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00:00 Sarah Crespi: Welcome to the Science Podcast for May 8, 2020. I'm Sarah Crespi. First off this week, staff writer Jon Cohen joins us to talk about the scramble to make monoclonal antibodies as a treatment for coronavirus. Then we have a researcher, Karen Holl. She is gonna talk about avoiding the pitfalls of tree planting campaigns for climate change. One such pitfall, massive tree planting projects can actually lead to deforestation. Now, we have staff writer Jon Cohen, he's been writing non-stop about COVID-19 this week, among many other stories he produced, he wrote about monoclonal antibodies as a treatment for coronavirus infection. Hi Jon.

00:47 Jon Cohen: Hi Sarah, how are you doing?

00:48 SC: I'm good. So immediately, we need to define some terms here, monoclonal antibodies. What exactly are these and how are they different from things people may have heard of like convalescent plasma?

01:00 JC: Yeah, so convalescent plasma is the idea that you had the disease, you recovered, and you can pull the plasma out of someone that has a gemish of antibodies and then give that to someone else. The monoclonal idea is you select the best antibodies out of that gemish or you can make those antibodies in mice or you can make them synthetically.

01:21 SC: Monoclonal means one clone, one thing, we're gonna just make a bunch of it and give it to people.

01:26 JC: People typically just think antibody is the thing, well, no more so than the ice cream store has ice cream. There are lots of flavors antibodies and some are far more effective than others, and some can even cause harm. So, you have to be careful.

01:40 SC: Right. And this is not like a vaccine where you're actually injecting a person with a piece of a virus or the whole virus killed and then the body is producing antibodies.

01:49 JC: Right. So, what a vaccine is doing is it's artificially teaching your immune system how to make an immune response, including antibodies. With a vaccine, you get the vaccine, your body then knows how to make the antibodies and other immune warriors. With the monoclonal antibody treatment, you have to keep getting it, you can use it either as a preventive like a vaccine or as a treatment. If you're gonna use it as either, you have to keep getting it because it wears off.

02:16 SC: Right. How do you administer monoclonal antibodies to a person?

02:21 JC: For treatment, you have to do it IV and in IV drip. For preventive, where you would get it before you got the disease, you can do it as an intramuscular injection.

02:31 SC: How has this been used to treat people for other infections or other disorders?

02:36 JC: There's a huge industry of monoclonal antibodies for cancer and for auto-immune diseases. But there are very few monoclonal antibodies that have made it to market for infectious diseases. They're rarely used. Two of them are for anthrax for example, which just isn't a big problem.

02:53 SC: Right.

02:54 JC: And another one that's on the market is for HIV infected people who fail all drugs, and then there's one other on the market for respiratory syncytial virus for a certain subset of infants, but that's it.

03:05 SC: So this is something that's been done and that people have taken, but it's not widely used for infection at this point?

03:11 JC: Not yet, but we're right on the precipice of an explosion of monoclonal antibodies for infectious diseases. Several have moved very far in clinical trials and we just had this great success story in the Democratic Republic of the Congo with Ebola, where everything failed, all these drug treatments failed, convalescent plasma failed, but monoclonal antibodies, two different monoclonal antibody preparations worked.

03:37 SC: Well, let's talk about how this is gonna be applied to coronavirus. Actually before that, we should take a little detour to neutralizing antibodies. This these seemed to be the goal of a lot of the research that's going on. Can you talk a little bit about those?

03:49 JC: Yeah, they're the superstars of antibodies. Basically, what neutralizing antibodies do is when they latch on to the virus, they prevent that virus from infecting a cell. In this case, the virus that causes COVID-19 has a protein on its surface called spike, and you have a region of spike at the tip that is really sensitive and needed for the virus to get into a cell, because it binds to a receptor on the cell surface, that's small. And that small region of spike has to hit the receptor just so. So the neutralizing antibodies by and large target that small region of spike. Basically, it's like taking a key that's heading for a lock and putting chewing gum all over it.

04:36 SC: So, we mention what an antibody that is not neutralizing, like a monoclonal antibody that's not neutralizing would do to prevent infection.

04:45 JC: Antibodies can bind all-over spike. They can also bind to the human cell. When they bind to the human cell, they can tell the immune system to turn on a separate arm of the immune system that brings out T-cells. We have a mop-up system of T-cells that can identify infected cells and clear them. And you really want these two things working in concert with each other.

05:10 SC: There are a lot of approaches that you investigated in your story, lots of researchers is going down different paths to try to get this treatment working. What are some of the things that they're trying to optimize about the antibodies?

05:24 JC: There are about 50 different efforts under way to make monoclonals. Start with the simplest thing. Find somebody who's recovered, and then try to pull neutralizing antibodies out of them and then you can actually optimize their neutralizing antibodies, you can mess with that stock of the antibody to give it a longer half life, so it lasts longer in the body. Another thing you can do is you can take the spike protein, and inject it into mice that have human B-cells in them, and they will produce antibodies that you can then fish into the pool you've made and find the best ones that are neutralizing. You can then modify those by making their half life longer.

06:05 SC: Lots of fishing going on, right?

06:06 JC: Lots of fishing going on. You can also create a library of antibodies with a completely synthetic system. And these are not naturally-made in an animal. You can then stick your fishing pole in there. You basically stick bait into there, like the spike protein or just the region of the spike protein that the neutralizing antibodies attach to. That's your bait. That's your worm. And then antibody jumps on that.

06:31 SC: You could have two antibodies that both bind to the spike protein, but different parts. So you kind of have the backup.

06:37 JC: In the case of one of the Ebola monoclonal antibody treatments in Congo that worked, that has three in the cocktail. There's no real limit to how many antibodies you can have, but there is a limit because of cost and manufacturing issues.

06:52 SC: Right.

06:52 JC: There is one other limit that's interesting, Sarah. I mentioned the spike protein has a small region on it that is where the neutralizing antibody wants to attach. That small region can only handle probably two different antibodies that don't overlap with each other.

07:07 SC: And as you mentioned, there are what? 50 different teams chasing this? But now, there's an organizing force out there. This is a consortium started near you?

07:18 JC: Yeah. So the Bill and Melinda Gates Foundation has funded Erica Allman Sapphire here in San Diego, to try and sort through all the different antibodies being made, and help prioritize triage, which ones look best. These consortium ideas make a lot of sense. In practicality, they're often hard to run because not everyone's cooperative. I'm optimistic because COVID-19 has led to more cooperation than I personally have ever seen in the scientific community. These are companies, too, that are competitive. But they're all pledging to work together, so we'll see.

07:53 SC: A lot of what we talked about so far is the mechanism. So we know where it should bind. We know how to improve the lifespan of these antibodies. But what about translating these ideas, these experiments into the clinic? How optimistic are you and researchers about this working in people?

08:10 JC: So antiviral drugs are a big ask when it comes to respiratory diseases. We don't have a lot of them that work. In fact, for viral diseases, in general, it's tough to make drugs. Monoclonal antibodies hold great promise. We know the structure of the spike protein, and how it attaches to human cells. We know how to make monoclonals now much better than we ever have because the technology has improved greatly, through cancer and autoimmune diseases. And we have some hints from convalescent plasma that it can work if used early enough. So, I think there's high hope that these monoclonal antibodies will prove their worth. And the Ebola experience, where everything failed other than the monoclonals, adds to the enthusiasm.

08:56 SC: I'm gonna keep picking at this a little bit longer. So you mentioned that Ebola had three monoclonals in the treatment, but that people are aiming more for two in treating coronavirus, because these are expensive, they're not necessarily easy to produce. Is that gonna be a problem if this does prove to be a really good treatment?

09:14 JC: Yes and no. First of all, in the democratic Republic of the Congo, a second monoclonal antibody that worked was a single monoclonal antibody.

09:24 SC: Oh. Okay.

09:25 JC: Yeah. So it's not necessarily better to have a cocktail. It might be better to avoid things like resistance that could build. But both of those work, the triple, combo, and the single against Ebola. Are they expensive? They have been in the past, but the cost has dropped, I've been told, tenfold in the past 10 years, just as manufacturing has improved. We also are seeing a rush internationally to provide support for treatment and preventives for COVID-19. And my hunch is that if something does work, a lot of money will pour out of wealthy countries. Will there be a problem getting these out equitably to poor people, and they're also hard to deliver? Yes, inevitably. Inevitably, it will be a problem. And there's also the risk of rich people getting it first.

10:21 SC: Right.

10:21 JC: So I think these issues are very real. The Bill and Melinda Gates Foundation's consortium is trying to address this upfront. But these are always sticky, Sarah.

10:31 SC: Oh, yeah.

10:31 JC: Historically, if we look back at what happened with pandemic flu and the vaccine there, the rich countries of the world said, "We'll donate 10% of our vaccines to the poorer countries." That's not the real solution to the problem.

10:45 SC: You talk about a race with vaccine. So if a vaccine comes to clinics before the antibodies do, is there any call for them at that point?

10:55 JC: So the antibodies can be used both as a preventive and as a treatment, in theory. And the antibodies are gonna enter the clinic in June. They probably will have an easier time proving whether they work and are safe than a vaccine. So in all likelihood, if antibodies are effective, they

will prove themselves first. Not necessarily, who knows, but that's how it looks to me today. And on May 1st, that's how it looks.

11:22 SC: Thank you for putting the date in there.

11:24 JC: Yeah, yeah. We're living in coronavirus time now, where everything is so accelerated. Who knows, weird things happen every day now.

11:32 SC: Yeah.

11:32 JC: It could be, we never have a vaccine. [laughter] Let's not get carried about it.

11:37 SC: No, John. No. [laughter]

11:39 JC: Of course, we desperately want one, but there are no guarantees. So could there be a scenario where a vaccine proves its worth before a monoclonal antibody does? Yes. But there also could be a scenario where a vaccine works, and we use monoclonal antibodies for treatment, because the vaccine is not gonna treat infected people. My best guess is we're probably gonna need both of them. And if a vaccine bumps out the preventive monoclonal antibodies, boy, would that be a great problem to have?

12:10 SC: Yeah, for sure. Thank you so much, Jon.

12:13 JC: Yeah, you bet, Sarah.

12:14 SC: Jon Cohen is a staff writer for Science. You can find a link to his story and all of our coronavirus coverage at sciencemag.org/podcast. Stay tuned for an interview with Karen Holl about planning a successful tree-planting campaign.

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12:32 SC: In optimistic or maybe naive moments, I think, why can't we just plant some trees to mop up all this excess carbon dioxide that humans are producing? Don't we have this supreme carbon sink that's optimized by evolution? But it turns out just planting trees is not the fix that many think that it might be. What kinds of trees? Where do you put them? Who takes care of them? All these questions come up as soon as you contemplate planting a tree. Karen Holl wrote about these issues and more in an article in Science this week. Hi, Karen.

13:07 Karen Holl: Hi.

13:08 SC: So in an abstract way, like if we just did the math, could we plant enough trees to suppress climate change?

13:16 KH: Planting trees is an important component of helping to slow climate change, but it's not a silver bullet solution.

13:25 SC: Yeah.

13:25 KH: The estimates of how many trees we can plant vary a huge amount. They depend a lot on how much area you consider would be suitable for planting land. It also depends on what species of tree, how fast they grow, how long the trees stay there. So planting trees is good, but it's not the only thing that we need to do. We absolutely need to reduce our greenhouse gas emissions. And we also need to keep the current forests standing and reduce deforestation.

13:56 SC: So what are some of the things that people are trying to do when they plant trees? It's not always carbon capture.

14:01 KH: People have a huge diversity of reasons that they plant trees. Some people wanna conserve biodiversity. Sometimes they want to improve water quality. Some people it's for aesthetics, in urban areas, they plant trees to provide shade. Other people do it to reconnect with nature. People also plant trees for income because they wanna provide timber, they want to use it for fuel or they wanna use it for fruits or other products from the forest. So that's one of the problems, is that people have different reasons for planting trees, and they aren't always compatible. Sometimes they can be. But if we really want to grow trees for timber, then you wanna have really fast-growing trees, and maybe only a few species is fine. If you wanna restore for habitat, then you want a diverse group of species that provide habitat for different fauna.

14:51 SC: What are some examples of problematic tree planting campaigns?

14:56 KH: So some of the examples of things that have happened, sometimes if you plant into land where people are using it for agriculture, they may just move somewhere else and cut the forest down for agriculture. In other cases, species of trees have been planted that are highly invasive, and then they go and invade the forest. Another negative consequence in really dry regions is that you could potentially actually reduce the amount of water available. Tree planting can have a lot of benefits, socially and ecologically if it's done right. But as you said, you need to think about where you plant, how you plant, or even whether you need to plant, because sometimes the forest recovers on its own without us actually planting the trees. And you can look at the Eastern coast of the United States, and see a huge areas of forests that have recovered without us planting. The really important point here is that we don't see tree planting as a silver bullet to solving climate change and other environmental problems. And also that we do it thoughtfully and carefully, so that we actually achieve the benefits that we'd like to get from tree planting.

16:00 SC: Can you talk about this example that you use in your story of what happened in a tree-planting project in China?

16:07 KH: The Chinese government has really ambitious goals to reforest China, and they're well-intentioned. They are trying to increase their forest cover, in particular, to reduce the amount of erosion of sand into the cities and to improve air quality. And it has had some positive effects. It's helped to reduce erosion. It's also helped to have some impacts to help with providing habitat. But some of the negative effects are that in some of the dry regions, it's produced water supply. They've

also done most of the reforestation, with just a few species of non-native trees. And as a result, the habitat value is much lower than that you would find in a native forest.

16:50 SC: How much did they spend on that? Do you remember?

16:52 KH: The estimates vary a lot, so it's really hard to say exactly, and it depends on what time period. So it's tens of billions of dollars that have been spent on reforestation.

17:02 SC: We should talk about drivers of deforestation. You talked about the fires in the Amazon, and how a lot of the response to that was focused on replanting, rather than a close examination of the causes of the fires.

17:18 KH: So that is one of my biggest messages, which is that we need to reduce the drivers of deforestation, that's even more important than tree planting. Because if we're trying to plant trees but at the same time we're clearing trees elsewhere, then we really don't have a net increase in trees. And it's like a Humpty Dumpty thing, it's a lot easier to cut a forest down than it is to put it back together again. I've spent my whole life trying to restore forest. And I can tell you, despite the best job we do, we're never gonna get exactly what was there before. So the most important thing that we should be doing is we should be protecting intact forests. And then after that, we should be trying to restore tree forests or plant trees.

18:05 SC: And this is a long term project. You can't just say, "Look how many trees we put in the ground."

18:10 KH: That's absolutely true. People think, "Oh, I'm gonna go plant a tree. I'm gonna dig a hole. I'm gonna put it out there. I'm gonna water it, and then I'm just gonna watch it grow." But in fact, it's a lot more complicated, because you need to maintain those trees over time. Make sure that people don't cut them down. Make sure that other weeds don't grow over them, and that they live and it takes... Planting a tree takes decades. They don't count how many trees do we have that are 20 years old or how much area do we have in forests that's 40 or 50 or however old it needs to be to have the values that you want of that forest.

18:44 SC: So, when you pay a credit towards planting a tree, when you buy an airplane ticket, maybe you need to look a little deeper into that.

18:52 KH: Yes, you should think about who is actually in-charge of the tree planting and have they actually figured out where they're planting, are they maintaining them, have they involved this local stakeholders in the project, so that they're actually going to maintain the trees over time? The good news is that some of these really large Trillion Tree Planting Campaigns, they do have principles that talk about these types of things. About involving local communities, about maintaining the trees over the long term, and also about incorporating tree planting as a broader strategy. What we need to do now is really develop better guidelines and practices on the ground and examples where we see tree planting done right. And there certainly are some good examples of that happening. It's going to be the challenge of how do we scale those examples up to that scale that's being proposed?

19:41 SC: Can you give an example of something that does a really good job of matching the context, the landscape, the needs of the local people, a tree planting project like that?

19:51 KH: There are definitely some examples that we talk about in the paper about some work in mangroves in Indonesia. There's also been some really good work done by scientists in Australia who are working in the Philippines, and they're working on looking at why the stakeholders want to plant, why do these farmers wanna plant, and then really working with them so that they maintain the trees over a long term. Another great example is the work that my co-author, Pedro Brancalion has been involved in, in the Atlantic Forest Restoration in Southeastern Brazil, where they have developed the Atlantic Forest Pact, where they have a consortium of over 250 different groups of nurseries, non-governmental organizations, government groups, and scientists who are working to coordinate regional efforts and work the local projects. And they provide scientific input, they help to develop planting protocols and monitoring schemes. And their goal is to be able to restore over 15 million hectares of forest by 2050, and so far, they've succeeded in restoring about a million hectares.

20:53 SC: Looking ahead as climate change continues to ramp up, we don't have a guarantee that trees will be able to reduce carbon as efficiently as they do now in a different environment.

21:04 KH: That's true. Another thing we don't know is how and where trees will grow in the future. We can say, "We're gonna plant trees in a certain area." But we're also losing trees in certain areas, because temperatures are getting warmer. In some cases, their growth rates are slowing. There's also issues with insect outbreaks and fire as the temperature warms and something we've seen in large areas of Canada. So there's definitely questions about how much area will be available for tree planting in the future? Another concern about planting trees is that sometimes people make these big maps of where we should plant trees, and sometimes they have us planting into areas that were formally grasslands. And so those areas that were historically grasslands, when you plant trees into those areas, oftentimes, you have very low success rates and you also are destroying the native habitat.

21:54 SC: Thank you so much, Karen.

21:55 KH: Thank you Sarah, and thank you for the opportunity to talk to your listeners.

21:58 SC: Karen Holl is a professor of environmental studies at the University of California, Santa Cruz. You can find a link to her article at sciencemag.org/podcast.

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22:07 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 listen to the show on the Science website, that's sciencemag.org/podcast. That's where you'll find links to the research and news discussed in the episode. And of course you can subscribe to the show on Overcast, Stitcher, Spotify, Pandora, Apple Podcast, and many other places. This show is edited and produced by Sarah Crespi, with production help from Prodigy, Meagan Cantwell, and Joel Goldberg. Jeffrey

Cook composed the music. On behalf of Science Magazine and it's publisher, AAAS, thanks for joining us.