SANDER HEEZEN

Q&A Hans Clevers
Banking on organoids

In 2009, Hans Clevers and Toshiro Sato (then a postdoc in Clevers' lab) demonstrated a powerful new model to study development and disease: a three-dimensional 'organoid' derived from adult stem cells that replicates the structure of cells lining the intestine. More than 100 labs worldwide are now working with different types of organoid to study cancer and other diseases. Clevers, at the Hubrecht Institute in Utrecht, the Netherlands, discusses the potential of this approach.

Why might it be better to screen drugs in organoids rather than in cell lines?
We don't currently understand why certain tumours are sensitive or resistant to particular drugs. With targeted therapies, you can make a prediction, but for classical chemotherapy drugs, such as cisplatin or 5-fluorouracil, it is totally unpredictable which tumours will respond. Tumours can be sequenced in great detail, but drugs against them cannot be tested effectively other than in clinical trials. Organoids are a very good genetic representation of the tumour, so they let us bridge the gap between deep-sequencing efforts and patient outcomes.

How do you see organoids contributing to the study of colorectal cancer?
We are collaborating with groups at the Broad Institute in Cambridge, Massachusetts, and the Sanger Institute in Hinxton, UK, to build a biobank of organoids from 20 or so people with colon cancer. We have organoids of the cancer and of normal cells from individual patients, as well as sequences of their protein-coding genes. We have established the non-profit Hubrecht Organoid Technology (HUB) to expand our organoid biobanks. The HUB shares these biobanks with academic groups around the world, and now works with about 15 companies on drug-development programmes. We can culture tumours from almost every person with colon cancer, sequence them and test them against drugs. Additionally, we can use research techniques that have been developed for cell lines, such as genetic tools, fluorescence-activated cell sorting and microarrays.

Is this research moving towards clinical trials?
Yes, my group and the HUB are collaborating with Emile Voest at the Netherlands Cancer Institute in Amsterdam on an observational trial. We already have some organoid models from people with colon cancer who receive chemotherapy. The organoids are screened against a panel of common colon-cancer drugs. The patients will be treated the same way the oncologists would normally treat them, but we'll see if we could have predicted the response from our organoids. We're also starting another trial in which we will enrol advanced-colon-cancer patients, for whom there is no standard treatment. We will make organoids, test drug sensitivity and resistance, and then advise the oncologists as to what drug to use for that particular patient. We will be looking at multiple drugs, so we need large numbers of patients — that's the only way we will be able to produce enough data to help us match drugs to tumour types.

To benefit individual patients, won't you need to test the drugs very quickly?
Yes — and that's really where we want to take this technology. When you have pneumonia, your bacterial cultures are tested and you get answers in three days. With this technology, we can tell the oncologist the best odds for a combination of therapeutics, maybe not in three days, but in several weeks. We have an organoid-based test in cystic fibrosis that gives us a result in about two weeks.

How does the organoid approach differ from patient-derived xenografts, in which patients' tumours are transplanted into immune-suppressed mice for testing drugs?
It's the same principle — you get a functional readout of the patient's tumour. But organoids can be tested against an unlimited amount of compounds and combinations. Furthermore, in contrast to xenografts, organoids can be established from almost all patients.

What are some of the next steps in your cancer research?
Organoids model the key component of the tumour but they lack some important elements. We want to combine organoids with other elements to make more-complete tools. For instance, we would like to introduce the immune system so that we can study the effects of the fantastic new immunotherapy drugs. We think that we can build it up in a reductionist way — take lymphocytes isolated from a tumour, bring these together with cancer organoids derived from the same tumour and watch what happens. And maybe we can also put microorganisms in these organoids. For example, we could add *Helicobacter*, a major cause of stomach cancer, to stomach organoids.

Can organoids also help to test drug combinations?
Yes, tumours are genetically heterogeneous, and there can be vast differences in drug sensitivity between clones for the same tumour. We can possibly advance sequence-based therapy by testing millions of drug combinations in organoids. ■

INTERVIEW BY ERIC BENDER