Nature Podcast

Introduction

This is a transcript of the 5th April 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.

[Jingle]

Interviewer: Benjamin Thompson
Welcome back to the *Nature Podcast*. This week on the show, we'll be taking a look at some grimy mice who may have a role to play in drug development.

Interviewer: Adam Levy
Plus, we'll be dissecting human influence on the Mississippi's flood risk. This is the *Nature Podcast* for the 5th April 2018. I'm Adam Levy.

Interviewer: Benjamin Thompson
And I'm Benjamin Thompson.

[Jingle]

Interviewer: Benjamin Thompson
Listeners, if you live in a big city, there's a fair chance that you've shared your living space with a mouse at some point. I mean, I know I have in the past. For many, these uninvited visitors are pests. But there are also some research groups interested in whether these wild rodents could be a welcome guest in research labs. Of course, mice are an important model animal in all sorts of research, including testing new drugs or other therapies. Laboratory mice are bred to be genetically similar which reduces natural variation, and allows researchers to more accurately compare the effects of a particular treatment. These mice are well look after, as David Masopust from the University of Minnesota explains.

Interviewee: David Masopust
Well a lab mouse lives a very privileged existence, so it lives in a sanitised environment, it drinks perfectly clean water, it eats very clean food and it lives essentially like a boy in a bubble, in a room that is designed to keep pathogens out. And so it is a clean, privileged existence.

Interviewer: Benjamin Thompson
This environment is important, as it helps prevent unexpected variables like infections from affecting results. Now though, researchers are wondering whether these squeaky-clean conditions are influencing a lab mouse's immune system. If so, these animals may not be representative of how a human immune system might react to the same treatments.

Interviewee: David Masopust
Humans don't live in a sanitised environment, even if we try to make it so. Certainly, we've evolved to live in a microbial world, and our immune systems sort of behave differently when we have a sort of, normalised history of immune experience or infectious experience. And because we are trying to model humans typically, then it raises concerns that if we only look at sanitised animals, that we may be missing something, or what we're discovering, even though it may be very true, may fail to translate to, sort of, the human existence.

Interviewer: Benjamin Thompson
David wanted to change things up and try and introduce a little of the outdoors in to laboratory mice. This required obtaining some wild mice, which turned out to be a bit more tricky than expected.

Interviewee: David Masopust
So about 15 years ago, I was a postdoc in Georgia, and the idea struck me then. I called a bunch of exterminators, who said sure we'll give you mice and then never called me back. It was surprisingly difficult… I ultimately found a petting zoo that allowed me to take a look at some of their mice that were infesting their property. And so, when I moved to Minnesota, it was actually one of the first projects I initiated. And ultimately, to turn this into a real experiment, and to go from just observation, to experimentation, we were fortunate that a facility was built on campus, that was what we call Biosafety Level 3.

Interviewer: Benjamin Thompson
Biosafety Level 3 labs are high-containment facilities that are typically used when working on serious diseases of humans. In this case though, it allowed the researchers to contain any diseases that the outdoor mice happened to be carrying, to prevent contamination of other mice experiments. David housed his outdoor mice, which he calls 'dirty mice', with groups of laboratory rodents. As well as sharing their living space, the dirty mice also shared their microbes, which of course included their pathogens.

Interviewee: David Masopust
We found that a number of infections moved over, you know it's kind of like being raised on a desert island for your whole life, and then I drop you off aged 20 into day-care. So, there's a commotion in the blood, there are a lot of immune responses that transpire. Things kind of settle down after a couple of months, but importantly the immune system never returns to how it was before. And it has adopted these characteristics that we were looking at that were more like humans'.

Interviewer: Benjamin Thompson
In a 2016 *Nature* paper, David and his colleagues showed that the immune system of dirty mice were more developed than those of laboratory mice, with higher levels of certain immune cells. The team co-housed mice bought in a pet shop, with laboratory mice, and while not all of them survived the exposure to outside diseases, the lab mice that did, ended up with themselves, with a much more developed immune system. David described the change in the immune system as going from resembling a human baby's, to that of a human adult. Now, it's tough to imagine how you could standardise the microbes that a co-housed lab mouse is exposed to, or how it's immune system would be affected. But David thinks

this variability could actually be a benefit, as it may be more representative of the variations seen in the human population. This could be useful when testing new drugs.

Interviewee: David Masopust
The idea that if you can have a reproducible phenomenon in mice that have different microbial experiences, just like humans, you know you and I have very different infectious histories, you might be able to filter out those therapeutics that really have a lower probability of being broadly successful in a diverse human population.

Interviewer: Benjamin Thompson
David wants to know whether the dirty mice could have been used to predict the failure of vaccines that work well in the traditional mouse model, but then turned out not to work in humans at a later stage. Others can see the potential of the dirty mice as well. Here's immunologist Eleanor Riley, who thinks the new system might offer some advantages.

Interviewee: Eleanor Riley
So, I think it's a bridge between the purely lab approach and the real world, and I think that's an important bridge. I think doing the very highly controlled experiments that we're used to doing is really important for unpicking basic biological principles. But then, when we take that information into a population of people, we're all of a sudden introducing a huge additional level of complexity, not just genetic diversity amongst our population, but all of those environmental complexities. And that jump is huge, from a very, very highly controlled lab mouse, to an essentially an uncontrolled human population. And I think the dirty mice offer that bridge to step from within the same species, clean mouse to dirty mouse, and then saying dirty mouse to dirty human.

Interviewer: Benjamin Thompson
Whether dirty mice and their immune systems will help give a better representation of humans remains to be seen. David is by no means the only researcher investigating their potential, but a lot of work needs to be done, both in terms of research and infrastructure, before these mice are ready to be used for testing new drugs and therapies. However, while the dirty mouse system might not be there quite yet, David can see a place for it alongside traditional mouse models.

Interviewee: David Masopust
I think it could become a standard way of doing things, but certainly not the only standard way, and it will never replace the standardised clean model, at least in the foreseeable future, and it shouldn't. I think the things that need to be done, are to sort of fully vet its value, and to sort of provide examples where it would have better predictive value for an outcome in humans, than maybe the clean mouse would've.

Interviewer: Benjamin Thompson
That was David Masopust from the University of Minnesota in the US. You also heard from Eleanor Riley from the Roslin Institute in the UK. You can read more about the research involving dirty mice in our feature article which you can find over at nature.com/news.

Interviewer: Adam Levy
Later in the show we'll hear about a tantalising signal, that may come from dark matter. Up next though, we're joined by Emily Banham for this week's Research Highlights.

[Jingle]

Interviewer: Emily Banham
The world's most massive mammals live in our oceans and seas, but why are animals like sea cows so sizeable? It could be as simple as the need to keep warm. A team from Stanford University weighed up body mass data on nearly 7,000 species, both living and extinct. They found that the majority of marine mammals, from dugongs to dolphins, have evolved to have a mass on average of 500 kilograms. Smaller mammals lose heat faster in water, while much larger ones have a greater need to feed, suggesting that the life aquatic has a sweet spot for size. Dive into the full paper at *PNAS*.

[Jingle]

Interviewer: Emily Banham
The dazzling display of a supernova over a billion lightyears away was cut short by dense gases, according to a group of researchers. Usually, when a dying star explodes the glow is visible for many weeks. A supernova spotted by NASA's Kepler spacecraft in 2015 surged to its brightest point in just over 2 days, before dimming to be half as bright fewer than 5 days after that. This brief moment of brilliance may have been sparked when the supernova's outer material struck a dense shell of gas that the star had shaken off earlier on its death throes. Within 3 weeks, the light had faded from view, making this the shortest-lived supernova seen to date – but at least it went out with a bang. Read this illuminating research over at *Nature Astronomy*.

[Jingle]

Interviewer: Benjamin Thompson
Now listeners, before our next piece we just wanted to let you know that the *Nature Podcast* has been nominated for a Webby Award.

Interviewer: Adam Levy
Yes, we are thrilled about it, but no we're not just telling you to show off. You see, this means we're also nominated for the People's Voice Award. This is selected by the voting public, in other words, you!

Interviewer: Benjamin Thompson
To vote for us in the People's Voice Award, head to vote.webbyawards.com. We're – somewhat predictably – in the Podcast and Digital Audio Science and Education category, and there's a big button there that says vote, so please click that, and while you're there have a look at some of the other great podcasts. Right Adam, back to the science.

Interviewer: Adam Levy
Yes, next up reporter Noah Baker has been investigating how humans have impacted one of the world's great rivers.

Interviewer: Noah Baker
The Mississippi – it isn't just one of the most important words to memorise before a spelling bee. It's also one of North America's most important pieces of natural infrastructure. The Mississippi feeds into the major shipping port of Louisiana, and it has great economic value.

Interviewee: Sam Munoz
It's how the US basically exports its agricultural products to the world.

Interviewer: Noah Baker
This is Sam Munoz from Northeastern University in Boston, United States. He's been looking back at the Mississippi's history to find out more about how humans have impacted the river over time, in particular how likely it is to flood. I spoke to Sam to find out more, and he started by giving me a bit of background about the Mississippi itself.

Interviewee: Sam Munoz
The Mississippi is the largest river in North America, and it's one of the largest rivers in the world. It's also one of the most heavily engineered rivers in the world.

Interviewer: Noah Baker
Tell me what kind of engineering projects are being done here, how is it being modified?

Interviewee: Sam Munoz
On the upper part of the river, the Mississippi itself and its major tributaries, the Ohio river and the Missouri river, have dams on them. Further downstream, more in the southern United States where we did our study, what engineering has basically done is what's called 'channelised' the river, effectively encased it in concrete to keep it from moving around. And we've also, on the lower part of the river, built levees, and again this is in an effort to help us channelise the river, and sort of keep water, when the water gets high in the river, to keep it from spilling out over the footplates.

Interviewer: Noah Baker
And flood risk was what you really focused on in this study, so what is it that you actually did?

Interviewee: Sam Munoz
We developed a long history of when the river flooded, when the Mississippi River flooded, and how big those floods were. And we went back 500 years.

Interviewer: Noah Baker
So how do you go back and try to measure floods historically over 500 years? How do you do that?

Interviewee: Sam Munoz
We used two different techniques to do this, just so we could sort of independently check them. So the first is to use tree rings, and so, if you have a tree that's living near the river, and it's a tree that doesn't particularly like getting wet, doesn't like getting its feet wet, we'll say, its roots. When the river does flood, and it floods for you know long enough, say a week or two, that tree is unhappy, it gets stressed, right? It doesn't like being wet. And so the growth ring in that particular year at a cellular level shows all kinds of, what my colleague calls 'anatomical anomalies', so that is the cells look funny under the microscope. And so we can identify those, what he calls 'flood rings' right, the growth ring in that year looks funny, and he can identify those and it gives us a really precise chronology over the time that that tree lived, when that tree was flooded. So that's one thing we did, we used trees. And the other thing we did was to use sediments, to use mud. We went to lakes that are right next to the river. These lakes, most of the time, are basically disconnected from the river. But, when there's a flood and that flood is big enough, suddenly the river rises and water and sediment that's being carried by the river ends up in that lake, and leaves a sort of layer of coarser material at the bottom of the lake. And so what we did, was we went and we collected sediment cores. And then we get a core, a record of when floods happen in that particular place, over time.

Interviewer: Noah Baker
Okay, so you gathered 500 years' worth of data about flood records, and you laid them out in front of you. What did you see?

Interviewee: Sam Munoz
Floods that we get today are much, much bigger than anything we've seen in the past. We also see that the river's flooding more frequently now than it used to.

Interviewer: Noah Baker
Okay, so there's an upward trend over the course over the 500 years that you were looking at, I guess the big question is what's causing that change?

Interviewee: Sam Munoz
Part of that increase seems to be explained by climate. Climate has changed a little bit over this time and so some of that increase seems to be associated with climate. But then there's this big, about ¾ of that change is not, doesn't seem to be explainable by what we've seen the climate system do. So what we think that is, is this engineering of the river that we've done.

Interviewer: Noah Baker
Would the engineers that originally did these channelisations, these dams and so on, not have had an idea that this could have an impact on flooding?

Interviewee: Sam Munoz
The infrastructure we have was really designed in the mid-20th century, and what they did, was actually take storms that had happened in the sort of mid to early 20th century and sort of project, and so our whole understanding of how much the river can flood is based on a sort of mid-20th century view of that river, and of course that is very likely to change over

the coming century. If flows are going to actually increase, and peak flows will increase under climate change over the future, is the infrastructure that we have in place now really appropriate for this future world?

Interviewer: Noah Baker
Okay, so looking forward, what lessons do you think can be learnt for scientists and for engineers from research like this paper that you've just done?

Interviewee: Sam Munoz
There's not an easy fix to fix this problem. I think the bigger message here about what this study is saying, is that usually when we try to control nature, it's more difficult and more expensive than we could have imagined in the first place. And I think this is a nice example of that. And so, as we continue to try to you know, sort of engineer nature, rather than trying to fight it, we might think about ways to sort of work with its natural rhythms rather than trying to impose our, sort of human will on it. I think that's the sort of bigger, philosophical message, but I think specifically for the Mississippi, you know, that's a conundrum that there's no easy answer to.

Interviewer: Benjamin Thompson
That was Sam Munoz speaking with Noah Baker. You can read the full paper over at nature.com/nature.

Interviewer: Adam Levy
Finally this week it's time for the News Chat, and senior reporter Davide Castelvecchi is here in the studio. Hi Davide.

Interviewee: Davide Castelvecchi
Hello Adam.

Interviewer: Adam Levy
First up this week, there has been a tantalising new result on dark matter. Before we get to that new result, let's have a quick recap. Why do we actually think dark matter exists in the first place?

Interviewee: Davide Castelvecchi
There are multiple lines of evidence. Originally it was seen that galaxies in galaxy clusters were moving in strange ways, that they seemed to be moving under the influence of some kind of unseen mass, and then later similar effects were seen inside galaxies themselves.

Interviewer: Adam Levy
And now an experiment has just returned some results. It was actually searching for a signal from the halo of dark matter. What would this halo of dark matter been?

Interviewee: Davide Castelvecchi
Most of the dark matter in the universe would be in these halos around the visible parts of galaxies. So there's dark matter that surrounds us, it's inside the galaxy but it also extends to this larger halo, and that's where the particles fly around the galaxy.

Interviewer: Adam Levy
And how is this particular experiment hoping to spot a signal from this halo of dark matter?

Interviewee: Davide Castelvecchi
Yeah, so the technique that this experiment and also other experiments apply, is to just place a chunk of cold ordinary matter in some like underground laboratory for example, under mountain where it's protected from other sources of radiation, such as the cosmic rays, and just wait. And so, you just hope that once in a while a particle of dark matter will bump into an atom and the resulting collision will release a flash of energy, and that's what the experiment looks for.

Interviewer: Adam Levy
How can you be sure when you look at all these flashes this experiment picks up, that you're not just picking up some other interaction that is happening between these atoms and radiation say, from the surrounding area?

Interviewee: Davide Castelvecchi
So the number of collisions with dark matter particles should peak in early June, and it should bottom out in early December. And so, on top of the background, which should be constant year round, the dark matter should be visible as this little up and down.

Interviewer: Adam Levy
Why is it that dark matter prefers summer to winter?

Interviewee: Davide Castelvecchi
Ah, that's because the solar system moves inside this halo at quite a high speed, something like 250 kilometres per second, but during certain parts of the year, the Earth's orbit moves in the same direction as the Sun inside the galaxy, and when it adds up they call it the effect of rain on the windshield when the Earth is moving faster inside the halo, a number of collisions should increase, and when it's moving slower it should decrease.

Interviewer: Adam Levy
And they thought before that they had seen this kind of annual, cyclical pattern, and now they seem even more sure that they're seeing it.

Interviewee: Davide Castelvecchi
Well, this has been a long operatic drama that's been playing out in the underground laboratories of Italy since 1997, when this experiment first announced, even with just a few weeks' worth of data, they were already seeing this fluctuation. And they announced it and nobody believed it, and they've been seeing it ever since and people still don't believe it.

Interviewer: Adam Levy
So what would people actually need to see to be convinced that this were a signal from dark matter?

Interviewee: Davide Castelvecchi

The one thing that would be that would convince at least some of the sceptics, is if somebody repeated the same experiment or a similar experiment in the southern hemisphere and still saw a peak in June and a minimum in December, because then it would be difficult to argue there that is some kind of effect from the seasons. On the other hand, if you see the opposite fluctuation, you know if it goes down in June and it goes up in December then, it's probably due to something that happens on the ground.

Interviewer: Adam Levy
Well, we'll have to keep an eye out to see whether anything can firm up this potential observation of dark matter, but in the meantime let's move on to our second story, which is on a push to relax rules for clinical cancer trials in America. Now, why would you want to relax the rules for cancer trials?

Interviewee: Davide Castelvecchi
It's quite astounding when you look at the numbers, to see that 1 out of 5 clinical trials for cancer drugs is unable to find enough patients to test the treatments. And so, a lot of researchers are now trying to push for this relaxation of the standards in the hope that they will be able to test their drugs.

Interviewer: Adam Levy
Who is actually suggesting this, that we should relax these rules?

Interviewee: Davide Castelvecchi
It's a combination of researchers and the authority that regulates the clinical trials which is the US Food and Drug Administration, and also stakeholders such as patients organisations.

Interviewer: Adam Levy
It certainly seems a shame if some studies aren't able to go ahead because they're not able to get enough participants, but surely these rules are in place for good, important reasons?

Interviewee: Davide Castelvecchi
Yeah, so originally these rules may have been put into place to protect either the, sort of, the statistical significance and integrity of the results, or to potentially protect patients from adverse reactions and so on, but sometimes, you know, researchers may have perhaps extended rules that were devised for earlier clinical trials to newer ones where perhaps they were not as necessary.

Interviewer: Adam Levy
So what's an example of one of the rules that researchers are actually looking to relax?

Interviewee: Davide Castelvecchi
Well, one long-standing rule has been to exclude patients who were HIV positive, and that may be a legacy of a time when being HIV positive almost always meant that your immune system was severely compromised, which maybe now is no longer the case.

Interviewer: Adam Levy

And one of the rules is, to me at least, a bit more controversial, in that it relates to the minimum age of participants in trials.

Interviewee: Davide Castelvecchi
Yeah, a lot of researchers have started to wonder whether if you're 15 versus 18, physiologically your response to medication may not be so different. But traditionally maybe researchers have been very risk-averse, you know, they've avoided including children from clinical trials. So again, this is one of the rules that is going to come under scrutiny and maybe will change.

Interviewer: Adam Levy
Davide, thank you for joining us. For more on those two news stories, and for others of course, head over to nature.com/news.

Interviewer: Benjamin Thompson
And our regular round table discussion Back Chat will be back in the next couple of weeks. Let us know what science news you'd love to get the behind-the-scenes gossip on. Get in touch by email: podcast@nature.com, or on Twitter: @NaturePodcast.

Interviewer: Adam Levy
And in the meantime, if you're after more *Nature* multimedia, then keep your eyes peeled for a new video about bee behaviour. Find that on *Nature News*' social media channels. I'm Adam Levy.

Interviewer: Benjamin Thompson
And I'm Benjamin Thompson. Thanks for listening everyone, see you next time.

[Jingle]