3D cancer cells library

A global effort to create a library of human cancer models using next-generation cell culture techniques launched last summer. The Human Cancer Models Initiative's founding members include the Hubrecht Organoid Technology Foundation in Utrecht, the Netherlands; Cancer Research UK, in London; the National Cancer Institute (NCI) in Bethesda, Maryland; and the Wellcome Trust Sanger Institute in Hinxton, UK. The project aims to make new cellular models of cancer directly from patients' tumors, which they expect will better represent the genetic diversity and physiological relevance of cancer than currently accessible cell lines. The initiative aims to make the library accessible to investigators around the world to study different aspects of the disease such as tumor heterogeneity, disease progression and mechanisms of drugs resistance, as well as to screen for new drugs and to define which treatment is best suited to which cancer.

In the first three years, the project will set up 1,000 cell lines, including lines from esophageal, pancreatic, prostate and rare cancers. If the new models prove valuable, the founders hope to expand the collection to 10,000, a number that could potentially capture the diversity of both rare and common genetic subtypes in cancer.

Different technologies will be used, among them a three-dimensional (3D) cell culture method known as organoids, derived from a technique developed by Hans Clevers's research group at the Hubrect Institute (*Nature* **459**, 262–265, 2009). It involves growing stem cells in suspension and, using the right conditions, coaxing them to self-assemble into organized 3D clusters. Researchers have attempted to model all types of tissue, including the brain, with this technology, and for this initiative will embark on making organoids directly from a patient's tumor. Because they are 3D, they are near-physiological models and reflect some of the characteristics present in that individual's cancer (*Cell* **161**, 933–945, 2015). "We can make a tumor model from most patients," says Robert Vries, managing director of the Hubrecht Organoid Technology Foundation. Additionally, the organoid cultures accommodate high-throughput drug screening. That paves the way for creating panels potentially useful for testing patients' responses to treatment. "That makes personalized medicine more than a word," says Vries.

> **"Until last year, influenced by European NGOs, the country [Tanzania] maintained such strict laws against plant genetic engineering that scientists were unable to continue their work. That has now changed."** Former anti-GM activist Mark Lynas, comments on Tanzania's field testing drought tolerant GM wheat variety. (*MIT Technology Review*, 5 October 2016)

obtain viral isolates directly from the field. The work resulted in a productive collaboration with researchers in Brazil and WRAIR to develop vaccine candidates. The groups published two papers this year (*Nature* **536**, 474–478, 2016; *Science* **354**, 237–240, 2016) showing that three vaccine modalities—a DNA vaccine, an adenoviral-based vaccine and a purified inactivated vaccine—protect mice and monkeys from infections with Zika isolates from both Brazil and Puerto Rico. "We not only showed that the vaccines work in mice and monkeys, but we showed that vaccination is possible for Zika, how it works, why it works, and most importantly, the antibody titers that are needed for protection," says Barouch. "Those can be useful guideposts in a clinical development program. The inactivated viral vaccine WRAIR will be taken forward into clinical development, under a cooperative R&D agreement between WRAIR and Sanofi. The Paris-based pharma already has vaccines under development for dengue and Japanese encephalitis virus. WRAIR will transfer the vaccine (ZPIV) to the French pharma, along with data on neutralizing antibody responses data. Sanofi will take on the tasks of scaling up for phase 2 studies and developing a regulatory strategy. In the meantime, phase 1 studies of the vaccine will be going on sponsored by National Institute of Allergy and Infectious Diseases (NIAID).

The two DNA vaccines, however, are first off the blocks. Both, one from NIAID and another from the Plymouth Meeting, Pennsylvania–based Inovio, are already in phase 1 testing. All the vaccines contain essentially the same viral sequences—pre-membrane and envelope—and have performed well in animal studies. Although there are no approved DNA vaccines for humans yet, NIAID's director Anthony Fauci is optimistic, given the results of animal testing, particularly in monkeys, which he describes as "outstanding." DNA vaccines allow investigators complete flexibility to choose which antigen and sequences to include, a practical advantage that has put them at the head of the line. However, DNA vaccines can be less effective than virally based vaccines: the Beth Israel/WRAIR DNA vaccine required repeated administration and was substantially less immunogenic than inactivated vaccines in monkeys. Fauci and others concede that in the final analysis, they may well not be the most efficacious.

At an October news briefing, Fauci announced that an 80-patient trial of its DNA vaccine VRC-ZKADNA085-00-VP, is underway at three sites, and is fully enrolled. In the meantime, NIAID is preparing for phase 2 trials of 2,400–5,000 individuals to take place at 15 sites where the virus is still active. The $152 million coming to the NIH as a result of the new funding measure will enable a smooth transition into the larger trials, as well as furthering preclinical development of other candidates.

Diagnosing the Zika virus is still a challenge, as tests are confounded by its similarity to other flaviviruses. "Anywhere where people are infected on multiple occasions with flaviviruses, their serum cross-reacts with almost every flavivirus on the kind of diagnostic tests that are available—even neutralization, which is generally the most specific test," says Scott Weaver, who directs the Institute for Human Infections and Immunity at the University of Texas Medical Branch in Galveston. PCR-based tests are more specific than serum reactivity, but because the virus is cleared from the bloodstream within five days after symptoms appear, these tests can only be used for early detection. Better diagnostics are in the works that use the non-structural protein NS1, which has greater structural diversity, but these tests are not commercially available yet.

So far, Brazil appears to be an outlier with respect to the incidence of microcephaly in comparison with other places where Zika has been, where the incidence of microcephaly did not rise above its natural rate of occurrence. The jury is still out in places like Colombia and Puerto Rico, which are a few months behind Brazil, but not for much longer. In the next few months, women infected in the first trimester will start having their fetuses diagnosed for microcephaly with ultrasound or amniocentesis. As far as controlling the spread, efforts to control the mosquito population through genetic engineering are running up against opposition from members of some of the communities where testing has been proposed (*Bloomberg News*, 6 October, 2016).

Even with these promising Zika vaccines and therapeutics in the pipeline, funding for the work remains the main hindrance to a timely response. Pharma companies that stepped up during the Ebola crisis felt burned, according to Weaver, as the waning of the epidemic left them without a population for testing drug and vaccine candidates, after pouring money into their development. And when Congress failed to pass funding bills, some manufacturers broke off negotiations with government agencies, according to NIH's Nicole Lurie. NIAID's Fauci suggests setting up a global health reserve fund, a health-based Federal Emergency Management Agency. For now, funding is patchy and for some programs, for example the Beth Israel/WRAIR vaccine program, it remains largely philanthropic.

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