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00:06 Sarah Crespi: Welcome to the Science Podcast for June 28th, 2019. I'm Sarah Crespi. In this week's show, I first talk with staff writer Kelly Servick about the difficulties of making animal chimeras by adding stem cells from one animal to the embryo of another with the ultimate goal of growing organs. And I talk with Yossi Yovel about how even though bats can detect a lot about the world around them using vision and echolocation, we're just learning now how they switch between these senses and why. And for this month's book segment, books editor Valerie Thompson talks with Lucy Jones about her work translating climate data into song.

00:52 SC: Now, we have Kelly Servick, staff writer for Science. She's here to talk to us about making chimeras from different animals. Hi, Kelly.

01:00 Kelly Servick: Hi Sarah.

01:00 SC: Okay. What's a chimera?

01:02 KS: A chimera is just any animal that has cells from two different species or even from two different individuals of the same species. It's a mixed-celled animal.

01:12 SC: Okay. How would one go about making a chimera?

01:15 KS: It totally depends on what you're trying to do. Chimeras are involved in all kinds of experiments where you are just engrafting human cells on to a mouse, for example, to study like how a tumor grows.

01:27 SC: Or like the famous ear on the back of a mouse?

01:29 KS: Yeah, so that would be a chimeric animal, but the kind of chimera that I wrote about this week, and that some of these researchers are working on, is that it's a more specific kind of chimera, where you would inject stem cells from one species into the very early stage embryo of another species. And so that would create an animal that was much more mixed animal. There are a lot more of those foreign cells, theoretically.

01:53 SC: The ultimate goal of this research is to make organs?

01:56 KS: That's one big goal. Yeah. A lot of these researchers are trying to grow a fully human organ in an animal, probably eventually, a livestock animal like a pig or a sheep.

02:07 SC: But if you introduce the cells so early in the development of the embryo, what would they do to get those cells to become a specific organ inside an animal, that unrelated animal?

02:18 KS: Yeah. The hope is that you would genetically modify the embryo first so that that animal is not going to be able to develop a particular organ of interest. You'd have an animal with a hole where that organ should be, and then the introduced stem cells would fill that niche as they develop and fill in the organ.

02:37 SC: Really interesting. How much of that has been done so far?

02:40 KS: A little bit of that has been done in rodents, so far. [chuckle] Researchers have been able to create a mouse pancreas in a rat and a rat pancreas in a mouse. And they've even been able to treat diabetes in a mouse by implanting pancreas tissue, mouse pancreas tissue that was grown in a rat.

02:58 SC: Oh, boy. This is like... You're getting to the organ transplant part?

03:02 KS: That's the thought eventually, yeah.

03:04 SC: What have been some of the big hurdles to doing this?

03:06 KS: After these really impressive mouse results, it became clear that it was not going to be this easy with any species and any random other species. And that's because...

03:17 SC: You mean like frog and pig?

03:19 KS: Yeah, or human and sheep. Basically, the cells from one species tend to not feel at home in the embryo of another species. And that's especially a problem if those two species are evolutionarily very further apart than a rat and a mouse.

03:36 SC: So a mouse and person or rat and person would, even though those are good animal models, are not very evolutionarily close to us.

03:42 KS: Right, and so in 2017 actually, a paper came out, where a group said, "Okay, let's just try this and see how these cells do." And they took human cells and put them into the embryo of a pig and they even implanted that embryo into a surrogate pig and let them develop for, I think, three or four weeks. And when they took those embryos out and looked at them, not only were about half of them really stunted and abnormally small, but even the ones that were normal size, they didn't have hardly any human cells in them. They had very, very few of these inserted foreign cells developing.

04:16 SC: So unlikely to live on to make an organ?

04:19 KS: Yeah, it was encouraging that they survived at all, I think, but it did not leave people thinking, "All right, great. We're gonna make these organs now."

04:27 SC: Well, once you get into human territory, once you start talking about putting human cells in a pig or a mouse, that's when the ethical quandaries come up. What are some of the big questions that people have about the future of this technology?

04:38 KS: The biggest concern that people have is that if this were very successful and you were able to insert human cells into an embryo and then end up with an animal that had a very large number of human cells, you might have an unprecedented mix between a human and an animal, and that's particularly concerning if that host animal is a primate that's very closely related to us.

04:58 SC: In particular, the concern is if the human cells end up in the brain, right?

05:03 KS: Yeah. The two places that are most concerning, I think, are the brain where theoretically, human brain cells could confer some special intelligence to an animal or in the gonads where if you had a human sperm or egg cell, then mating animals with these cells could either result in a fully human embryo or what's called the hybrid, which is where every single cell would be a mix between a human and another animal, which most people are not interested in seeing.

05:31 SC: Right. This sounds almost like science fiction. This sounds really far out, but there are regulations in place, even today, that are trying to prevent something like that from happening. For example, Japan has some regulations, although they've changed recently.

05:44 KS: Japan is one of the few places I know of that has actually put in place legal restrictions on creating chimeras. A lot of other places, it just hasn't come to that yet. It's more something that is being discussed by ethicists. But in Japan, until recently, they had a restriction that you couldn't create a human animal chimera and grow it in a dish past 14 days, even if you weren't planning on implanting it. And in March, that changed, such that you could grow that embryo and also implant it into a surrogate with proper ethical permission from a government board.

06:16 SC: Okay, so Japan might be taking on some new kinds of experiments in the next few years?

06:21 KS: Yeah, there have been applications now to try and grow human cells in rodents and pigs and implant them, but remove those embryos before they came to term.

06:29 SC: What about here in the US? I know there's a lot of restrictions on embryo research, but does this cross into chimera territory?

06:36 KS: A little bit. There are no legal restrictions, but the National Institutes of Health, which is the huge funder of this kind of research in the US, has said that it will not review applications or fund research that involves putting human stem cells into a very early stage vertebrate non-human embryo.

06:54 SC: Vertebrate nonhuman means basically everything with a backbone?

06:58 KS: Right, yeah.

06:58 SC: We are talking frogs, pigs, mice.

07:00 KS: Lots of things that you would wanna study, you could not get NIH funding to do that.

07:04 SC: Okay, but non-government funded research could take place in the US.

07:07 KS: It could and it has been taking place.

07:10 SC: Okay, what are the next steps for this research? It sounds like we had a good start in the rodent models, but now as we get into primates or larger more evolutionarily close animals, things are getting a little dodgy.

07:21 KS: The steps are getting smaller as what it seems like to me. One of the things I wrote about this week was a pre-print paper that describes a chimpanzee cells growing in the embryo of a rhesus macaque monkey. These are two pretty closely related primate species, where they were able to get the chimp cells to survive for a couple of days in a dish, in the embryo of a monkey. You can't really develop that embryo much further without implanting it into a surrogate mother, so that's something that these researchers are planning to do soon.

07:53 SC: Right. So they have two evolutionarily close non-human primates?

07:58 KS: That's right. And the idea is it would not be sort of ethically reasonable to use human cells as one of those two primates, but the chimpanzee cells are sort of trying to stand in for the human cells. The thinking is that if they can sort of modify those cells in ways that make them more robust, more able to survive in this foreign embryo, the same might apply to humans.

08:18 SC: So at some point you could put human cells in a macaque?

08:21 KS: At some point, you would jump over, but probably, you would be trying to get those human cells into a pig or a sheep. It would not be very, for one thing, economically feasible to try and have a lot of primates someday producing human organs at scale. It would make more sense with a livestock animal.

08:39 SC: I have heard of growing organs in other animals like pigs, but not using this approach. Are those methods much further along or are they gonna happen before we end up... Is this gonna work before the chimera system works?

08:51 KS: It seems like it probably will. That approach called xenotransplantation is where you would genetically modify a pig so that its organs were more compatible with a human recipient, but it's still a pig organ. And so, that approach already has companies behind it that are testing how long pig organs can survive in non-human primates. But this chimera research, they don't even have the organs yet. It's much earlier days, but there's also this optimism that eventually, you would end up with an organ that was human and that would be an even better match for the person that needed an organ.

09:27 SC: Alright, thank you so much, Kelly.

09:29 KS: Thank you, Sarah.

09:30 SC: Kelly Servick is a staff writer for Science. You can find a link to her article at sciencemag.org/podcast. Stay tuned for an interview with Yossi Yovel about how bats choose between vision and echolocation.

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12:29 SC: How do we integrate sensory input: Sights, smells, sounds into our perception of the world around us? When does vision dominate over hearing? There are a lot of challenges to answering these types of questions. And this week, a research group writing in Science Advances worked with Egyptian fruit bats to get some interesting perspective on these sensory trade-offs. Yossi Yovel is here to talk about this. Hi, Yossi.

12:55 Yossi Yovel: Hi, Sarah.

12:56 SC: Why are bats a good model for working on understanding which senses are used and when?

13:02 YY: Most people think that bats are blind, but actually, all bats can see. And the specific species that we were working with, the Egyptian fruit bat sees very well. If you just look at the photo of this bat, you will see that it has large eyes. Most bats also have this sixth sense which allows them to perceive the world. They're using sound, which we call echolocation. This makes them very interesting in terms of integrating two distal sensory modalities. If you think of yourself, you integrate vision and hearing. But these two sensory modalities give you very different types of perception. With bats, both echolocation and vision give you high resolution distal input about your surrounding.

13:42 SC: You had a number of really unique setups that you were able to use to tease out what the bats are using and when. Can you describe one of these experiments where you had to train the bats in this room, and they had to use one sense over the other?

13:57 YY: The easiest to explain and maybe also the most interesting one was training bats on a classification task, so they have to differ between two objects. Basically, you do it like you train a dog, you reward them for landing on one object and not on the other. In this case, the objects were two cubes, but one cube had holes in it and one did not. Once they showed very convincingly that they can perform the task, so they will only, always land on the correct object, then for the first time we tested them using vision. Until that moment, they've never seen the targets and the question was, can they transfer acoustic information into a visual representation.

14:35 SC: How did they do on this task, once you flipped on the lights and let them use their vision?

14:39 YY: First of all, you have to allow them to use vision but you also have to eliminate echolocation, and we did this by placing the targets or the two objects inside transparent boxes so their reflection, their acoustic image is identical, but visually, you can see the differences between them. The truth is that some of the bats performed amazingly well while others did not. But for me, even if one bat can do it and you can prove that it is really using vision, so we had to prove that it's not using, for example, olfaction or something else, then it means that they can do it because there are many reasons for the bats not to perform the task. For example, when we turn on the light, we stop rewarding them. We don't feed them anymore because we don't want them to learn the targets again, visually. We taught them based on reward which is the correct object acoustically, but we do not want to train them visually and therefore we stop rewarding them. So the bats quickly learned, "Okay, I don't get rewarded when the light is on, why should I perform at all?" and still, about half of the bats were able to perform it, which proves to me that to some extent, they can translate echoes into a visual representation.

15:46 SC: So you found... In through your experiments that they can make this transfer, but you also found that they seem to have a preference, that in some cases, they use vision and in some cases, they use echolocation. What circumstances did they seem to prefer one modality over the other?

16:01 YY: Bats will prefer vision in many situations, much more than we would expect. And that is because vision gives you very high special resolution. Echolocation is very good for... If you're in complete darkness of course, echolocation prevails, there's no question there. Echolocation is also very good for ranging, if you're a fruit bat, like the ones we've worked with and you want to land on the target, then echolocation gives you accurate distance information, which is hard to get with vision, but in most cases, vision will give you better resolution. We ran two different experiments. In one experiment, we asked the bats, once again, to differ between two objects. In this case, we had a triangle and a cylinder. Unlike the previous experiment, we allow them to use both vision and echolocation, so both were available to them. The bats echo located and there was also light in the room.

16:52 YY: And later on, we examined them using only one of the modalities, so either in complete darkness or by placing the objects in these transparent cubes like we did before. Eliminating the possibility of using the other modality, and the assumption was that if they used this modality before, they will quickly perform the target only with this modality. And what we saw is that when allowing them to use vision, they immediately performed the task. They definitely used vision when they were trained. But when letting them use only echolocation, they did not perform the task, suggesting that even though they echo located during the training, they did not use this information in order to distinguish between the two targets.

17:32 SC: Very interesting. You ascribe that to the high level of resolution that vision gives them in most circumstances. Do you think that other bats with less acute vision might behave differently?

17:43 YY: Yes. I'll say one more sentence about these bats and then I'll answer you, and that is that where they're using echolocation and that goes back to what I said before, they were probably using echolocation to range, to estimate the distance to the target and to land on it. And yes, I think you're completely right. We know that other bat species do not rely on vision to the same extent. A very simple rule of thumb is you just look at the size of the eyes of the bat relative to its body and you can see that some bats have really tiny, minute eyes and probably don't use them, and those bats will probably not rely on vision to classify the targets.

18:19 SC: What was it like working with bats in these types of experiments? How easy are they to train compared with some of the other animals used for this kind of testing?

18:30 YY: First of all I should say that all of the experiments were performed by a PhD student, Sasha Danilovic, so she was the one actually spending the many, many hours with the bats, but I have done it in the past so I can also give some feeling of how it is. The main problem when you train an animal like a bat or any animal, I would say, there's a long phase in which the animal is afraid of you and doesn't understand. If I put it in human terms, doesn't understand what you're asking it to learn. Once you pass the stage, then you can really ask whether the animal is able or not to do this. On a more personal note, I can say that when you spend many hours with these animals in the dark, first of all, you observe them a lot and you get to know them very well, but they also get to know you very well. When I trained bats in the past, they would recognize me by voice, they would land on me voluntarily while I would enter the room. They would hear me and immediately come and land on me and expect, of course, a reward. You develop a personal connection with these animals.

19:28 SC: Yeah. Going back to understanding these trade-offs and when these modalities are used, how do these results that you found help us understand further sensory integration and the trade-offs that we make?

19:40 YY: Yeah, so of course there is the bat level and there is the more general level. On the bat level, I would say we understand a few things. First of all, we understand more and more about the importance of vision in echo-locating bats. People tend to neglect this thinking, "Echolocation is such a wonderful thing, let's study it," including me myself, by the way. But we realize more and more that vision is very important. There's a very fundamental question in echolocation, and that is, what kind of perception do you get using echolocation? Some people would pose the question as, "Can bats reconstruct a 3D image of the world using echoes?" Is it possible? We don't know And there are a lot of debates about this. And since you cannot enter the bat's brain or be a bat, it's probably impossible to answer. But I think the experiments of the kind that we have done can allow you to get a better understanding of the answer to this question because we've now shown that the bat can perceive an object with holes and translate this into a visual representation. By training the bat on different 3D shapes acoustically, and then testing its ability to perform the task visually, we can have a better understanding of what kind of representation it is able to build using sonar, using sound.

20:55 SC: And what about the general level, kind of abstracting away from the bat?

21:00 YY: As you said in your opening, inter-sensory integration is a big question. There's more and more evidence, for example, that brain regions, even in humans that were previously believed to be auditory only or visual only, now we realize that they're actually processing inter-sensory data. I think bats are just fascinating models because they have this strong reliance to modalities. And indeed, one of our future plans is to look into their brain, for example, using a functional MRI in order to try to understand which brain regions are in charge of processing information coming from the vision and from echolocation separately or together.

21:36 SC: You've worked with robots that are built, to some extent, like bats in the past. Is this research gonna contribute to that work as well?

21:45 YY: Yeah. It's funny that you ask, because originally, the robot was supposed to be a multi-sensory robot. It was supposed to have vision and olfaction, as well. I was only in charge of the acoustic part. The truth is that we never got to really integrate the vision with echolocation on this robot. But definitely, that's part of the idea. And whenever people talk with me about robotics and the advantage of sonar, I always say, the idea is not to replace vision because we know that cameras give you a lot of information. The idea is to somehow integrate the advantages of each of the sensors and get a better robot altogether.

22:20 SC: Okay, Yossi. Thank you so much for talking with me.

22:23 YY: You're welcome.

22:24 SC: Yossi Yovel is a professor in the School of Zoology and Sagol School of Neuroscience at Tel-Aviv University. You can find a link to his science advances paper at sciencemag.org/podcast. Please stick around for our book segment up next, with books editor, Valerie Thompson and seismologist Lucy Jones.

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22:48 Valerie Thompson: Welcome back to the book segment of the Science Podcast. I'm Valerie Thompson, the book review editor here at Science. And today, our guest is seismologist Lucy Jones who's here to talk, not about earthquakes, but about another existential threat facing humanity, climate change. And she's not actually gonna be discussing a book. We're actually going to be chatting about a haunting new song that she's composed that allows listeners to hear earth's temperature data over the last 138 years.

[music]

23:23 VT: Before we get into the song itself, can you tell me what was it about climate change that caught your attention? Was it because it was something that we're all talking about now? Was it a natural extension of your research? Was it something in your personal life that made it really resonant for you?

23:37 S5: As a researcher in disaster science, I can see that what's coming with climate change is going to be dwarfing the earthquake risk. For most parts of the country, it becomes something that we really have to grapple with. As I was completing the piece, actually my son entered a PhD program in Climate Science. So it's added a very personal touch to it, as well.

23:58 VT: The first time that I listened to the song, I was like, "Yes. This is such a perfect way to communicate the urgency of global warming." But I don't think I would have come up with that myself. Was this something about the data that made you think, "I should write a song about this."

24:12 S5: It was a odd confluence where someone else, a cellist and atmospheric scientist, had made a video that just had taken the climate data and turned the temperature into pitch and just played it. Of course, that's just a random series of notes. At the same time, I was at a meeting of the Viola da Gamba Society of America, and taking a class in a traditional style of music called In Nomine where one of the instrument voices in a group of instruments plays what is called the cantus firmus, a base song. And it was the juxtaposition of those two events, seeing the climate data, at the same time, I was really looking at how that music of In Nomine was constructed and played that I got the idea of putting it together. Just the climate data. There's no cadence. [chuckle There's no chord progressions. It's just random notes. You don't perform it in that sense. It's just a sound.

25:10 VT: The piece is called In Nomine Terra Calens, which, I gather, is Latin for in the name of a warming Earth.

25:17 S5: Right.

25:18 VT: Let's talk about the structure. How did you interpret the global temperature data musically?

25:23 S5: Okay. I took this idea that I had seen where I came up with a scaling function. It's 0.03 degrees centigrade represents a half-step in pitch. There's 12 half-steps in an octave. So 0.36 degrees centigrade is an octave change. And then, I just arbitrarily started it at a pitch that allowed me to go to the lowest note on the instrument for the coldest days. And three octaves above that, which is the top of the comfortable range for a Viola da Gamba. And that was in 2013, when I first made that scaling. When I was finally finishing it up and realized it had been several years, I needed to add a few more years of data. I ended up having to go another fifth higher because of the rise in temperature, just since 2013, which literally took the piece off the end of the fingerboard of the instrument. I can luckily play it because it's a harmonic. But it's literally the highest note that can be played on the instrument now.

26:25 VT: So we'll play a longer passage at the end of the segment, but let's listen to a short clip here.

[music]

26:43 VT: You've mentioned the viola da gamba, tell me about that instrument.

26:47 S5: Okay, the viola da gamba is a quite old instrument. It evolved parallel to the violin family, so it's a viol. And in the 16th and 17th century, a very common form of music was a viol consort, a group of these instruments playing together. It ended up losing popularity because it was the aristocrat's instrument. When Cromwell's Revolution happened in England, his people destroyed most of the viols in England, less than 100 survived. And then Marie Antoinette played the gamba, so the French Revolution had a way of sort of finishing the end. But at the early 20th century, people started bringing it back. And when I went to college in the '1970s, it was the beginning of what was called the Early Music Movement, and I got the opportunity to study it in college and play it and I've kept with it ever since. Somebody I know called a viol consort music, a musical dinner conversation, where you have ideas and you pass them back and forth. And at this point in music's evolution, it is much more an instrument that people play together and share rather than as much a performance instrument.

28:03 VT: And how does it feel to play this song as compared to some more traditional piece that you might play?

28:09 S5: It's rather in the style of the older music. We used to joke that once I discovered the 17th century, I never saw a reason to return to the 20th.

[chuckle]

28:18 S5: It's the music that I've lived with for many years, and so what I wrote is more in that style. It is a very odd experience to be performing music I wrote. That's a first for me at the end of a pretty long life that's involved a lot of playing of the gamba and it's exciting. It's the first time I've had music that's got a reason to be played beyond the music. I think that's what helped me get over my reticence to share music I wrote. It's much more personal than sharing a scientific publication, I can tell you that. [chuckle]

28:51 VT: I'm sure, I'm sure, it must be so strange to hear someone else playing something that came out of your mind.

28:56 S5: And the recording of it is actually done by a professional group. We had a premiere performance at the Natural History Museum here in Los Angeles and I played the data line, partly of course, 'cause I'm the scientist, the others were all professionals. And part of this tradition was having this cantus firmus line that was drawn out, it was also a much simpler line to play. When you had an aristocratic patron who thought himself a good player and probably thought himself better than he actually was, you could invite him to play with you because he would be given the cantus firmus part.

[chuckle]

29:30 S5: And then you could have a lower-level person playing with you. So I thought it was rather appropriate that I played the cantus firmus while the professionals played the rest of it. [chuckle]

29:39 VT: And for you, which came first, was it your passion for music or for science, or did they kind of evolve together?

29:45 S5: They very much evolved together. My father was an aerospace engineer and a pianist. I grew up in a Welsh family where the only question was which instrument you played, [chuckle] not whether you played.

29:57 VT: And have you ever tried to put any of your own data to music before, or has this project inspired you to try to do that?

30:03 S5: Earthquakes are harder 'cause they actually are frequency-based and temporally-based, so there's not that quite the scaling function. Actually, there's another USGS seismologist, a guy named Andy Michael, a very good trombonist, who wrote a piece for trombone, soprano, cello and earthquake. And used earthquake recordings as the percussion line in the piece. And I performed that with him but I sort of feel like he already did that idea, I can't imagine trying to copy from that.

[chuckle]

30:36 VT: Okay. Well, with that, we'll wrap up the book segment this month, but not without letting you hear a bit more of In Nomine Terra Calens.

[music]

30:57 SC: And that concludes this edition of the Science Podcast. If you have any comments or suggestions for the show, write to us at sciencepodcast@aaas.org. You can subscribe to the show on iTunes, Stitcher, Spotify, many other places. Or you can listen on the Science website at sciencemag.org/podcast. There, you'll find links to the research and news discussed in the episode. To place an ad on the podcast, contact midroll.com. The show is produced by Sarah Crespi and edited by Podigy. Jeffrey Cook composed the music. On behalf of Science Magazine and its publisher, AAAS, thanks for joining us.

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