cells are very different and one of the things we find is that there?s not one solution that fits all tissue types that you might like to grow and so some cells will work like that.
The other thing that cells do is they lay down their own molecules, what?s called the extracellular matrix is the material that cells produce and like to stick to around themselves. So that is also laid down as cells grow and so you can get the cells to help with the process. Biology can help us out hopefully.

SHANE HUNTINGTON
When you?re putting together some of these structures and hoping the cells go in there and make a home for themselves, what kind of parameters do you have to consider in order for that structure to be appropriate for the cells or different cell types to make it their home?

ANDREA O?CONNOR
There?s lots of parameters that, as engineers, we can consider in designing the materials. There are things like, the chemistry is very important. So many biomaterials don?t look like a protein or another molecule that a cell would normally encounter in the body. So that?s one thing, getting the chemistry of the material right so the cells can actually adhere to that surface and will behave in the appropriate way.
Also, if you?re going to have a scaffold it will have holes or pores inside it, making those the right size is important so that the cells can get in and migrate and ideally get the right three dimensional environment. So they may need to be able to sense nearby neighbours, their other cells, so getting the pore size right. The other thing that is becoming clear increasingly is that the mechanics of that environment is also important. So whether the material is soft or hard can also influence the way cells behave so there?s a lot of parameters. There?s a lot of detail also in the chemistry

that I haven?t gone into but is important.
SHANE HUNTINGTON
So when you?re actually in the lab and you?re producing these materials, how do you go about controlling something like pore size, for example?
ANDREA O?CONNOR
There?s a wide range of ways that we can make porous materials so the kinds of materials we?re talking about might be ceramics like silica or hard materials if you?re trying to create bone or hard tissue. Or they might be polymers and there?s lots of technology already fairly well characterised about how to make foams out of these materials or porous structures. So just like the chairs that you might sit on have a foam inside them, we can use the same technology to make a foam out of a material that could be placed into your body.

But as well as that, an exciting new technology is 3D rapid prototyping where we can actually use printing technologies to produce three dimensional objects and that?s something that we?re investigating now.

SHANE HUNTINGTON
It sounds very interesting. When you look at the materials that you?re using, is there a trade-off between them being functionally appropriate and able to be put in the body? Do they have to be biodegradable to break down in the body or can they stay there forever?

ANDREA O?CONNOR
Certainly there are medical devices that are designed to stay there forever but in tissue engineering what we?re aiming to do is end up with only a healthy piece of tissue at the end. So we would like the materials to be biodegradable, to be able to be naturally broken down and ultimately the by-products to be excreted from the body. So controlling that degradation process is very important and it?s not enough to just have the right conditions at the start of the implantation. You need the right behaviour right throughout that degradation process and that can be very challenging to design and predict. There?s a lot of parameters involved in all of this.

SHANE HUNTINGTON
This is Up Close, coming to you from the University of Melbourne, Australia. I?m Shane Huntington. Our guest today is Associate Professor Andrea O?Connor and we?re talking about tissue engineering.
Andrea, when you engineer artificial tissues, how do you go about dealing with the required blood supply in order to keep those tissues alive once they?re put in the body?

ANDREA O?CONNOR
You?ve hit on one of the biggest challenges for the field there Shane.
Vascularisation and the formation of blood vessels is key to being able to produce particularly tissues that are three dimensional. So something like a piece of fat or muscle or a piece of organ needs a blood supply. Even if you can produce a piece of tissue in a dish in the laboratory or a bioreactor, getting that to connect to the

patient?s blood supply is a big challenge. So one of the strategies is rather than producing that tissue in the laboratory and then transplanting it is actually to try and create the environment in the body to help the body grow that tissue in vivo, in the patient themselves, so using the human body like a bioreactor, getting the body to do some of the work because the biology works so beautifully at its best.

SHANE HUNTINGTON

If you were to look at a particular organ and the sort of scaffolding needed to grow a large part of that organ, how big does the scaffold need to be? Does it need to take up the entire area where you want the tissue to be or does the tissue tend to take over its own task of growing on itself after a time?

ANDREA O?CONNOR

You need to provide a space that is of the size that you want the tissue to grow so typically tissue will not grow if there?s not a space provided. So you need either a scaffold or a free space where tissue has the potential to grow. Yes, if you want a certain size piece of tissue you will need to provide some space or scaffold of that size.

SHANE HUNTINGTON

When you start with the scaffold, what actually makes the cells want to grow there? What?s the formation process of the tissue that works on the particular scaffold compared to other parts of the body?

ANDREA O?CONNOR

There are a number of factors at play. Cells sense their local cell density so we?ve done some work on cell migration and cells will move from a region that is crowded and high density - lots of cells close to each other - into a region where there is a lower cell density if the environment is favourable. So if you make a scaffold or an environment where it is cell friendly, it?s biocompatible and the cells are happy in that environment, they?re getting suitable signals, they will tend to move from high density to low density regions.

Of course, you can do things to encourage that like putting particular molecules into the environment that encourage cell migration. So in our body there are molecules that send signals to cells to move so we can use those maybe to help us to get cells to migrate in and things like lack of oxygen sends signals to cells that blood vessels are required. So there?s complex feedback already in the body to help cells sense and respond to that.

SHANE HUNTINGTON

You can use those to presumably trick the cells artificially to do the sort of task faster that you?re asking them to do?

ANDREA O?CONNOR

You can use them to your advantage in some cases, yes. So the natural wound-healing process, if you cut yourself, involves a wide range of cells migrating to that wounded site and we?re really trying to use the same wound-healing processes in tissue engineering. Of course, if you don?t simply want scar tissue to form you need to have the right environment to get a different kind of tissue to grow and that?s where some of the complexity comes in.

SHANE HUNTINGTON
Does this bring into the picture the possibility of very rapid wound healing in addition to just repair?
ANDREA O?CONNOR
There?s certainly research in that area. There are people looking at molecules that might encourage wound healing and wound repair. There?s always a caution though that if you try to play with biology and modify that too much you might have adverse effects. So some molecules which will help with wound repair could also potentially be carcinogenic if used in the wrong way so we need to be very cautious and I think the body?s natural speed of tissue growth is not something that we can probably alter particularly much.

SHANE HUNTINGTON
When it comes to that growth, how well do the techniques you?re using in the lab in the dish as it were, translate into the body? Do they translate across very cleanly, use the same techniques, the same chemicals or is the body kind of your enemy in that regard?

ANDREA O?CONNOR
I think you need to design the processes that you use with the body in mind so good research in this field would always look at what will happen in the body and how do we optimise things to be used in the body. As we talked about, blood vessel formation is one of those key challenges, so getting that connection and the blood vessel supply so that the cells will have enough oxygen and it?s one of the problems in the field that a lot of research has been done in the dish, in the laboratory in vitro that doesn?t necessarily represent what will happen in vivo. So it?s a big challenge for researchers in the field to try and predict what will happen from what we do in the laboratory to what happens in the body.

SHANE HUNTINGTON
That leads well into my next question which is how do you go about modelling the way in which these things will work in the body before you actually start creating them?

ANDREA O?CONNOR
That?s a very big challenge for us. We work with a number of mathematicians here in the Department of Mathematics and Statistics with Kerry Landman and Barry Hughes in mathematics to model cell migration, cell movement and tissue formation. So we can use mathematics to help us try to understand the transport of molecules like oxygen and the movement of cells, the growth of tissue. We also do a lot of laboratory tests to try and screen and understand as well as we can how materials and cells will interact together. So there?s a lot of screening that goes on to try and test that but ultimately we need, at this stage, to test things in vivo so we also use animal models to do that before we can gain the confidence and the knowledge required to be able to test these things in people.

SHANE HUNTINGTON

How well do those models line up with the in vivo studies? Are they good at predicting the way in which these scaffolds and these building blocks of the tissue work?

ANDREA O?CONNOR
They work well in some circumstances but I have to say that there are gaps in the ability currently to predict exactly what will happen in vivo. When you have such a complex system and the interplay between the material, the cells, lots of signalling going in the local environment where the tissue is growing and also throughout the body. It is very difficult to predict that so there is a challenge there for researchers to try and improve the in vitro or laboratory testing so we can predict better what will happen in vivo.

SHANE HUNTINGTON
There is obviously quite a difference between the importance of certain organs in the body relative to others and what they mean for our life expectancy. Is there a corresponding drive in your research area towards particular types of tissue that would be needed in those organs in the body?

ANDREA O?CONNOR
There?s interest in almost every tissue in the body in terms of development and one of the things that has driven progress in the field is really about which tissues are more difficult or easier to engineer. We would love to be able to engineer all of the organs of the body but it is very challenging and so areas like bone and cartilage are relatively well developed because they can be engineered with a lesser blood supply so that makes it a little bit easier.
Skin has also been well developed. There?s a high demand for replacement skin for victims of burns and ulcers and skin is relatively thin so getting the blood supply to that tissue is not so difficult.

SHANE HUNTINGTON
I?m Shane Huntington and my guest today is Associate Professor Andrea O?Connor. We?re talking about tissue engineering here on Up Close, coming to you from the University of Melbourne, Australia.
Andrea, how do we actually in the laboratory, go about studying the way the cells do interact with each other? You indicated that they communicate in a variety of ways. How do you determine that?

ANDREA O?CONNOR
One of the things that we do is we do live cell imaging so we place cells onto surfaces of different materials that we?re interested in. We might include different molecules that we want to test the response of and then we put that under a microscope in a controlled chamber so we make the environment the right temperature and a gas environment for the cells and then we watch what happens. So we?ll look at things like how close packed are the cells, how are they moving. We use image capture on our computers to track the movement of the cells and then we can feed that data into our mathematical models to see how quickly the cells are

moving and what differences occur when we change something about that environment.

SHANE HUNTINGTON
How do you simulate a wound, for example, in that scenario?

ANDREA O?CONNOR
Well there?s a simple thing called a wound-healing assay where we simply grow cells on a surface and then scrape some of them away. So then we have a region where we have a high density of cells and another region where the cells have been removed and we watch those cells move back into the area where they were scraped away.
SHANE HUNTINGTON
When you start putting these structures into the body how does the body actually respond? We know how it responds with some donated organs. We need to put people on drug regimes to keep them healthy but how does it respond to this sort of engineered tissue?

ANDREA O?CONNOR
There can be a wide range of responses and we have a lot of experience of using biomaterials in the body largely in the form of degradable sutures or dissolving stitches that many people will be familiar with. So there?s a lot of history of using these kinds of simple biomaterials in the body and you can get fantastic results but one of the problems that does arise is what?s called the foreign body reaction. Our body is quite good at recognising something that doesn?t belong and will tend to form a capsule around that. It tries to wall it off and stop it interacting with the rest of our body and that can really thwart tissue engineering objectives so it?s a big challenge to get the right reaction. We need to design the materials carefully with that in mind.

SHANE HUNTINGTON
I assume that?s a type of inflammation that the body puts out. Is that something that damages the tissue itself that you?re putting in the body?

ANDREA O?CONNOR
It can restrict the transport of molecules and cells to that. So if we place a piece of plastic, a polymer, into the body and the body recognises that as foreign there?ll be an inflammatory response. Cells will be recruited from around the body via the blood supply and chemical signals that are sent out and it tends to make a lot of collagen. So it makes like a bag around that object and then other cells can?t get in and out very readily so that can really be an adverse outcome. If you want to grow a healthy piece of tissue that will integrate well into the body that foreign body reaction can really stop you doing that.

SHANE HUNTINGTON
Are there any particularly interesting new materials that your group is using to get past this particular problem?

ANDREA O?CONNOR
We?re doing a lot of surface engineering around that problem so we?re keen to use materials that have some history of being used successfully in the body because new materials are being developed certainly by researchers but it takes a very long time and a lot of testing to get those approved for clinical application. So one approach we?ve taken is to use some of these established materials but to engineer their surfaces, to modify their surfaces in clever ways that can trick or change that response in vivo. So we lay down different molecules that naturally appear in the body on the surface of a biomaterial and that can change the way cells interact so we can turn off or turn on the cell binding to a biomaterial and we can also incorporate molecules that will be gradually released from the material and effect its response in vivo.

SHANE HUNTINGTON
Are the cells you?re using from the patient?s own body in the first instance?

ANDREA O?CONNOR
That will be the goal. So ideally, if a patient doesn?t have any underlying medical condition that would stop you doing that, you would like to use autologous cells, so cells from the patient themselves. Then you don?t have the problems of rejection so the beautiful idea of tissue engineering is that you could take a small biopsy, a small number of cells from a patient, take those to a laboratory and grow them so you get more tissue or more cells and then use those to create the new tissue for the patient and it?s a natural part of them.

SHANE HUNTINGTON
In the case where you would like to use the person?s own cells to start to generate tissue but it?s a problem with their cells that has caused the failure in the first place, where do you go to from there?

ANDREA O?CONNOR
There are certainly some medical conditions that would mean you can?t use the patient?s own cells, that wouldn?t be a safe or effective treatment for them, then you can get donor cells or donor tissues. Instead of having to require a complete organ you might be able to work from a very small donor piece of tissue and you would do tissue typing and tissue matching just like we do with blood donations to try and minimise the differences there.

SHANE HUNTINGTON
Is there a distinction between the area of tissue engineering and what?s called regenerative medicine?

ANDREA O?CONNOR
They?re very similar and closely related so regenerative medicine is a field that has attracted a lot of attention and tissue engineering is a form of regenerative medicine really where people are trying to engineer new tissues, using cells and biomaterials and some of these strategies in the laboratory and in the patient to grow new tissue.

SHANE HUNTINGTON
Andrea, when we?re talking about growing organs essentially, I know a lot of our listeners would be questioning some of the ethical scenarios that may come to pass as a result of that. Can you speak to what they might be and how we would go about addressing those ethical concerns?

ANDREA O?CONNOR
Certainly the ethics are a significant concern, I think with donor organs, donor tissues, stem cells and certainly tissue engineering. It?s something that we have very much at the forefront of our minds and all of the research that we do involving animals or moving to clinical trials requires ethical approval. So we go through the ethics panels of the university and the hospitals where we work and have to give a lot of consideration to the ethics of every step that we take that the work is well justified. So some of the challenges you might have are the sources of donor tissue, the sources of stem cells.
There?s a lot of exciting work in the area of stem cells where the induced pluripotent cells, you might have heard of - or IPS cells - are showing a great potential and might be an alternative to embryonic stem cells, so maybe could avoid some of the challenges of the ethics of using certain kinds of stem cells. But in creating organs, there are very many ethical issues but there?s also a great potential to help patients and I think people may hopefully recognise that that would be a justified outcome.

SHANE HUNTINGTON
Is this sort of work owned by anyone in particular or is it part of the greater knowledge of the research community?

ANDREA O?CONNOR
It?s an area where there?s a lot of entrepreneurship. There?s a lot of people involved internationally in commercial development so there are a lot of patents in this field and it?s one of the challenges for doing research in this area that a lot of the technologies around bioreactors and biomaterials and strategies you might use are covered by patents internationally. There?s a lot of quite aggressive commercial development in the field so that?s a challenge.

SHANE HUNTINGTON
Associate Professor Andrea O?Connor, Department of Chemical and Biomolecular Engineering at the University of Melbourne, thank you for being our guest on Up Close today.

ANDREA O?CONNOR
Thanks Shane.

SHANE HUNTINGTON
Relevant links, a full transcript and more info on this episode can be found at our website at upclose.unimelb.edu.au. Up Close is brought to you by Marketing and Communications of the University of Melbourne, Australia. This episode was recorded on 8 September 2010. Our producers for this episode were Kelvin Param

and Eric van Bemmel. Audio engineering by Gavin Nebauer. Background research for this episode conducted by Christine Bailey.
Up Close was created by Eric van Bemmel and Kelvin Param.
I?m Shane Huntington. Until next time, good-bye.

VOICEOVER
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