Ten years ago Shinya Yamanaka and colleagues from Kyoto University (Japan) described the creation of induced pluripotent stem cells (iPSCs), first from mice, then humans a year later. The ability to ‘reprogram’ mature cells into iPSCs by introducing genes that encode specific transcription factors, enables them to divide indefinitely and give rise to any cell type in the body. This pioneering feat won Yamanaka the Nobel Prize in 2012 and revolutionized stem cell biology.

The biomedical promise was great: it was hoped that patient-derived iPSCs could be used to replenish damaged or diseased tissue. However, the inability to predict iPSC behavior when injected in vivo has hindered their direct regenerative utility. This was exemplified when the first clinical trial using cells derived from human iPSCs was recently suspended owing to genomic abnormalities, as reported by Nature Biotechnology on September 8, 2015. While iPSC researchers are spending considerable efforts circumventing this challenge, their use as an in vitro platform to model disease has flourished.

There is a constant need to develop highly relevant preclinical disease models. The better the model, the greater the chance of finding clinically-useful answers. The advent of patient-derived iPSCs offers several advantages over traditional cell culture. First, unlike regular somatic cells that divide a limited number of times, iPSCs can self-renew, thereby offering a limitless supply of human cells to develop in vitro models. Second, iPSCs derived from patients with a disease can recapitulate the genetic and epigenetic features of that disease more faithfully than existing established cell lines. iPSCs provide an opportunity to dissect the underlying pathophysiology and interrogate them with therapeutic agents to assess and tailor their response.

Kevin Eggan and Clifford Woolfe, from the Harvard Stem Cell Institute (USA), harnessed this potential by deriving motor neurons from iPSCs made from patients with the fatal neurodegenerative disorder, amyotrophic lateral sclerosis (ALS). They found that ALS patient-derived motor neurons that harbor mutations in superoxide dismutase 1 (SOD1) display a hyperexcitability phenotype due to a deficit in potassium channels at the cell membrane. Furthermore, they demonstrated that retigabine, an anti-seizure drug that opens potassium channels, can normalize this phenotype and increase their survival. This finding precipitated an interventional Phase 2 clinical trial and ALS patients are currently being recruited to receive retigabine (NCT02450552).

This dish-to-patient study exemplifies the translational potential of iPSC technology. It also challenges the traditional practice of testing drugs in animal models, expediting the process and bypassing a costly, ethically problematic and often scientifically-flawed system.

It was also discovered that iPSCs, when grown in specific culture conditions, had an intrinsic capacity to form self-organized clusters of cells. These 3D structures were termed ‘organoids’, after their ability to mimic certain aspects of an organ’s in vivo physiology. Organoids provide a unique means to study aspects of organ development in a stable and tractable model system. Many comprise multiple tissue-types, recreating the reciprocal cellular interactions found in the body. Kidney, hepatic, intestinal, pancreatic, gastric, lung, fallopian tube, testicular and salivary gland organoids have already been described and used to address biological questions that were otherwise impossible using standard 2D culture. In 2013, Madeline Lancaster, now at the University of Cambridge (UK), developed a protocol for culturing cerebral organoids — had the last and grandest biological frontier been conquered? Analyzing their gene expression programs revealed remarkable similarity to the fetal neocortex. However, tissue and batch heterogeneity remain a challenge, driving the quest for new protocols that can enrich specific neuronal cell types and direct organoids towards a desired neural phenotype.

Nevertheless, organoids derived from patient-iPSCs have already been deployed for clinical gains. For example, human intestinal organoids have been used to study cancer, cystic fibrosis (CF) and inflammatory bowel disease in the laboratory of Hans Clevers at Hubrecht Institute (The Netherlands). Interestingly, organoids derived from rectal biopsies of CF patients fail to ‘swell up’ when cultured in forskolin, unlike healthy counterparts. This functional organoid assay enables the identification of patient responders to a given drug, saving time and money on administering ineffective drugs and providing a personalized approach to tackle CF.

If iPSCs can model disease at a cellular level, and organoids can model disease at a tissue level, is there a way of modeling disease at an organ or even systems level? Several institutes have embarked on organs-on-a-chip technology, a platform that combines cutting-edge bioengineering devices with multiple cell types to create a microchip with organ functionality. For example, The Wyss Institute for Biologically Inspired Engineering at Harvard University (USA; http://wyss.harvard.edu/), have created a lung-on-a-chip that comprises a porous membrane separating lung and capillary cells, and flanking channels that recreate mechanical stress, air flow and the blood stream. This chip has been used to mimic pulmonary edema, the immune response to bacterial insult, and personalized by incorporating patient cells to understand their function and response to therapy. Their ultimate goal is to recreate 10 different organs-on-a-chip, then test if they can function together when placed in parallel to replicate a system, the so-called body-on-a-chip. The deadline for this ambitious challenge is early 2017 and the world will be waiting to see if this goal can be achieved.

The ability to meld scientific disciplines to develop state-of-the-art disease models has entered an extremely exciting phase. It is important that biorepositories are effectively characterized, cataloged and coordinated to maximize the useful information that can be gleaned. John Gurdon, co-recipient of the Nobel prize with Yamanaka once said “It is
particularly pleasing to see how purely basic research, originally aimed at testing the genetic identity of different cell types in the body, has turned out to have clear human health prospects. “The full extent that human health will benefit remains to be seen, but this truly is translational medicine in action.”