Welcome to the Science Podcast for April 16th, 2021. I'm Sarah Crespi. Each week, we feature the most interesting news and research published in Science and the sister journals. First up, staff writer Adrian Cho joins me to discuss how a recent measurement of a muon's magnetism has the potential to turn into a field day for a theoretical physicist. Then I talk with researcher Charles Marshall about his project to calculate the total number of Tyrannosaurus Rexes that ever lived. Finally, in a sponsored segment, director of custom publishing, Sean Sanders talks with researcher Imre Berger about a 2020 science paper that describes finding a druggable pocket on SARS-COV-2's spike protein, and a ligand that jams it shut.

First up this week, we have staff writer Adrian Cho. He's gonna tell us about a new measurement of the magnetism of a muon that differs from predictions made by the standard model, and whether this difference upends physics, introduces new forces, new particles, lots of hype. But Adrian, you're here to tell us how real it all is. How you doing?

Very good. And how are you, Sarah?

Good. Okay, the basics here. What is a muon and why might it be a dowsing rod for unknown forces and particles?

The muon is a heavier cousin of the good old common electron. The muon is much like the electron, except it's about 207 times more massive, and it's very short-lived, so it can be produced in particle collisions and pop into existence, but it'll only last for a couple of microseconds before it actually decays into an electron and other particles called neutrinos, but except for its mass and its short lifetime, it's much like the electron. It was the first exotic unstable particle that was discovered after the electron and after the atomic nucleus was discovered and all that, way back in the 1930s, I believe.

And the reason that muons are interesting is because over the decades, physicists have developed this very refined theory of the structure of matter called the standard model, and we now know things like the proton and the neutron in the atomic nucleus, each of them consists of three fundamental particles called quarks, and there are heavier quarks. The muon's magnetism turns out to be a kind of barometer for whether there might even be more particles out there than the standard model has identified. Thanks to quantum mechanics, the muon is never really isolated. Any fundamental particle, thanks to quantum uncertainty, always has particles and anti-particles popping in and out of existence around it, and you can't directly detect those particles, you can't pull them away from the muon, but they can very subtly affect the muon's properties, and in fact, they can make it slightly more magnetic.

So the standard model particles that already do this add to the muon's magnetism by about a tenth of a percent and is known to exquisite precision how much that should be, like two parts in a billion, but if you measure that and it's off by a few parts in a billion, then it might be
signs that there are unidentified particles popping in and out of the vacuum, and so it could be a sign that there is something just beyond the reach of the world's most powerful atom smasher, the Large Hadron Collider.

0:03:40.1 SC: Alright, well, let's talk about how you measure the magnetism of the muon. Basically the g-2 experiment yielded some new numbers for that.

0:03:50.6 AC: Right. So the g-2 experiment is this storied experiment that started way back in the 1990s. It got moved to Fermilab in 2013, and they rebuilt the whole thing and they made it much, much better, and they measured the magnetism of the muon again. The basic thing that you need to know is that because the muon acts like a little magnet, you can make it twirl in a magnetic field. They have these muons, their magnetic moments as they're called are all... They set it up so they're all lying flat in a plane. They expose them to a vertical magnetic field, and they all twirl. The rate at which they twirl before they decay tells you how magnetic the thing is, and these folks have measured the magnetism of the muon to just blinding precision, and they find that it's about 2.5 billionths, parts in a billion, bigger than the standard model predicts. So this is an incredibly small amount of extra magnetism, but it's also about 4.2 times the total uncertainty in both the predicted value and the measured value, which is not quite to the level of five that you need to claim that there's something definitely wrong, but it's pretty close.

0:05:07.6 SC: Okay, so just to repeat back to you, they measured it with more precision than ever, it solidifies earlier measurements that were done as well, and they both differ from the standard model by a substantial amount, but not necessarily the level of precision that people would say this is a for real thing.

0:05:26.9 AC: Right, but what is crucial is that they reproduced the result that they got before it. They reproduced it pretty closely, and if you combine the two, because the two results overlap, it's fair to average them, you get something that looks even slightly more solid than it did before. They've only taken about 6% of the total data that they're gonna accumulate... They're still taking data right now. And so their uncertainty is gonna shrink by another 75%. If this value holds out, then the disagreement with the standard model prediction may very well go over this artificial but very important five times the error threshold.

0:06:07.5 SC: But the standard model's prediction for the magnetism of the muon has also changed over time. How has it changed? Has it swung further away from this number we're getting experimentally?

0:06:19.3 AC: The value has stayed about the same, but the uncertainties have come down, so yes, the theoretical side has changed. Through the history of this thing, there have been some interesting ups and downs. There was an incident in the early 2000s where somebody found a sign mistake. This calculation is incredibly difficult, and that had to be corrected, but the uncertainties have come down. Starting three years ago, there's a group that numbers about 130 theorists who have this consortium that their charge is to come up with a consensus value for the standard model prediction, and they came up with one last year, and that's what this has been compared to.
0:07:00.0 SC: There's a paper that came out at the same time as this new measurement, and the new paper uses a different way to calculate the magnetism of the muon using something called a lattice calculation. Does this new calculation method and their result change how we should feel about the discrepancy between the predicted value and the measured value for the muon's magnetism?

0:07:24.4 AC: It all has to do with what kind of particles are popping in and out of existence around the muon, and you have to account for all the different ones, and it turns out that one particular set of these processes that's very hard to calculate is the one that accounts for particles called hadrons, and these are particles made up of quarks that pop in and out of existence around the muon, and in fact, this is the biggest uncertainty in theoretical number. To get around the computational intractability of this thing, the standard approach actually uses data.

0:08:01.3 AC: There's another way to approach making these computations with things that involve quarks, which is called lattice QCD. If you will, it's a very sophisticated numerical method, and this is an effort that requires massive amounts of super computing time. It's very difficult. They've been developing it for decades. There are half a dozen groups who've been trying to calculate the magnetism of the muon using these lattice calculations, and a group this week came out with a value that has the precision that they claim rivals the consensus theoretical value, and lo and behold, it's a lot closer to the measured value, and they claim that there's no real discrepancy here. So...

0:08:46.3 SC: So, no problem. No more difference between what's measured and what's predicted.

0:08:51.2 AC: It seems like at some level that it's kind of a white knight riding in and saving the standard model, but maybe it's not quite as simple as it seems. And it's really kinda neat because it gets into the whole issue of what you mean by uncertainty. The uncertainty in the consensus value that they hammered out is actually just derived from the measurements that went into it. The uncertainty on the side of this lattice calculation is actually a measure of how well the method works. And those two things are very different.

0:09:32.9 AC: And what's more, there are other lattice measurements, including one that comes much closer to the consensus calculation, and since these errors are not really quantifications of statistical uncertainty, or uncertainty in measured things, but are really measurements of how well does the method work, there's really a problem if you got two results from this new technique that are farther apart than their errors claim they should be. So something is going on here. But this idea that the lattice folks have simply found the mistake that all these other folks were making, that's gonna be a hard sell.

0:10:17.2 SC: Well, let's talk about this discrepancy between the consensus calculation and the experimental observation of the muon's magnetism. It's a difference, it's a small difference, but what can fit in there? What kinds of ideas might theoretical physicists put forth and say, "Okay, this is what particle might be in there?"

0:10:40.2 AC: Yeah, see now this is where it gets really tricky, because this method of looking for evidence of new particles that you haven't blasted directly into creation with an atom smasher, it's very sensitive, but it's not very specific. It's a little bit like taking your temperature and it says
101.5. You know something's wrong with you, but do you know what it is? No.

0:11:04.7 SC: No one's looking at this discrepancy value and saying, "Aha, this thing I was thinking was around fits that. That fits my ideas."

0:11:12.2 AC: Well, I would say it somewhat differently. There are gonna be hundreds of people claiming that. The problem is that they're all gonna have different ideas. This is not a smoking gun for anything. There are lots of ideas, new force carriers that act a little bit like the carriers of the weak nuclear force, these weird things called leptoquarks, which are kind of a bit like a quark and a bit like a quark. But the real strength of this method is that it can be extremely sensitive to new things that you can't quite yet blast into existence directly.

0:11:46.7 SC: So it sounds like the field day is going to happen, that there is going to be a lot of room here for theoretical physicists to explore their ideas and see if they fit with this measurement, this discrepancy, and then look for it in the future in other experiments.

0:12:02.5 AC: The g-2 experiment is gonna have more data. They're gonna shrink their error bar. If this thing really holds up, and it really looks like there's a problem, then there's a chance the LHC is supposed to take this gigantic step in event rate, which will make it easier for it to look for these very subtle differences from standard model predictions, and so if this one holds up, and the LHC gets this big boost in event rate, which is supposed to happen in the late 2020s, then yeah, you could actually imagine that this will all start to come together, and if it won't point to an exact answer to what comes beyond the standard model, what extra particles specifically do we need to add, it's at least plausible that by the late 2020s, there could be between this measurement and things that become more clear at the LHC, some really strong indication that the standard model is just out of kilter and can't completely explain nature.

0:13:09.0 SC: This is not a bad thing, right, this glitch with the standard model's predictions?

0:13:13.3 AC: I think one thing that's kinda hard for people who are not steeped in particle physics to get their heads around is that particle physicists have perhaps the most elaborate and precise theory in all of science that just accounts for basically everything seen with atom smashers to great precision and you would think that would be cause for amazing celebration, but the problem is, it's been this way for going on 40 years, and these people are really desperate for some sign of what comes beyond the standard model, because they know the standard model can't be complete, it doesn't include dark matter, it doesn't include gravity. It's gotta be a provisional theory, but everything you see under the atom smasher, it covers it so far, so that's why there's so much excitement that it might not actually explain the muon.

0:14:04.8 SC: Alright, Adrian, thank you so much. Adrian Cho is a staff writer for Science, you can find a link to the story we discussed at sciencemag.org/podcast.

The Tyrannosaurus Rex lived 66 to 68 million years ago, and we have fossils to prove it, but it's not an easy calculation to go from the number of fossils to the number of Dinos. Charles Marshall joins me next to talk about his approach to counting up T-rexes.
0:14:36.5 SC: How many Tyrannosaurus Rex roamed the earth 66 to 68 million years ago? We have lots of fossilized bones from them, but what does that number, the number of bones we have, tell us about how many T-rex actually lived? This week in Science, Charles Marshall and colleagues wrote about a way to calculate the T-rex population millions of years ago. Hi, Charles.

0:15:00.4 Charles Marshall: Good morning.

0:15:01.4 SC: Okay, well I mean yes, these are basically the definition of charismatic megafauna, but what made you decide to focus on the T-rex and to ask this question?

0:15:11.0 CM: So one of the things that happens, you find a fossil on the ground and you pick it up, and you realize it was a living animal 66, 67, 68 million years ago. So there you are holding it in your hand and you know that it's a rare find. And the question that always pops into my mind is just well how rare is it... Is it one in a 1000, one in a million, one in a billion? I've asked this question most of my life, and I was talking with my graduate students and with some of my colleagues on the corridor, and said, "Well, maybe we can work out how to do this." And then it turned out we focused on T-rex part because it turns out we have an exceptionally rich knowledge of T-rex more than most Dinosaurs, in fact, more than most fossil beasts.

0:15:49.8 SC: Is one of the reasons this is a tough problem, because it's hard to predict what gets fossilized.

0:16:11.0 CM: We have a broad understanding of which groups we expect to see fossils from and which not. Clams and snails in the ocean living in the sediment, and so get buried quickly and easily, so we expect lots of those, and we find lots of those. Small animals that live deep in the forest are unlikely to be fossilized when they die, they just rot and get scavenged. So we broadly know the general correlation, the more abundant the species, the more likely you are to find fossils of it, but that's a very, very crude measure. George Gaylord Simpson one of the great paleontologists in the mid-1950's, basically said, "We can say something as a large population size or a small population size, but really can't say anything else."

0:16:55.6 CM: What we realized, and this had been realized before, is you need data from living species, you simply can't do it based on the fossils alone. And so it turns out that for animals today, there's a fairly strong relationship between the population density, the number of individuals per square kilometer and their body mass. There are relatively few elephants or giraffes, there are many more small antelope and there's a bazillion little mice in the same area. We realize this that if we had an estimate of the body mass of T-rex and we knew a little bit about its physiology, we can actually make a rough estimate of what it's population density was, and then we could use the geologic and paleontological record to then extrapolate out to look work at how many individuals...
they must have been altogether.

0:17:34.9 SC: So if you knew its range and its density, then you can say how many there were.

0:17:38.8 CM: Exactly, and then if you knew how long they lived for and you knew what the generation time was, therefore how many generations that lived for, then you could multiply the two numbers, standing population size and the total number of generations, and presto, you get the total number that ever-lived.

0:17:53.7 SC: But in order to do this, you did have to make some assumptions about what Tyrannosauruses were like.

0:18:00.4 CM: The relationship between population density and body mass is very strong, and so we felt relatively comfortable extrapolating out to body sizes that are much larger than anything alive today.

0:18:12.9 SC: You also mentioned physiology was important for this calculation, lower body temperatures means that the animals lived more densely. How did you decide what to assume for T-rex, warm-blooded, cold-blooded, something in between?

0:18:26.9 CM: Most people feel that most dinosaurs are warm-blooded. There's a general consensus that they may have been a little less warm-blooded than mammals. Some people have suggested that they had the same physiology as the Komodo dragon, which is relatively warm-blooded compared to all the other lizards. Most dinosaur biologists think that's too low, and so we simply pick the difference between the two, the Komodo dragon, being the low end and mammalian carnivores, lions and tigers as the high end and we split the difference. The thing that's very interesting, is that the relationship is very strong and you have to work out at what the physiology is, but ecology makes an even bigger difference.

0:19:07.0 SC: What do you mean by ecology?

0:19:08.5 CM: So for example, jaguars and spotted hyenas have about the same body mass, but for every jaguar, there's 50 hyenas in the same area. They don't live in the same place. And so even if you knew the physiology perfectly, and even if you knew the body mass perfectly, there's still a huge uncertainty just to ecological differences between species, what the food availability is, what the habitat is like, what the temperature is like.

0:19:34.8 SC: So that introduces the uncertainty, right?

0:19:37.0 CM: It introduces an uncertainty of about 100 fold.

0:19:40.0 SC: When you calculated all this with the uncertainties that we kinda have to take here, what kind of values did you get for the density of the T-rex population?

0:19:50.6 CM: For this study, we took a completely different approach because it's so hard to get
precise numbers. And so what we decided to do is try to bracket the numbers, I could be really conservative and say, I bet you they were somewhere between one, well, I'll say two and an infinite number of T-Rex, and I'd be a 100% right.

0:20:10.7 SC: That's the universe of possibilities. Got it.

0:20:12.7 CM: But it's not useful. We spend a lot of time trying to narrow down what a reasonable range was for each of the variables, and then we simply did random draws from each of the distributions and multiplied them up to see how those uncertainties compounded as we went through our calculations. So to answer your question, the population density we got, the middle value, given all the uncertainties is about one individuals per 100 square kilometers.

0:20:39.9 SC: Okay, put that in context for us. We've been talking about all these living species, is there something like that alive today?

0:20:47.0 CM: No, because the body mass is so much higher today, but it's about a fourteenth the population density of lions and about a sixth the population density of tigers. So it translates out to about 3800 T-rex in an area of the size of California, or about two in the size of Washington, DC.

0:21:11.0 SC: Wow, so we have this number now with the density, and as we talked about before, if you combine that with range, you get how many there were all together.

0:21:20.1 CM: The total number is something like 20,000 alive at any one time. I should, note, these are post-juveniles.

0:21:27.1 SC: These are the ones that survived to adulthood.

0:21:29.0 CM: Yes, and so about 20,000. Now, the uncertainty is a very large, because mostly we don't know what the specific ecology is. The number could be as low as 1300, and the high number is about 330,000. So the uncertainty said are fairly large, but tens of thousands.

0:21:47.4 SC: Right. So we're gonna just add a little bit more uncertainty on top of this and say, Well, how many lived all together through time if you take how many is in a standing population and multiply it by all the generations that lived?

0:22:00.7 CM: Yeah, so the number we get for that middle value is about 2.5 billion, so about half the number of human adults living today.

0:22:09.5 SC: Well, let's do one more mathematical transformation, and this actually takes us back to what we talked about at the beginning, which is how many of these are preserved? What did you calculate that the preservation rate was considering this range of values for the number of Tyrannosaurus Rex that ever lived?

0:22:27.4 CM: It turns out that we have at least 30, 32 skeletons or partial skeletons that have sufficient material that you can guesstimate their age, so that means that we have in our hands then
in the order of 1 in 80 million of every T-Rex that ever lived in our current fossil collections. I should add too that counting individuals turns out to be very tricky, sometimes you just find a tooth, but they shed their teeth, so you don't know if I'm finding 15 teeth, how many individuals that is, or I might find just a partial leg bone, there isn't enough to tell that it's T-Rex, except that it's in the right place at the right time and the only giant theropod we know is T-Rex, so we infer that it's T-Rex. So the number of bones that we have that are probably from T-Rex is probably in the thousands or more.

0:23:22.0 SC: What can you do with these numbers? How do you see this work extending further?

0:23:26.3 CM: So one of the things that one can do, for example, is T-Rex turns out to be very well known, and there's quite a lot of fossils, triceratops is even more abundant, but going in the other direction, how many species are there that were present that we simply have no fossil record off? So with these numbers now, if you have the preservation rate being roughly the same, the species that lived, say a tenth the duration or a tenth the range, that means I expect about a hundredth the number of fossils, and that means I probably will have missed it in the fossil record, and so I can start to estimate how many things I might have missed. It's sort of the known unknowns, which currently we don't know how to assess easily.

0:24:10.2 SC: Yeah, why is this a good time to take a look at this? What parts of our understanding are making this easier to do now than it was decades ago?

0:24:19.7 CM: One of the things that our calculations relied upon was the fact that there are quite a lot of fossils are known, but also that we can do a lot more with them than say George Gaylord Simpson realized that one could do 70 years ago. You can cut the bone and look at the bone histology and make an estimate of the age. If you have the estimate of the age, then you can develop growth curves, you also can develop survivorship curves, what's the probability of living to a certain age? We can estimate maximum age, that means it's possible to estimate the time of onset of sexual maturity from the growth curve, it means that we can estimate the generation time. So there are a lot of biological aspects of it that if you just hold one fossil in your hand, see impossible. How old was it? Was it sexually mature, how likely was it... When was it likely to die? How lucky was it to reach the age that it currently was? And so this study exploited our fairly rich knowledge now of T-rex.

0:25:17.4 CM: I'm also struck when I look at the papers that we cited, how many of them are 2020, 2019. And so there's a lot more information flooding in that we were able to take advantage of. My graduate students, my lab group have very diverse research interests, and so part of my motive for starting the study was just to say, "Let's all do something together, and let's see if I could work them through the process of starting from scratch to publication," 'cause we had no idea we'd finish up in Science.

0:25:50.7 SC: That's great.

0:25:51.5 CM: Ask an interesting question, and sometimes you get an interesting answer.
0:25:54.2 SC: Absolutely. Thank you so much, Charles.

0:25:56.7 CM: You are most welcome. Thank you.

0:25:58.4 SC: Charles Marshall is Director of the University of California Museum of Paleontology and Professor of Integrative Biology at the University of California, Berkeley. You can find a link to his study at sciencemag.org/podcast. Up next, we have a custom segment sponsored by Oracle for research, custom publishing director Sean Sanders chats with researcher Imre Berger about finding a druggable pocket on the novel Coronavirus.

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0:26:28.0 SS: Hello everyone and welcome to this custom-sponsored interview from the science AAAS custom publishing office, brought you by Oracle for research. I'm Sean Sanders, Director and Senior Editor for custom publishing at Science, and I have the pleasure today of interviewing Dr. Imre Berger, Professor of Biochemistry at the University of Bristol in the UK. He researches essential proteins in human health and disease, using this knowledge to create synthetic vaccines as well as to develop enabling technologies for this purpose. Imre welcome, and thank you for taking the time to talk to me today.

0:27:03.8 DB: Hi, Sean. It's my pleasure.

0:27:05.9 SS: So, Imre in 2020, Science published a research report authored by you and your collaborators, describing an important discovery about SARS-CoV-2, the virus that causes COVID-19. Can you tell us briefly what you found?

0:27:21.7 DB: Yes, certainly. Sean, as you remember those unprecedented times. Remember we had the first lockdown and everything, including the University was shuttered. Bristol turned into a ghost town, just incredible, really kind of spooky. At our University, a handful of clinicians, virologists and a few other scientists continued to work digging deep, trying to understand what was going on and to do something about the pandemic. For what they were doing, they needed SARS-2 antigens, and a major antigen of the SARS-2 virus is the spike protein and the virus, what it does, is, it uses this spike to attach to the cells and then to infect them. And so we made this spike and because we use a slightly different method than most everybody else, we had to quality control what we were doing. So we had to show that it really looks like what you would normally have on the surface of the virus. And we use cryo-electron microscopy for this, that's a technique, which you can look at the outer structure of the sample you produce, and we also needed high-performance cloud computing. And when we did this, to our great surprise, we had a new, entirely unexpected feature. We found a druggable pocket. And we did not only find this pocket, but we actually found a ligand, a small molecule, linoleic acid, tightly bound in this pocket and jamming it shut.

0:28:58.0 SS: Now this is a really, interesting and surprising discovery, but why is it important?

0:29:03.9 DB: It took us a while to actually, like understand this because we are not coronavirus people and we also have never researched something like linoleic acid. But we then looked into the
details. And so now, the spike as it happens on the surface of the virus is known to exist in two forms or two shapes which are different. So there is an open form of the spike protein, and that's actually the form which the virus uses to attach to the cells and get in. And then there is a closed form, and this closed form is actually not infectious, so people think that what the virus does is use its closed form, when it travels through the body, to hide these important parts of the virus with which it would attach to the cells to avoid the immune surveillance. But then when it comes to a cell, and once we're infected, then it opens up and it attaches to the cell. And it goes in, starts to replicate, sets of this chain reaction, and then all these bad things happen.

0:30:08.9 DB: Now, according to our data, the linoleic acid in the pocket had lost the spike in the not infectious form, and we were very excited about this, of course, because that would mean that the virus cannot attach to the cells, cannot get in, cannot replicate and there is no chain reaction. So we confirmed our discovery experimentally and then we applied a method where you can yank out the linoleic acid out of this pocket. And indeed it spiked and became more infectious again. So this told us that we had something amazing in our hands. We had this pocket, which is like a lock, and we could apply this lock to arrest the virus in a non-infectious form.

0:30:56.8 SS: Imre, back to the actual discovery. Could you explain in a bit more depth how you reached the breakthrough and what some of the technical challenges were?

0:31:05.3 DB: The key to the discovery was using cryo-electron microscopy. So how that works is that you take the spike which you made and you purify it, and then you put it into the electron microscope and then you record thousands of movies of that spike from every possible direction. And all you need to do now is to put this together into a three-dimensional representation, but it's easier said than done, because you have literally terabytes worth of data which you collect. And in order to piece this all together, you'll need massive computation, the number crunching starts. And it used to take weeks and months until you got this done, but here we got incredibly lucky. Just shortly before the pandemic, we had finished a different project, that's when our collaboration with Oracle research started because with Oracle, we together figured out how this immensely intensive type of computation can be done much faster than had been possible literally within hours and days. So what you'd do is you'd put all these movies you have and you put them on Oracle's cloud.

0:32:17.2 DB: Oracle's Cloud is a gigantic rep of computational nodes distributed all over the world and ready to crunch numbers whenever you need it. So rather than taking each frame one after the other and calculating through them, we just blasted it on the cloud distributed it to everywhere and then the frames would come back. They were processed in parallel. Speed is everything in a pandemic and our colleagues at Oracle made things happen at an incredible pace.

0:32:44.9 SS: So what are the next steps? How will you move this work forward to benefit patients in the real world?

0:32:52.6 DB: That's a very good question, Sean, and this was exactly the question we faced when we had figured out what we actually had. To translate this potentially game-changing, discovery, what we did was that over Christmas, we founded a new company called Halo Therapeutics. We had to do this because we needed to put together the legal framework to actually get this undertaking funded and get it to the clinic and to sponsor clinical trials and to move it forward, and
we had to raise money, of course, and we were amazed how literally everybody we talked to wanted to get involved and do something about the pandemic. So we put together a seed funding grant, we collected amazing, great people, experts, key researchers, clinicians, drug development guys, manufacturing guys, and we are now at work 24/7 to translate our discovery and bring a range of products to the market as we can.

0:33:56.6 SS: What types of drugs are you planning to develop at Halo?

0:34:00.6 DB: Well, basically, we want to follow what the virus does when it enters your body. What happens is that first the virus goes into your nose and starts to replicate, so that's the first hot zone. And a few days later, it slides into your throat, and then yet again, later it goes into your lung and that's when mayhem starts. So you need to catch the virus as early as possible. So we want to attack the first hot zone first, and this we plan to do it with a nasal spray that will be used to treat patients immediately when they feel that they have possibly contracted the virus. And we also plan to develop an inhaler that we would be to target the lungs. So when you are already a bit further ahead in the disease progression and you have already difficulties breathing and you're developing those symptoms, which are typical for COVID, then the inhaler would be deployed so that when the patients present to A&D at early stage, breathing difficulties can then immediately be treated.

0:35:07.6 SS: Imre, how do you think the antiviral approach that you're using with the linoleic acid will work on the variants that are coming out of the coronavirus and even future potential mutants?

0:35:20.1 DB: That is a key question, especially if you think now what's going on that. We have now already the South African mutant, we have the Brazilian mutant, and here in the UK, we have this UK mutant and they are much more infectious, apparently, than the ones... We don't know yet either, there even more, deadly, but they pose big challenges. So what we did is, when we had the structure, we compared the structure to previously determined spike proteins from SARS and MERS. So we had already these three outbreaks and we looked very carefully and extrapolated from the structure which we determined, and indeed we have now the data that SARS and MERS, that they also have this pocket and they also have this linoleic acid binding modality. And in addition, we then had a look what's going on actually with the SARS mutant which are now coming out. And there is a resource on the web, which tracks all of these mutants which are sequenced all over the world, and you can then have a look where do the mutations occur. And interestingly, the pocket is extremely conserved, so there are no mutations which target the pocket. You get mutations all over the spike protein and as well in the SARS-CoV-2 genome, but not in the pockets. So there is a reason why that pocket is there, and it means that we can catch all of them, also the new mutants which that are coming out.

0:36:47.0 SS: Well Imre, thank you so much for agreeing to sit down with me. I've thoroughly enjoyed our conversation. This is really fascinating work, so thank you again.

0:36:55.2 DB: Thank you so much, Sean. It was my pleasure.

0:36:57.4 SS: And our thanks to Oracle for Research for making this conversation possible and to the Science podcast audience for your interest and attention. Until next time.
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 listen to the show on the Science website at sciencemag.org/podcasts. On the site, you'll find links to the research and news discussed in the episode. And of course, you can subscribe anywhere you get your podcasts. This show was edited and produced by Sarah Crespi with production help from Podigy, Meagan Cantwell and Joel Goldberg. Transcripts are by Scribie, and Jeffrey Cook composed the music. On behalf of Science Magazine and its publisher, AAAS, thanks for joining us.