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Mini-organs attract big pharma

Hans Clevers, head of Pharma Research & Early Development at Roche, discusses the role for organoids in drug discovery and development.

Asher Mullard

Credit: Roche

Hans Clevers has always been drawn to scientific blank canvases. “There's a human tendency to ask small questions, where you already know most of the answers, because it feels comfortable to confirm your thoughts. That's not, at least in my experience, how we make unexpected big discoveries,” says Clevers, an immunologist turned molecular geneticist turned developmental biologist. “In my lab, we push ourselves out of the comfort zone — into areas where we may not even know what questions to ask. And then we set up an experimental system, stir it up and see if anything happens.”

With this 'disturb and observe' approach to basic research, Clevers has gleaned key insights over the years into T cell development, gut maturation and colon cancer. Then, in 2009, he stumbled across a way to transform stem cells into organoids — ‘mini-organs’ that thrive in test tubes — and his interests veered into translational research.

“We realized this is not only great basic science, but that it also has a lot of applications,” says Clevers.

Ever since, he has been exploring organoid opportunities — in drug screening, disease modelling, clinical trial design and personalized medicine — in his academic lab, through biotechs and via scientific advisory boards. When he was offered the job as the head of Pharma Research & Early Development (pRED) at Roche, he jumped at the chance to take this organoid research to the next level.

Now one year into the job, he has a fuller grasp of the challenges ahead — not just for organoid innovation but at every step of the drug discovery and development process. “I thought I knew how complicated drug development is. It is even more complicated and unpredictable than I’d expected,” says Clevers. “It's a miracle that it occasionally does work.” Emerging technologies, including organoids, stand to

improve the odds of success, he adds.

What is your vision for organoids at pRED?

Even before I joined, there were already efforts to try to see what organoids could mean for drug development. Within pRED, there was quite an extensive effort to apply human organoids, essentially little human organs, for safety, toxicity, pharmacokinetic/pharmacodynamic (PK/PD) studies, and things like that. But it was scattered throughout the organization, not really centralized.

My belief is that human organoids will eventually complement everything we are currently doing. I'm convinced, now that I've seen how the whole drug development process runs, that one can implement human organoids at every step of the way — from target identification and target validation to safety and toxicity and PK/PD studies, to stratification in clinical trials, and as a tool to predict an individual patient's response in personalized medicine.

But to get there, organoids need to be well validated. And 'validated' is a key word here. Many of the ideas about how to use organoids are not new, but they have not yet been validated at the standards of the industry or of the regulatory authorities. And this validation is something that can only happen at companies.

But I dream of applying organoid technologies everywhere along the drug development pipeline at pRED. And we're building a large, concentrated effort around this — with strong ties with academia — that you'll hear more about in a few months. I hope, through this upcoming initiative, to better connect our scientists to the academic world.

You said organoids will "complement" other approaches. How do you foresee organoids co-existing alongside cell and animal models?

My sense is that organoids will eventually replace cell lines, because you can actually standardize organoids and grow them for as long as cell lines. The cell lines we've been using over many, many years are pretty stable. Organoids are too, and they carry more information. And you can personalize them. You can make a bank of ten different organoids from ten different individuals — carefully selected by age, gender, ethnic background, for instance — and then use these as cell lines.

For high-throughput screening, it's a little more complex. Organoids don't grow flat on plastic, and they are a little bit harder to handle than cells. But people are building 3D screening assays — often driven by image-based analysis, supported by AI approaches — that can be used to extract much more information from a 3D screen than you could ever get from a 2D screen. I'd call this a 'no-brainer'. This will happen.

As already mentioned, and this predates me at pRED, organoids will be used as model systems when no other models exist for safety and toxicity screening. We already have examples where a significant amount of data — and one case where all the data — in an Investigational New Drug application was from organoids or other human models. That is probably going to happen faster.

But of course, there are many old assays on which pharmaceutical sciences rest, and some of these will be hard to replace because they are the gold standards. We are now trying to see what happens when you put a human organoid model right next to the gold-standard model. Does it predict as well, or better? That's something that we need to find out, that we are actively pursuing already.

With the recent passage of a new law in the USA, the FDA no longer needs to require animal data before trials of new drugs can begin. Animal welfare groups have hailed this as a win, but is the science sufficiently advanced for this new law to make much of a difference?

There are a number of simple, straightforward safety assays that can be done in in vitro models now. In the Ames test, for example, bacteria are treated with a drug to see whether it causes DNA mutations. I think we can do better than that, using human models rather than bacterial ones. That's easy.

But animals are of course more than an assembly of a number of simple organs. And organoids are an abstraction of a real organ, not perfect replications. So, if a compound is given to an animal and metabolized in the liver and then has an effect in the gut and the brain, that would be extremely hard to model with organoids. You would have to set up a chip with three different organs on it, and flow them in the right direction. And be it animals or humans, we're dealing with complex organisms. I think there will always be reasons to test drugs in real organisms too.

How is the organoid community working to make its models better?

Organoids right now are made up only of the organ's cells, and they mimic these cells very well. But they don't have an immune system, or blood vessels or other supporting structures. There is a huge unmet need in drug development right now for good models of immune-mediated diseases, including immuno-oncology but also inflammatory diseases like rheumatoid arthritis and multiple sclerosis. Our current models for these disease states have strong limitations, and I'm convinced that if we are able to build more complete organs — and there are many efforts already ongoing to get the elements of the immune system into organoids — then we can get to better disease models.

This is going to be a big task of the next 5–10 years for this field.

The other thing, again, is validating our assays — to convince our colleagues in high-throughput screening facilities and at regulatory authorities that these are useful.

What about more clinical applications, such as organoids as cell therapies or as tools for enrolling patients into clinical trials?

The first thing we thought about with the discovery of organoids was that we could grow organs and transplant these into patients, to solve a huge worldwide problem. But that is exceedingly hard.

Companies have also been thinking forever about how to best use cell therapies, and the CAR T cell therapy space probably provides a business model that is sustainable. I'm part of a large international community of stem cell biologists who are struggling to figure out how to best apply all these insights to advance the use of cell therapies. But, ultimately, I think it's going to be easier to use the growth factors — the proteins that we use to coax stem cells into becoming organoids — than it will be to use the organoids themselves.

As we learn more about the growth factors that each particular stem cell needs, we may be able to turn those insights into the medicines. But that's something that I don't think we will pursue at pRED.

There are also efforts to build organoid biobanks parallel to phase I and II trials. As we follow the patients in these trials, we can see how well their responses were predicted by the patient-derived organoids. The papers that are out there now report a very high percentage of correct predictions — in the order of 85–90%. In the real world, the success rate will probably be less than that. This is something that we currently don't have at pRED, but that we hope to do.

Yet another application would be to use organoid-based drug-sensitivity assays for personalized medicine purposes [to guide patient care in real-world settings].

How long does it take to make patient-derived organoids?

There are now reports that this can be done in about a week, using automation and microfluidics approaches. So it is fast enough in the context of treatment decisions.

What other technologies have caught your eye since joining pRED?

We are active in two fields that have turned out to be difficult: gene therapies and oligonucleotide-based therapies. I find both of these extremely interesting.

When I did my molecular biology training in the 1980s, we thought that we could draw out the exact path to gene therapies — and that it would take another 3 years and everybody would be treated with these. 35 years later, we've realized it's extremely hard. The same is true for the field of oligonucleotide-based therapies, such as antisense and siRNA drugs.

Of course, our bodies are built to keep foreign genetic information out. That's how nature works. And the challenge for these fields is the delivery of the genes and the nucleic acids to the tissues you want them to go to. That's been the struggle for the whole industry. But I find it exciting to see what's been tried before, and we now know that it can work in both fields. These are fields that we are focusing heavily on within Roche.

These are new modalities, and we have only just scratched the surface of how to use them.

Given your interest in the unknown, do you think that your scientific curiosity will take you back towards more basic research questions?

I think any scientists will recognize that when you work on a particular question, you find it is the most important question. But then if you by chance work on a totally different question, you read and you talk to some people and you can quickly get totally absorbed by that other question. And that has happened to me here. I find this

whole challenge of translational science to be so much more unpredictable than my previous life. In an academic lab, you can control almost everything and you still occasionally get surprised. The further you get into drug development, the more and more surprises you find. My mind is now totally focused on these huge intellectual challenges.

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