Nature Podcast

Introduction

This is a transcript of the 3rd May 2018 edition of the weekly *Nature Podcast*. Audio files for the current show and archive episodes can be accessed from the *Nature Podcast* index page (http://www.nature.com/nature/podcast), which also contains details on how to subscribe to the *Nature Podcast* for FREE, and has troubleshooting top-tips. Send us your feedback to podcast@nature.com.

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Interviewer: Benjamin Thompson
Welcome back to the *Nature Podcast*. This week on the show, we'll be learning how to build an early embryo, and finding out how mice react to danger.

Interviewer: Adam Levy
Plus, what ancient rhino remains are teaching us about hominin history. This is the *Nature Podcast* for the 3rd May 2018. I'm Adam Levy.

Interviewer: Benjamin Thompson
And I'm Benjamin Thompson.

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Interviewer: Adam Levy
In mammals, when a sperm cell fertilises an egg they merge forming a structure called a zygote. The zygote then divides into 2 cells, then 4, 8, 16 and 32, at which point it's known as a blastocyst. Blastocysts are of great interest to developmental biologists, but they are difficult to study, not least because harvesting the relatively rare embryos at the right stage of development is tricky, even in mice. Enter Nicolas Rivron. He and his team decided not to harvest blastocysts for study, but to make them instead. Reporter Noah Baker called up Nicolas, who started with an overview of the blastocyst itself. And, just a heads-up listeners, there's some background noise in this interview. Nicolas was in a somewhat busy hotel lobby in Nepal when Noah spoke to him.

Interviewee: Nicolas Rivron
The blastocyst is the very early mammalian embryo, and this is a structure that has an outer thin layer that is called a trophectoderm and that is going to form the whole placenta. And inside there is a cavity, a fluid-filled cavity, and within this cavity there is about 10 cells that are going to form the whole embryo.

Interviewer: Noah Baker
And at this stage most mammals, or if not all mammals, look relatively similar?

Interviewee: Nicolas Rivron

That's correct, it's quite surprising. However, when you look more in details at the molecular level, there are quite some differences.

Interviewer: Noah Baker
And you were interested in studying the blastocysts, but you decided you were going to take a very different route.

Interviewee: Nicolas Rivron
Yeah, we took a little step aside, because I'm actually not a biologist, my background is in polymer physics, and in tissue engineering we always have the idea that we can build stuff. So, what we did, is to reconstruct the blastocyst from the bottom up using stem cells.

Interviewer: Noah Baker
Now that seems like really impressive, sort of, levels of engineering, but it's actually quite simple in terms of the cells that you use. You started off with two types of cell.

Interviewee: Nicolas Rivron
Stem cells have a tremendous capacity to self-organise into all kinds of mini organs, and we call those mini organs organoids. However, it was never really achieved to do this for embryos, and so what we did, is we mixed two types of stem cells. The first one is the famous embryonic stem cells, and the second one are called trophoblast stem cells, and these are the cells that are on the outer of the blastocyst, and that are going to form the whole placenta. And, by finding the right conditions, we could just pull those cells together and they spontaneously organised into what we called a 'blastoid'.

Interviewer: Noah Baker
You mentioned that you had to get the conditions just right to make these two stem cell lines sort of self-organise into the blastoid. What kind of conditions are we talking about?

Interviewee: Nicolas Rivron
Yeah, this is the key question, and this is what we've been working on for a couple of years, and it was hard. But there are two elements that were key at the end, the first one is to be able to pull a very small number of stem cells together. Once you have pulled those right number of stem cells, you must find the exact cocktail of proteins and small molecules that is going to trigger the reaction. And, in order to do this, we looked into all the molecules that are expressed in the blastocyst, we looked back into everything that was discovered previously, and we made a list of, you know, potential candidates. But then after, you have to like, find exact cocktail.

Interviewer: Noah Baker
The blastoid that you created – what does it look like if you were to look at it under a microscope? How similar is it to the blastocyst and where does that similarity end if you look at it on a molecular level?

Interviewee: Nicolas Rivron
It is actually remarkably similar to a blastocyst when you look at it under a microscope. We played the game of like trying to differentiate a blastoid and a blastocyst, and it is not an

easy game, you know. However, it is clear that the deeper you look, the more you see small differences.

Interviewer: Noah Baker
What you've created here is not a blastocyst, it resembles a blastocyst, it's a blastoid, is what you're calling it. And this isn't going to be able to grow into a fully-fledged foetus.

Interviewee: Nicolas Rivron
So, at this point we don't know. Because we formed this blastoid, we were able to transfer it back into the uterus of a mouse and this is the most stringent asset that can be done in order to test the potential of those blastoids. And, at the moment they implant very nicely into the uterus of mice, and they proliferate, multiply, differentiate from all kinds of cell types that are very irrelevant. However, it's not properly organised, so we know that it has probably the potential of doing it, but we are still missing some elements here.

Interviewer: Noah Baker
What really interests me here, is that you're constructing the progenitor of an entire organism using cell lines which have been independently grown and put together again. This seems like it has some pretty fundamental ethical questions here.

Interviewee: Nicolas Rivron
One of the questions is actually, whether or not those blastoids should be considered as embryos or not. And we are discussing this with philosophers at the moment, philosophers and ethicists, and it is not clear whether this type of structure should be falling under the lo of an embryo, or if it should just be considered as kind of nice tool, in order to answer scientific questions in the lab.

Interviewer: Adam Levy
That was Nicolas Rivron. He splits his affiliation across two institutions in The Netherlands: The Merlin Institute for Technology-Inspired Regenerative Medicine, and the Hubrecht Institute for Developmental Biology and Stem Cell Research. To read his paper, head over to nature.com/nature.

Interviewer: Benjamin Thompson
So, this week in *Nature*, a discovery from the island of Luzon in the Philippines sheds new light on when ancient hominins first got to the country. Our story begins a long time ago, in an area now known as the Cagayan Valley, as first author Thomas Ingicco from the National Museum of Natural History in France explains.

Interviewee: Thomas Ingicco
You have to imagine that once, there used to be a river flowing in the area. Now it's quite arid, it's quite a dry area, it's full of grass. And if you have a river, then you can expect fauna to come to drink there, and also you will find pebbles that are suitable for making stone tools. Once upon a time, a rhino died there, we don't know how, but we know it died, and there it was butchered.

Interviewer: Benjamin Thompson

Now, ancient tools and the remains of megafauna have been discovered in this area before, but their exact age was ambiguous, as many were found on the surface of the ground. To get an idea of how old the hominin population in the area might have been, Thomas and his colleagues needed to find evidence buried within the sediment that could be dated. So, the team started to dig.

Interviewee: Thomas Ingicco
So, we started the excavation, and it was a 2-by-2 square pit, and at about 1-metre-20, we found the tooth of a rhino, right. And so, we decided to extend a bit the square, that was in a clear sedimentary context, and then we found the very first stone tool, in the very same layer. So, little by little we decided to extend the excavation which is now 16 metres squared, and that's where we found, actually, an almost complete skeleton of a rhinoceros. The bones were not connected to each other, but all the bones were there in this small area, and around this skeleton were stone tools.

Interviewer: Benjamin Thompson
This rhino was a member of the now extinct species *Rhinoceros philippinensis*, and its skeleton and the stone tools were secured in a layer of clay sandwiched between two layers of sand.

Interviewee: Thomas Ingicco
That was the very first time we could see direct evidence that hominin species was there by the time rhinos were roaming around in the Philippines.

Interviewer: Benjamin Thompson
While the rhino's cause of death is unknown, Thomas thinks he knows what happened to it shortly afterwards.

Interviewee: Thomas Ingicco
We found on the surface of the bones, several marks of butchery activity, so cutting marks on the surface of the bones that have the thinnest amount of flesh, so these are the ribs, for example, because you have to imagine that this rhino could have a large amount of flesh on some of its bones. And also, once the rhino carcass was partly de-fleshed, some of the bones have been intentionally broken, and most likely with the idea to get access to the marrow.

Interviewer: Benjamin Thompson
The team were able to get an estimate of how old the rhino skeleton was, by dating the sediment sandwich where the bones were found, along with one of its teeth. They estimate that the rhino died around 709,000 years ago when hominins were there to butcher it. Until this discovery, the oldest dated evidence of hominins in the Philippines came from a single foot bone that was found in a cave and has been dated back only around 67,000 years. The Philippines isn't believed to have ever been connected to the mainland by land bridge, so how did these hominins get there? Some water crossing will likely have been involved.

Interviewee: Thomas Ingicco

How did they cross those sea barriers is a big question. We suspect that such an old humanity was not capable of sailing, of mastering navigation. But you also have older hypotheses that have been raised in the past for reaching such distant islands, after a typhoon you can have some part of the coast that is disconnected from mainland, and that will float for days, and allow some species that are on this floating island to reach new and pristine lands. That's another hypothesis.

Interviewer: Benjamin Thompson
And there are more questions too. The team behind the work don't know what species of hominin might have made the stone tools, for example. Although they have found a lot of bones from different animals at the site, including deer, turtle, and an ancient elephant relative called the stegodon, so far, they haven't found any hominin bones. The site is still being excavated, and maybe if more remains are uncovered, we'll get some answers about who butchered a rhino beside the river more than 700,000 years ago, and maybe even how they got there. In the meantime, you can read Thomas' paper over at nature.com/nature.

Interviewer: Adam Levy
Coming up in the show, we'll be talking about plans to build virus-proof human cells. That's in the News Chat. Right now though, here's a quick public service announcement. If you listen to the *Nature Podcast* over at nature.com/nature/podcast, you'll be noticing some changes as we're currently updating the site. Of course, website updates always do go perfectly smoothly, but on the off chance that you do experience any technical issues, drop us an email on podcast@nature.com. Right, back to the show now, and Shamini Bundell is here with this week's Research Highlights.

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Interviewer: Shamini Bundell
A world distance migration record has been set by a whale shark named Anne. A team of researchers tagged Anne, a 7-metre-long filter-feeder off the coast of Panama in 2011, before tracking her for over 20,000 kilometres as she travelled from the Eastern Pacific across to an area near the Philippines. Much of Anne's journey followed the North Equatorial Current, and her tags last transmission came from the Marianas Trench, 841 days after she set off. The authors hope that Anne's epic journey will shed new light on the complexities of protecting endangered animals with long migration patterns. Journey over to *Marine Diversity Records* to read more.

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Interviewer: Shamini Bundell
And in other feats of endurance news, by some measures children might be fitter than elite athletes, according to a group of researchers in France and Australia. The team compared three groups – university students, endurance athletes and 8-to 12-year-old boys, and found that after a period of strenuous cycling, the children's heartrates returned to normal the fastest. They were also able to eliminate lactate, a by-product of strenuous exercise, from their blood faster than the adults. This work may help us understand how metabolism

changes from childhood to adulthood. If you have the endurance, you can exercise your brain reading the full paper at *Frontiers in Physiology.*

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Interviewer: Benjamin Thompson
Adam, what's the scariest thing you can think of?

Interviewer: Adam Levy
Showing up at my PhD viva unprepared and naked.

Interviewer: Benjamin Thompson
Oh, you've had that dream as well?

Interviewer: Adam Levy
Yeah, I think it's ubiquitous among our type.

Interviewer: Benjamin Thompson
Well, there are lots of scary things in life listeners, and for a researcher studying fear, figuring out what scares people is quite important, but that's just a start. Andrew Huberman wants to understand the neural pathways involved in the brain's response to scary situations. Here's Shamini again, who called him up to find out more about his latest piece of research.

Interviewee: Andrew Huberman
The focus and topic of this study is to really try and understand how we make decisions about what to do when we are confronted with threats or scary things. How does the brain take what it sees in the outside world and combine that with what we call our arousal state, which is our kind of level of stress in the body, in order to make good decisions about what to do.

Interviewer: Shamini Bundell
And this brain response to threats of fear only something that applies to life-and-death type situations?

Interviewee: Andrew Huberman
So, you can image this in a variety of contexts. For instance, somebody who has some social anxiety walking into a crowded room full of people and having to socialise. There's things like confronting somebody to tell them something challenging, or to ask for something you're afraid to ask for. Now that person that may or may not be threatening you physically, but it increases your autonomic arousal, meaning heart rates, sweating, pupil size – they all increase.

Interviewer: Shamini Bundell
And, you studied this kind of fear response in an animal model so you could study what was actually going on in their brains during it.

Interviewee: Andrew Huberman
Yeah, we took a simple paradigm of exposing mice to a simulated aerial predator. So, mice are very afraid of expanding dark things coming in from above because that evokes the same feelings as a predator coming in to eat it. And so, we put mice into a chamber and exposed them to expanding black dots, and the mouse would typically freeze or run, and then we used some molecular tricks and genetic tricks to ask which areas of the brains became most active under those conditions. And so, we were excited to discover this brain area which essentially includes two output pathways, and one of the output pathways we discovered when we selectively activated it, made the animals more fearful. The other caused the mice to be really confrontational, they would wander right out in face of the threat, they would even rattle their tail which for a mouse is kind of a threatening almost like chest-beating response, saying 'come and get me let's fight'.

Interviewer: Shamini Bundell
And now that you've identified these brain pathways and the key areas involved, you can apply that to humans?

Interviewee: Andrew Huberman
That's right. So, we have a human lab in which we can expose people to different types of threatening scenarios using virtual reality, and we're monitoring these brain areas in so-called 'normal' people, or typical people as well as in people who have generalised anxieties or phobias to particular types of visual threats like heights or spiders or snakes or social stressers. So, we're doing all that, and we're also looking in patients to try and figure out, you know, how is it that we can manipulate this circuitry to try and ameliorate some of these really debilitating conditions.

Interviewer: Shamini Bundell
And aside from highlighting the relevant brain areas and pathways, what have you learnt from this mice-work that could apply to humans?

Interviewee: Andrew Huberman
Yeah, so in addition to telling us where some of this might be occurring in humans, the mouse-work gave us some really interesting insights. The first one I would say is that this brain area when it's stimulated, it makes them feel good in a sense. When the animal confronts the stress that arousal state becomes reinforcing, and this, I think, is an extremely valuable piece of data because it tells us that threat confrontation, provided there's an adaptive outcome, is actually a positive experience for the nervous system.

Interviewer: Shamini Bundell
And is that why fear can be enjoyable? People go to see scary movies because it's fun.

Interviewee: Andrew Huberman
Right, the arousal that people experience when they go to see scary movies is positively reinforced because they always survive.

Interviewer: Shamini Bundell

So, if you're experiencing the fear, but then you're not actually getting hurt, then that gets rewarded in your brain. And then on the other side, if you're experiencing fear and so you avoid something and then you don't get hurt, that also gets rewarded, which is probably useful for a survival mechanism, except when it starts sort of reinforcing fears too much and maybe even turning into phobias.

Interviewee: Andrew Huberman
It makes logical sense when you think about it that way, that these brain areas don't know the difference between good and bad. They only know whether or not outcomes were good and bad, and they reward good outcomes, and they essentially punish bad outcomes by, you know, if you confront somebody and they shoot you, that's a bad outcome, that's not adaptive. And then the last thing I think is really interesting in light of phobia and PTSD, is that this brain area shows reduced activity as you expose an animal to a threat over and over. So, when you expose an animal to a threat repeatedly, eventually the animal or the human has a kind of relaxed response to it, it habituates as we say, doesn't have as much of an impact. Like, imagine seeing a scary movie 5 or 6 times – it just doesn't have the same impact as it does the first time. And so, we wonder whether or not over-activation of this brain area might be what's going on in people that have things like phobias or PTSD, that this area fails to habituate.

Interviewer: Shamini Bundell
And so, what's the next step of moving this research on to actually apply what you've found to people?

Interviewee: Andrew Huberman
We've spent the last year building a human equivalent to the mouse study and the goal of this work is to really understand not just how fear and where fear occurs in the body, but to understand how is it that we can encourage adaptive confrontation to these fears. We definitely don't want to cure fear, fear is a healthy response. We want to make people more adaptive in the face of fear so that they can lead better, more complete lives.

Interviewer: Benjamin Thompson
That was Andrew Huberman of the Stanford University School of Medicine talking to Shamini Bundell. We've got more on this story over at nature.com/nature, with a News & Views article and the original paper. If you'd like to see what the flight, fright and freeze response looked like in these mice, we've got a short film. That's over at youtube.com/naturevideochannel.

Interviewer: Adam Levy
Finally, this week it's time for the News Chat, and Features Editor Richard Van Noorden joins us here in the studio. Hi Richard.

Interviewee: Richard Van Noorden
Hi Adam.

Interviewer: Adam Levy

Now first up, there's what sounds like a very ambitious plan to synthesise the human genome. This plan's been around a little while I believe, but what are they actually originally hoping to do?

Interviewee: Richard Van Noorden
Yeah, this effort launched in 2016 called Genome Project-Write, as opposed Genome Project-Read. It's a public-private partnership with around 200 scientists and originally, they wanted to make from scratch, all of the genes in the human genome. And the intention of that was to essentially improve DNA technology, to sort of showcase what you can do, you could build the whole thing from scratch. And it sounded very, very ambitious, and our news story this week is saying that, well yeah, instead of making 3 billion DNA base pairs, we're going to scale it back and instead they're going to do, they want to do something very ambitious, which is to create a human cell and its genome is recoded or edited so that the cell cannot be infected by viruses.

Interviewer: Adam Levy
Wow, so it really seems like they've lowered their ambition dramatically – just a virus-proof human cell.

Interviewee: Richard Van Noorden
Yeah, just that, just that, easy, ey? So that's incredibly difficult, and the point of this? Well, it does have an application because you grow vaccines in human cells, and you make antibodies and other biological drugs in human cells, in theory there could be viral contamination during the production process. So, if you could make a cell that couldn't be infected by viruses, you would get rid of that problem. So, it has an application but really the backers of this project say, our main goal is still to kind of show case how we can do this cheaply and efficiently. Now, the problem is that they still don't probably have nearly enough money to get this going, and it's beginning to sound like a group of scientists want to show off what DNA gene synthesis can do, and they're wanting to sort of get the whole field together in something really ambitious, but they really don't have enough money to get going on it yet.

Interviewer: Adam Levy
How much money are we actually talking about? How much money does it cost to make a virus-proof human cell?

Interviewee: Richard Van Noorden
It's probably going to cost tens, if not hundreds of millions of dollars, and it could last a decade or more, so it's a lot of money. Now, George Church, a very famous genome scientist at Harvard Medical School, he is behind this project and he says, ah, we've already got more than $5,000,000 in related funding. Slightly weasel phrase 'related funding', he's including some of the money he's got in grants for his own work on synthetic biology. He's also including a lot of investment money raised by loosely affiliated biotech companies, some of which George Church is a shareholder in, so. And some of these companies, like Ginkgo Bioworks haven't actually been active in this idea, this GP-Write project at all, and they said they were rather surprised to see that Church included them on his list of funding. But, regardless of the money, just making a cell line that viruses can't infect is itself

extremely difficult. So, Church's lab before now has taken *E. coli* bacteria, and they tried to recode the genome to make that bacteria resistant to viruses. So, a virus came in, the cell could no longer assemble that virus, so this is recoding, and that's what this project is going to try and do for the human genome. Unfortunately, that will require hundreds of thousands of changes of DNA, and that's why this team says well why don't we just synthesise large bits of the genome, rather than taking an existing cell and edit 100,000 letters one by one. So, it makes sense what they hope to do, but as you can see it's very ambitious.

Interviewer: Adam Levy
I feel like we keep coming back to that adjective ambitious. Certainly, I mean, they want it to be ambitious, they seem to have found an ambitious project to work on.

Interviewee: Richard Van Noorden
Yeah, to be fair to them, other synthetic biologists like the priority shift. They say it's a terrific idea, and it is more geared towards applications, it's not just DNA synthesis for its own sake. So, they like the way this has shifted.

Interviewer: Adam Levy
So, next up we've got some news from the European Union, and it's some pretty good news if you're a bee. Now, what's the news regarding bees coming from the EU?

Interviewee: Richard Van Noorden
Yeah, so last week the European Union voted to ban three very common pesticides because they harm bees, and by ban they mean that you can't use them outdoors at all. You can use them in greenhouses, but not outdoors. So, scientists have just generally welcomed this, which has followed years of debate about the risks that these pesticides called neonicotinoids pose to bees. And, by now it's pretty clear that three of these neonicotinoids can cause some serious harm to bees, can cause them to lose their way when they're foraging for nectar and food, and various studies have shown that even outdoors in fields, bees are affected by neonicotinoids which are used to treat seeds.

Interviewer: Adam Levy
I think a lot of our listeners will have heard of the potential damage these pesticides can cause bees, and heard about it really, quite a few years ago. Why has it taken so long to get from that stage to actually having this ban?

Interviewee: Richard Van Noorden
Well, scientifically it's been a bit unclear. Back in 2013, the EU imposed a temporary moratorium with some exceptions, and part of the difficulty was not just showing this in the lab, but showing this outdoors in the field. And to show that these neonicotinoids cause damage to bees outdoors, you've got to have a lot of fields, coat some seeds, wait for months to see what the effect is on bees the next year, so it did take some time for the science to come in, and some of that science was sponsored by the companies themselves. And, to be fair, the companies and farmers are quite angry about this, and they're still arguing about it, and some scientists said well, this is great news. But these neonicotinoids might just be replaced by similar compounds or more harmful ones because farmers have

gotten used to using pesticides to protect their fields. And it took a long time to show that these chemicals harm bees, well, what about their replacements, or other ones that are coming on the market? So, some biologists are saying, you know, okay we can ban these one by one, or three by three, but we need to move to new farming methods that minimise pesticide use, and encourage natural enemies of crop pests and support biodiversity.

Interviewer: Adam Levy
Bees are obviously amongst the cutest insects, but why do they actually matter for farming, for humans?

Interviewee: Richard Van Noorden
Well, by pollenating wild plants and flowers, they effectively underpin biodiversity because they help maintain the habitats that other species need to flourish. And they also underpin food production and generally the environment, so they are kind of seen not just iconic, but also a keystone species for the environment.

Interviewer: Adam Levy
Well we managed to make our way through that story without any awful bee puns, so we should both be very proud of ourselves. Thank you, Richard, for joining us, and for more on both those news stories, head over to nature.com/news.

Interviewer: Benjamin Thompson
Well, listeners, that's it for this week's show, but before we go I just wanted to flag up a new film that *Nature* has made, well, specifically that Adam has made. Adam, maybe you can tell us a bit more about it?

Interviewer: Adam Levy
So, this is a short documentary that is to tie in with a written Feature that's also been published in *Nature* this week, and it's following on from the 2016 peace treaty between Colombia and several guerrilla groups which have been fighting in Colombia for decades, actually. And it's looking at how fighters can be reintegrated into society after fighting, well, for years.

Interviewer: Benjamin Thompson
And you spent a bit of time out there as well, speaking to the folks involved?

Interviewer: Adam Levy
Yeah, so, the documentary features interviews with ex-combatants as well as with academics who are hoping that their research can have a positive influence on this reintegration process. And this trip was enabled by a grant from the Pulitzer foundation.

Interviewer: Benjamin Thompson
Well listeners obviously, I'm biased, but I do think it's a great video, and you can check it out at youtube.com/naturevideochannel, and for the accompanying Feature, that's over at nature.com/news. We'll be here again next week with more stories from the world of science. I've been Benjamin Thompson.

Interviewer: Adam Levy
And I'm Adam Levy, thanks for listening.

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