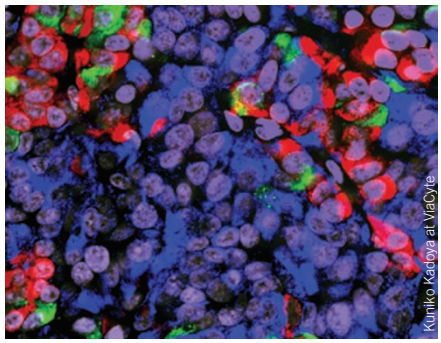
Human iPSC and ESC translation potential debated

The first meeting dedicated to charting a road map for pluripotent stem cells to move into the clinic held jointly by the US National Institutes of Health (NIH) and the Food and Drug Administration (FDA) took place in March. Industry, academia, clinical scientists, the FDA and the NIH gathered for a two-day workshop, "Pluripotent Stem Cells in Translation: Early Decisions," in Bethesda, Maryland, to debate challenges and issues in the commercialization of stem cell therapies—whether derived from human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) (**Table 1**).



ViaCyte's pancreatic islet-like structures (shown above) obtained by transplanting hESC-derived pancreatic progenitors into rodents. The structures contain cells responsive to glucose (blue for insulin, red for somatostatin; and green for glucagon).

As the human ESC and now iPSC fields make rapid strides, researchers are praising federal programs that support and regulate this research. Mahendra Rao, vice president for Life Technologies in Carlsbad, California, commends the FDA for being "ahead of the curve" in formulating regulations in this area.

Work on iPSCs faces many of the same regulatory and technical challenges as that on human ESCs—but less in the way of political opposition. FDA officials at the meeting were vague about what they will be expecting from sponsors developing clinical products, but safety issues were clearly further to the fore than efficacy at this early stage. Companies were advised to undertake early and repeated consultations with the agency on any candidate products that would demand proprietary consideration.

The FDA and NIH are not the only government agencies proving helpful in guiding clinical development of iPSCs—so are the National Institute of Standards and Technology and the National Institute of Environmental Health Sciences. The federal investment in stem cell science comes mainly from NIH, which supports about 550 'activities' and spends about $1 billion annually, or ~3.5% of its overall budget, according to Story Landis of NIH, who heads the National Institute for Neurological Disorders and Stroke and chairs the NIH Stem Cell Task Force. Although NIH does not track its specific investments in iPSC research, that area is increasing but "not at the expense of human embryonic stem cell research," she says.

Federal support and FDA precocity in this area notwithstanding, researchers developing iPSC products face plenty of hurdles. "We need tests for every stage," says Life Science's Rao, including tests that will help "define the quality of cells" when procedures are scaled up for commercial production. Consider iPSCs that yield differentiated dopaminergic human cells, which the company is developing to treat patients with Parkinson's disease, he says. "Manufacturing variability ranges from 20% to 40%; it's not a pure population by any stretch. Is this okay, or do we need higher purity when we go into the clinic?" A related question comes from testing such dopaminergic human cells in mice. "We have made cells that look like a transplantable product and that work in animals in standard tests," he says. "Can I use them in humans? It's still an open question." Similar questions apply to cells derived from hESCs, he notes.

Unpredictable changes in the reagents used to grow such cells also give rise to quality control issues according to Gordon Keller of the Ontario Cancer Institute in Toronto. Not only is "each cell line different," he says. They also sometimes behave in unexpected ways when grown on different batches of supposedly identical reagents. "We're nowhere near where we need to be with these reagents."

IPSCs have unique safety concerns according to Melissa Carpenter of the Carpenter Group in San Diego. One question is whether genetic and epigenetic errors introduced while reprogramming iPSCs might be transferred into terminally differentiated cells intended to be transplanted into patients. "The jury is still out" as to the extent of this risk, but it raises tough questions about establishing proper criteria for releasing cell lots for clinical use, she says. These questions are difficult to address experimentally, particularly when it involves testing human cells intended for clinical use in mice.

Another concern is whether, once transplanted, ESC- or iPSC-derived cells could give rise to teratomas in recipients. That possibility

IN brief

Melanoma antibody approved

BMS headquarters in NYC.

The March 25 US Food and Drug Administration (FDA) approval of Bristol-Myers Squibb's Yervoy (ipilimumab) for metastatic melanoma was expected, but the breadth of the approval was not. Yervoy, a human monoclonal antibody targeting cytotoxic T-lymphocyte activator-4 (CTLA4) developed by the New York–based company, is the first agent to prolong survival in a phase 3 trial in metastatic melanoma (*Nat. Biotechnol.* **28**, 763–764, 2010). The FDA has given the green light for Yervoy to be used in a first-line setting even though the pivotal trial included only individuals who had progressed on other treatments. It was "exactly the right decision," says oncologist Mario Sznol of Yale University in New Haven, Connecticut, as no current first-line treatment improves survival in metastatic melanoma. FDA approval also allows patients who respond initially to Yervoy, but who later relapse, to receive another course of the drug. Sznol expects rapid adoption of the drug by oncologists, despite a $120,000 wholesale price tag for a single four-infusion course of treatment. "The first thing that has to be on your mind when somebody comes in with metastatic melanoma would be ipilimumab, based on the data," Sznol says. Chris Schott, a pharma analyst at JP Morgan in New York, raised his earlier Yervoy estimates based on the higher-than-expected pricing, and now forecasts sales of $170 million in 2011, growing to $1.25 billion by 2015. Defending the price, Bristol-Myers Squibb spokesperson Sarah Koenig stresses the company's aggressive patient-assistance program. In the US, this "will enable coverage of virtually all, approximately 98%, of uninsured patients," she writes in an e-mail. Another metastatic melanoma drug likely to win approval in the near term is PLX4032 (vemurafenib). PLX4032, a small-molecule inhibitor of mutant BRAF, was developed by the Berkeley, California–based Plexxikon, which was acquired by the Tokyo-based Daiichi Sankyo on April 4. PLX4032 produces higher response rates than Yervoy and an undisclosed survival benefit, although virtually all individuals taking the treatment relapse. So the drug probably won't hurt Yervoy sales even in the roughly half of metastatic melanoma patients who qualify for PLX4032, says Sznol, as most will end up taking Yervoy eventually. Plexxikon plans to apply for FDA registration this year.

Ken Garber