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Imaging electrons' behavior

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Researchers could be forced to turn over data to anybody who asks.

CELL BIOLOGY

A Versatile Cell Line Raises Scientific Hopes, Legal Questions

Imagine being able to reach into the freezer, take out a cell culture, treat it with growth factors, and produce almost any tissue in the human body. Sounds like science fiction? Today, it is. But the raw material for such human tissue engineering—in the form of a type of universal cell called a "stem" cell—is now growing in the laboratory. In a long-awaited announcement, biologist James Thomson and his team at the University of Wisconsin, Madison, report in this issue of *Science* that they have isolated stem cells from human embryos and coaxed them to grow in five "immortal" cell lines.

Other biologists are hailing the work, reported on page 1145, as an important advance that will provide a powerful tool for biological research. In a matter of years, some researchers say, it may even be possible to use such cells to repair blood, bone, and other tissues. But the achievement has also created a dilemma, which will only intensify as other groups who are close behind Thomson's report similar feats: Many researchers who would ordinarily jump at a chance to use and develop these cells may not be able to do so, because they may be blocked by a U.S. law that forbids the use of public funds for research on tissues derived from human embryos. As *Science* went to press, the National Institutes of Health (NIH) was reviewing whether these cell lines come under the law. The law may apply in this case because the cells used to create Thomson's cell lines came from embryos donated to research by couples at in vitro fertilization (IVF) clinics in Wisconsin and Israel.

Thomson had to carefully wall off his own research from any public funding, by setting up a separate lab in a building "across campus" from where he does NIH-funded research. All the equipment and personnel in the duplicate lab are funded privately, mostly by the Geron Corp. of Menlo Park, California, plus a grant from the Wisconsin Alumni Research Foundation, the university's patent agent. In return, Geron expects to get an exclusive license for commercial uses of Thomson's technology.

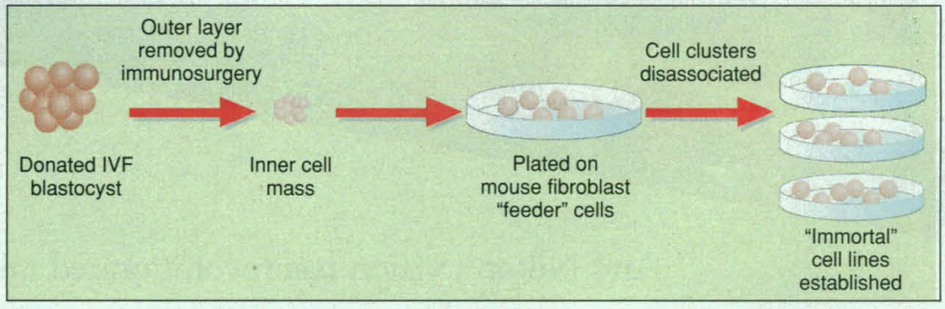
The challenge Thomson faced was to create an environment that was neither too harsh, which would prevent the cells from thriving, nor too cozy, which would allow them to differentiate into specialized forms. Thomson, who began working with embryos from rhesus monkeys 5 years ago, stimulated cells from days-old human embryos, called blastocysts, to grow on a layer of mouse "feeder" cells in a lab dish. Other researchers had gone this far, but Thomson took the next step: He coaxed the balky cells to continue growing without differentiating—making an irrevocable commitment to grow into a particular type of tissue. Thomson nudged the cells gently into this new state through very "labor-intensive" tending, he says, and their chromosomes survived intact. (Tumor cells are immortal, too, but their DNA is usually deranged.) And judging by the presence of a critical enzyme called telomerase, which repairs frayed chromosome ends, Thomson concludes that the cells are capable of reproducing indefinitely. Yet tests showed that the cells retain the potential to develop into all the basic tissue types.

Only a few of Thomson's peers had learned of his accomplishment last week, but those who knew of it said they were impressed. Austin Smith, a stem cell researcher at the University of Edinburgh in Scotland, called it an "extremely important" milestone. Molecular biologist Brigid Hogan of Vanderbilt University in Nashville, Tennessee, a pioneer of mouse stem cell technology, calls the development "very encouraging." John Gearhart, a developmental geneticist at The Johns Hopkins University School of Medicine who is using a different method to establish a culture of human embryonic cells, describes Thomson's research in a commentary on page 1061 of this issue as "a major technical achievement with great importance for human biology."

Gearhart was in a close race with Thomson to publish first but wasn't able to move his project along quite as rapidly. In a paper coming out in the 10 November *Proceedings of the National Academy of Sciences*, Gearhart will announce that he, too, has established a line of embryonic stem cells. His are derived from primordial germ cells, precursors of sperm and oocytes, isolated from medically aborted fetuses. Gearhart and his team have sustained some of these cells in culture for as long as 9 months, but he concedes that "Jamie [Thomson] has done a lot more" to characterize his stem cells and deserved to be first. Like Thomson and Roger Pedersen, another stem cell researcher at the University of California, San Francisco, Gearhart turned to Geron for support because it was unclear whether he could do the work with public funds. And, like the other two U.S. groups, his team plans to license patents to Geron.

Other developers of human embryonic stem cell technology are close behind. Martin Pera at Monash University in Clayton, Australia, reports that his team—together with scientists at the Hadassah Medical Center in Jerusalem and the National University of Singapore—has "achieved extensive serial cultivation" of cells from human blastocysts, which he expects will meet the criteria for human embryonic stem cells. Smith says that his team at Edinburgh has been trying to develop a human stem cell line, too, but doesn't yet have anything to announce.

Thomson says the first big payoff will be to aid fundamental research on human devel-



Labor-intensive. James Thomson's technique requires a deft touch for cells to grow without differentiating.

opment. He points out that the details of human embryo development after implantation are essentially unstudied. Animal models haven't been useful, he says: "For example, the placenta and all the extraembryonic membranes differ fundamentally between humans and mice." Now, scientists may be able to produce cells specific to stages of human development that have been inaccessible to research. By manipulating gene expression in these cells, they might be able to probe how development can go wrong.

Another payoff, one that could be lucrative for Geron in the not-too-distant future, according to Geron Vice President Thomas Okarma, will be drug screening. Okarma says, "The potential to supply unlimited quantities of normal human cells of virtually any tissue type could have a major impact on pharmaceutical research and development." Cell lines used for drug screening are currently derived from animals or "abnormal" human tissue, such as tumor cells.

"Home run." Geron VP Thomas Okarma sees potential for tissue repair.

The real "home run" of this technology, Okarma says, is the "enormous" possibility that researchers might be able to tailor stem cells genetically so that they would avoid attack by a patient's immune system, then direct them to specialize into a particular kind of tissue and transplant them into diseased organs. Geron suggests it might be possible to repair damaged heart muscle by injecting new cardiomyocytes, for example. Okarma points out that researchers have already used mouse stem cells to produce cardiomyocytes that were successfully transplanted into a mouse heart.

But that possibility also remains the most distant. "Right now," says Thomson, "we don't know how to direct [stem cells] to become any specific cells." And developing cells that can be immunologically suitable for transplantation will take even more work. Still, Thomson says, "it's no longer in the realm of science fiction; I really believe that within my lifetime I will see diseases treated by these therapies."

For some researchers, however, the complicated legal issues associated with the cell lines may prove discouraging. Federal law governing this topic was updated most recently in the 4000-page appropriation bill Congress passed on 20 October. It says U.S. funds may not be used for "the creation of a human embryo" for research purposes, or for "research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death. ..." The embryo is defined as any organism not protected as a human subject under other laws (such as those applying to fetal tissue) "that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or diploid cells."

When NIH officials learned of Thomson's work, their initial reaction was that federal funds could not be used for research using his cell lines. But director Harold Varmus sought legal counsel, and a top aide told *Science* that the cells may be exempt from the law because they could not grow into embryos. NIH was scrambling to come up with a final ruling by the time Thomson's paper was published. The cell line Gearhart is developing may not have the same legal complications because it was derived from fetal, not embryonic, cells.

The law clearly prohibits the use of federal funds for the initial development of an embryonic stem cell line, however. Okarma says Geron carefully considered the ethical implications before proceeding. "We recognize and affirm that there is moral authority associated with this tissue," he says. Geron has established a panel of ethical advisers, chaired by Karen Lebacqz of the Pacific School of Religion in Berkeley, California, representing "five different religious traditions," Okarma says. The panel approved the stem cell project, he says, on the basis that Geron was making beneficial use of fetal tissue and IVF embryos that would have been discarded or frozen indefinitely.

Researchers are hoping that the legal uncertainties hanging over Thomson's cell lines can be cleared up quickly. "People have been a little scared off by the controversy" already, says Smith, and "it would be a tragedy if [legal barriers] exclude the best people" from the field.

–ELIOT MARSHALL

U.K. RESEARCH FUNDING

Life Sciences Win Bulk Of Cash Bonanza

LONDON—When the British government announced in July that it would pump an additional $1.1 billion into science spending over the next 3 years, researchers whose budgets had been squeezed hard for more than a decade greeted the news with delight. Last week, the government released the details of how this new largess will be distributed, and life scientists were left cheering the loudest.

Among Britain's six research councils, which provide most of the government's funding for basic research, the biggest increase—6.8% above inflation—will go to the Medical Research Council (MRC). "I'm enormously pleased," MRC chief executive George Radda told a press conference in London when the allocations were announced last week. The MRC subsequently said it would spend part of its increase on three major new initiatives: in mouse genetics, cancer research, and the study of the human form of mad cow disease. Not everyone is celebrating, however. The council responsible for particle physics and astronomy is slated to get no significant increase in real terms.

These increases are the fruits of a yearlong comprehensive review of government spending launched by the Labour government soon after it was elected in May last year. The first results of the review, announced in July, put science among the most favored areas of spending (*Science*, 17 July, p. 314). When he announced the allocation of the promised money last week, trade and industry secretary Peter Mandelson, the Cabinet minister responsible for research, said he wanted the increases to tackle the "post-genomic challenge": helping British scientists exploit advances in genetic research in which they have been key players.

All smiles. John Collinge will head new CJD center.

This is reflected in the allocations: Alongside the MRC's 6.8% boost, the other two councils involved in life sciences—the