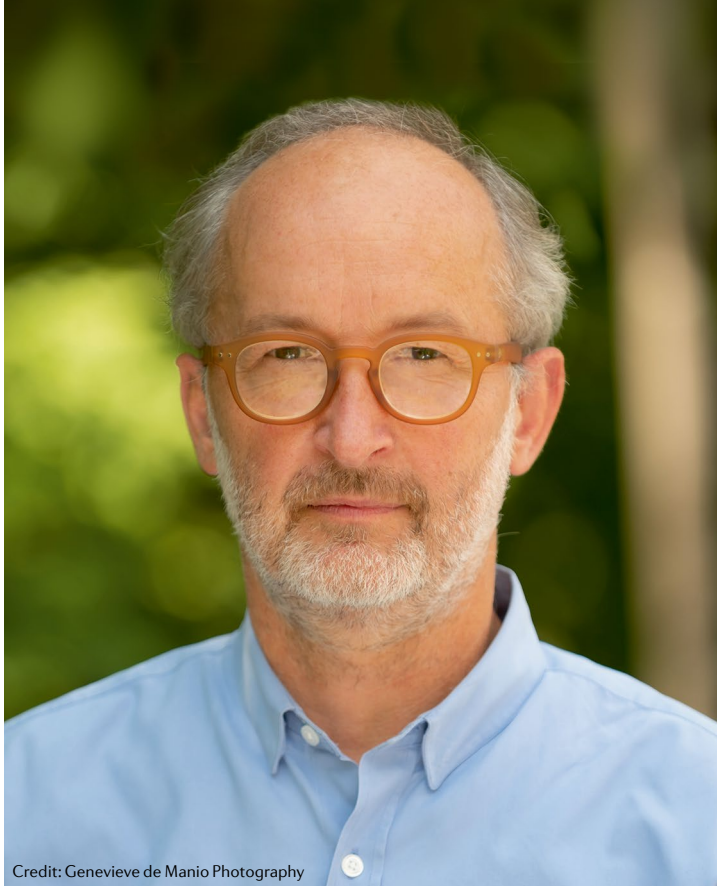
AN AUDIENCE WITH…

Tillman Gerngross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When Tillman Gerngross co-founded Adimab in 2007, his goal was to build a one-stop antibody-discovery shop for biopharma partners in need of biologic therapeutics. In the years since, the company has worked on over 350 programmes from more than 70 partners, helping advance 41 antibodies into the clinic — without ever being tempted into drug development programmes of its own. The onset of COVID-19 has changed that. Although dozens of biopharma firms are already working on therapeutic antibodies that might help keep the SARS-CoV-2 virus at bay, Gerngross and his co-founders of the Adimab spin-out Adagio Therapeutics see an opportunity to use antibodies to tackle coronaviruses more broadly. And, while much of the drug discovery world is laser-focused on the current pandemic, perhaps now is the time to also start preparing for the next outbreak. Gerngross spoke with **Asher Mullard** about broadly neutralizing antibodies for the prevention of coronaviral infections, and more.

When did you start thinking about launching Adagio?

The core mission of Adimab is to focus on accelerating the process by which people's ideas and novel insights into disease biology or disease mechanisms can be turned into high-quality antibody or bispecific drugs. There are a whole bunch of technical challenges associated with that, and I think we solved many of those, but that is our core business.

With the pandemic, however, Laura Walker, Adimab's director of antibody sciences and Adagio CSO, had an important insight into the whole COVID-19 problem. If you look at previous pandemics, the interest in these is typically short lived. Some people may ramp up a drug discovery programme, but these never go anywhere because by the time they can run clinical trials the pandemic is gone. Her view, however, was that coronaviruses have been spilling over into the human population for decades now, as documented by SARS in 2003 and MERS in 2012. Just to be clear: in the past 20 years there have been three coronavirus spillovers into the human population. Probably in your lifetime, most likely even in mine, there is going to be another spillover, right?

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Now, the family of coronavirus called sarbecoviruses — which includes the viruses that cause SARS and COVID-19 — in particular both use the same ACE2 receptor on human cells as their entry point for viral infection. And so Laura said, why not use this as an opportunity to holistically solve the problem of coronavirus spillover? Is it possible to identify antibodies that don't just neutralize the current virus, she wondered, but that will also neutralize the viruses that cause SARS and other related viruses currently circulating in bat populations that could spillover?

That way, next time there's an outbreak, we're not caught again flat footed, playing a game of whack-a-mole. At that point, we'd already have something that we know can hit the domain required for a viral entry, and we have a solution.

The aim here is to find and advance a single broadly neutralizing antibody, or a cocktail of these, that will bind conserved epitopes on related coronaviruses, with therapeutic and prophylactic activity. Dozens of companies are working on SARS-CoV-2 antibodies of their own, with several already in the clinic. Is there any evidence that any of these might also act as broadly neutralizing antibodies for coronaviruses?

We do know what some other folks have, because they've published their work. We've made their antibodies, we've tested them, and they are not broadly neutralizing or they are not very potent. Now, that's not a definitive statement because not everyone has published their sequences. But there's no reason to believe that the sequences we don't yet have would have activity against SARS. In our labs, however, we have found antibodies that are broadly neutralizing, and that potently neutralize SARS-CoV, SARS-CoV-2 and related viruses that are circulating in bat populations.

There is typically a tradeoff for antibodies between specificity and potency. Why don't you think that will be the case here?

That is a true statement. But if you dig one layer deeper, you'll understand why that may not be relevant.

If I have two viruses with epitopes that have, say, 70% homology, I might have tight binding to one and weak binding to another. That means I will always have to compromise between the two, right? But if you can hit epitopes that are highly conserved, you can neutralize both.

Now, the only way to get that antibody is to mine antibody diversity very deeply at the beginning: you're not going to pick five antibodies and get lucky. The long and short of it is that we did not have to compromise on potency: our antibodies are as potent, if not

more potent, than any of the others that are out there. And they are super potent against SARS-CoV and some circulating bat viruses that could yet spill over.

Q Do you think similar epitopes might also exist for other viral threats, like influenza virus? Do you anticipate eventually tackling other virus types at Adagio?
I think the answer is maybe. But that was not the impetus for starting this company. The impetus was that there's a global pandemic, and we had molecules that we think have something to offer that others don't. So, let's advance those as fast as we can.

Q Biopharma's response to this pandemic has been laser-focused on COVID-19, which makes sense given the urgency and gravity of the situation. With Adagio, however, you are thinking a little more broadly about future possible pandemics as well. Do you think there is a need for more, broader-based efforts now to get ahead of future outbreaks?
That is very consistent with our thinking. We really thought about this, and decided that if we just had another SARS-CoV-2 antibody, we would have not started Adagio. There are already other people chasing this. The thing that got us into this is that we had an asset that we thought was differentiated, and our strategy sort of covers an entire class of pathogens as opposed to just one particular virus.

But also, the data coming out of convalescent patients suggest that maybe 30% of people who have had COVID-19 have no neutralizing antibodies. That was a warning sign for us that the vaccines that are in development are unlikely to provide a durable response. When we saw that data, we all of a sudden found ourselves in a world where we realized that the chance of there being a highly effective, safe vaccine that you take once a year, I think is pretty slim.

Q This is Adimab's first spin-out. Do you anticipate others?
I hope not.

Q Why not?
My life is extremely busy. And I'm really only interested in problems that are differentiated and important. In this case, it was all differentiated, important and urgent. So it made sense. But if I'm just another guy solving drug development problems, you don't need me.

Q Adimab has now been involved in more than 350 programmes. Given this breadth of work, what patterns are you seeing in the antibody space?
You know, science is subject to fashion trends like everything else. A couple of years ago, we saw this huge wave of immuno-oncology targets. Everyone was targeting similar pathways. Everyone had similar ideas around combining them. And this played out here, week after week, in our campaign reviews. We had a pretty good insight into the amount of overlap in terms of how people were thinking about this problem. In fact, it was a little bit of a concern because we thought this is going to end at some point, what's going to come next?

What I've found very surprising is that there's just a lot of interesting new biology. And we're just seeing a lot of new interesting applications and new biology. We're doing 50 programmes a year now, and I would say it's getting more diverse, for sure.

Q From the projects you are seeing, have we passed peak immuno-oncology?
Yes.

Q Adimab researchers attempted to establish Lipinski's rules for antibodies, reporting their findings in PNAS in 2017. How has this played out?
Let me give credit to the person that really pushed this, Adimab's co-founder Dane Wittrup. In 2014 or 2015, people were starting to talk about this idea that antibodies discovered in in vitro systems, most notably phage, had developability issues. We didn't know anything about this because we don't use phage. But Dane wondered whether that was true. So he said: "Let's figure it out. Let's make all of the antibodies that are either in phase II, phase III or that are approved, and look and see whether there are metrics that can be used to predict outcomes". This was a huge effort, as you can imagine. And sure enough, there are correlates. And there are red flags. And the more red flags an antibody has, the worse it is likely to do in the clinic.

But with this, we turned a question mark around "should we be concerned about antibodies that have come out of in vitro systems" into a benchmark. Antibody developers have to meet all these criteria, and, if they meet them, there is a good chance they have a developable antibody.

I think what we did is raise the bar, giving the industry tools to assess future outcomes. The reception to this was incredibly strong. It has resulted in us engaging in many, many different collaborations, and that has just helped us build out the data set and refine the rules, if you will.

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Q This paper set thresholds to aim for on 12 different biophysical properties. Do all of your candidates always have to meet all of these thresholds?
We don't actually look at all 12 biophysical properties routinely early in the discovery process, and have found that a subset of these have sufficient predictive power to obviate the need for a full characterization. Once we get to final lead selection, the scope expands to a more complete data set.

If we find an antibody against a very unique epitope, and there's nothing else that hits that epitope, we flag it. We tell our partner, "Look, it has this flag. And don't be worried about that flag yet. But keep it in mind as you select the ones you want to move forward." And we also do have the ability to engineer out those flags later on.

Q What technological challenges still need to be improved or addressed in terms of the discovery and optimization of antibody treatments?
I'm always interested in how technologies develop over the years. If you look at the internal combustion engine, it's not a super elegant piece of engineering. But decades of refining have made that the most dominant heat engine for human transportation. And it's only now being substituted or displaced by electrical engines.

If you look at antibodies, researchers used to have to make cell lines to produce their antibodies. And this is all completely industrialized now. It's unbelievable how plug and play antibody manufacturing has become. Anyone can go to Lonza, or WuXi, or Samsung, or whatever, and get an antibody out the back end. And that's an enormous advantage of this modality over others in my opinion. But the outstanding big risk for this modality, at the end of the day, is just the complexity of a human body.

I've been there. Entire companies are built on this hope that an antibody will work in the clinic. And then they fail. It happens all the time, and it's heartbreaking.