will probably take 1.5 million cells, there will always be numerous cells that are not of the cell type intended to deliver to the patient.

The pluripotency of ES cells is not only their virtue, but also their vice. As Kenneth Chien of Massachusetts General Hospital and Harvard Medical School in Charlestown, Massachusetts, who served a consultant to the FDA Cellular, Tissue and Gene Therapies Advisory Committee when it met last April, admits, hES cells are "probably the most complex human therapeutic imaginable." ES cells can produce teratomas, an accumulation of many different cell types resulting in a benign form of tumor. But teratomas can grow and fill confined anatomical spaces, such as the central nervous system and spinal cord, which could prove disastrous. In addition, teratomas have some tendency to lose their differentiated status to develop into frankly malignant teratocarcinomas.

hES cells are "probably the most complex human therapeutic imaginable."

Developing a standard screening for teratomas, or teratocarcinomas, is a "key barrier" to overcome, says Chien. Committee member Savio Woo of the Mount Sinai School of Medicine in New York agrees that every commercial sponsor will need to demonstrate to the FDA what number of cells is safe for each such product. Rigorous criteria will be needed "before jumping into patients." Many committee members concurred that it would be unacceptable if cancers derived from hES cells developed in patients involved in pioneering clinical trials. Another unanticipated outcome could result from hES cells entering a site and either not doing what they are supposed to or increasing susceptibility to the very disease they are intended to treat.

Yet, Ole Isaacson of McLean Hospital of Harvard Medical School, in Belmont, Massachusetts, believes this complexity might work in the opposite way, proving beneficial to patients. Because hES cells are subject to "feedback control," they are unlike "conventional pharmacologic agents" and thus may behave properly when situated in a particular anatomic site, he suggests. To make matters even more complicated, another committee member, Doris Taylor of the University of Minnesota in Minneapolis, felt that accessory cells within the hES donor mix—which are distinguishable from the 'main' cells and somehow aid them—could prove critical to the overall potency of hES cell batches, adding to the difficulty of defining product purity.

Indeed, there was wide agreement among the FDA committee that setting cell purity standards too high could also "backfire." Within a batch of hES cells administered to a patient, there may be a minority of accessory cells that may be necessary for poorly understood cell-cell signaling—possibly to provide feedback, for instance to insulin-producing cells to either boost or shut down their activity. Nonetheless, defining the degree of tolerable differentiation for cells, acceptable thresholds for their "heterogeneity" (in regard to their states of development), and other criteria for releasing cell lots will be needed. Requirements will doubtless be tailored to reflect the specific hES cells products for specific clinical applications and particular kinds of patients.

Such uncertainties need to be addressed with extensive studies in animals before hES cells can venture into the clinical arena. Generally, the aim is to "mimic the human setting as well as possible," says Jane Lebkowski, senior vice president of regenerative medicine at Geron, referring in this case to hES cells being developed to treat spinal-cord injuries that are being tested in rodents. Yet, even here, complications set in, according to Melissa Carpenter, former vice president of R&D at Novocell. Such testing of hES cells in rodents requires giving the animals immunosuppressive agents so that they can tolerate hES xenografts, or using 'nude' mice with genetically impaired immune systems that accept transplanted cells—deviating from the anticipated clinical protocols, which would involve transfers of cells between individuals of the same species. One exception is the hES retinal pigment cells being developed to treat macular degeneration, because the eye is "privileged," meaning that such cells are not subject to rejection, according to ACT's Dinsmore.

Dosing issues might be best addressed in nonhuman primates, or other species bigger than mice and rats, to gain a better idea of how many cells to use. But because of immune-suppression complexities and the spiraling costs involved in moving away from mice into larger animals, the panel steered away from insisting on this option. Despite the immunogenicity caveats, safety and efficacy are needed for the lead-up to any clinical trial, and hES cells are no exception.

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IN brief

Canada charts biologics path

Health Canada has posted a draft guidance for the approval of biogenerics, which it has termed subsequent entry biologics (SEBs). According to the government agency's guidelines, manufacturers can include a slimmed-down clinical package in their submission as long as they can show similarity between their product and a previously approved biologic, even one not approved in Canada. Manufacturers can rely in part on publicly available information, but must show—through side-by-side comparisons—that the quality, safety and efficacy of the SEB is comparable to those of the original biologic. Andrew Storey, vice president of Cangene, a biopharmaceutical company based in Winnipeg, Manitoba, welcomed the guidance but has reservations. "You want doctors to be able to prescribe it like a generic drug, but [Health Canada] is suggesting that additional studies will be required. That's not the case for generic drugs and that shouldn't be the case for [subsequent entry] biologics." Health Canada will convene a stakeholder consultation in early June. In the US, California has recently introduced a bill that paves the way for biogenerics legislation. 'The Pathway for Biosimilars Act' proposes a minimum of 12 years' exclusivity, plus another 2 years for a medically significant innovation. The European Agency for the Evaluation of Medicinal Agents has already implemented a regulatory pathway for 'biosimilars' and is reviewing a raft of new products. *—Hannah Hoag*

FDA gets personal

New guidelines published by the US Food and Drug Administration (FDA) bring the prospect of personalized medicine a giant step closer. The document, released in April, aims to ensure that consistent definitions of key terms in pharmacogenomics are applied across the US, Europe and Japan, the three regions covered by the International Conference on Harmonization, a project gathering together regulatory authorities and pharma experts. "If we don't have a commonly agreed upon understanding of the terms that we are using, we cannot harmonize on issues for which these terms are critical," says Felix Frueh of the Center for Drug Evaluation and Research at the FDA, in Silver Spring, Maryland, who helped compile the report. "Adherence to this terminology will facilitate and streamline drug applications and submissions," he says. The document defines a 'genomic biomarker' and the difference between 'pharmacogenomics' and 'pharmacogenetics'. It also aims to unify the way that biological samples and their associated genomic data are coded. The guidelines came just as ParagonDX of Morrisville, North Carolina, received FDA clearance for its warfarin-sensitivity kit. At the same time, the National Institutes of Health has put out a call for researchers' input into current needs in pharmacogenomics research. The initiative's objective is to "highlight opportunities, reveal gaps, and aid in identifying specific, achievable goals that will advance the field." *—Henry Nicholls*