examined samples of mammary gland cells to see when extra centrosomes appeared. That turned out to be just 90 days after the carcinogen treatment began, when the tissue showed precancerous changes but had not formed full-fledged tumors, Brinkley says.

Salisbury has also detected centrosomal abnormalities in ductal carcinomas in situ—an early stage of human breast cancer. And Doxsey and his colleagues report in the March issue of *Cancer Research* that they have found the abnormalities in a variety of early cancers, including 15% to 20% of prostate cancers.

Doxsey and his colleagues are now exploring whether centrosome abnormalities, or concentrations of the centrosome protein pericentrin, can be used to help clinicians assess the aggressiveness of prostate tumors. Most of the tumors that are detected early will grow so slowly that they won't be a danger to the patient, but right now they can't be distinguished from the fast-growing ones. As a result, many men may have their prostate glands removed unnecessarily.

Doxsey notes that the percentage of early prostate tumors in which he found the centrosome abnormalities is about the same as the percentage of dangerous tumors. His team's work also shows a correlation between the degree of centrosome abnormality and cytological indicators of tumor seriousness. If those abnormalities can be used as a prognostic indicator, the tiny centrosome may prove a big help to patients with prostate and other cancers. **–JEAN MARX**

DEVELOPMENTAL BIOLOGY

The Hottest Stem Cells Are Also the Toughest

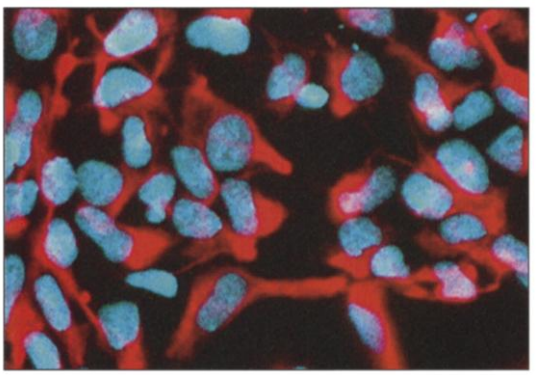
Although political uncertainty is rampant, researchers are making progress in the effort to tame human embryonic stem cells

DURANGO, COLORADO—In the United States, public funding for work with embryonic stem cells looks ever more uncertain, as the National Institutes of Health has put on hold its process for approving cell lines that government-funded scientists can use (see ScienceScope). That move comes as the handful of privately funded labs already using the cells are reporting progress—albeit limited—in manipulating these temperamental cells.

Although the cells were first derived more than 2 years ago, work has been frustratingly slow; indeed, only a few researchers have published *any* results with human embryonic stem (ES) cells. Not only are ES cells fussy about their growing conditions, but they also tend to differentiate spontaneously into a range of cell types other than the desired one, confounding research efforts. But at a recent Keystone meeting here,* researchers described new techniques to get around these obstacles.

Several teams are tackling the "very labor-intensive" process of growing human ES cells, as James Thomson of the University of Wisconsin, Madison, described it. Most researchers grow the cells on a feeder layer of mouse cells to keep them from differentiating. But before these cells can be used to treat disease in humans, researchers need to come up with a culture free of mouse cells. Melissa Carpenter and her colleagues at Geron Corp. in Menlo Park, California, reported that they have managed to grow cells on Matrigel, a commercially available gel commonly used to culture cells. They bathe the cells in a serum-free medium that is first "conditioned" by incubating it with irradiated mouse cells. The scientists do not yet know what the mouse cells add to the medium; they are working to characterize its active components. If they succeed, they might be able to produce a synthetic medium that could keep the cells dividing but not differentiating.

Stem cell researchers eagerly await the day when they can grow an unlimited supply of human liver cells. Not only would they be extremely valuable for tests of drug toxicity, but they might also be useful for treating some liver diseases. Geron scientists have taken a first step, reported Carpenter, coaxing their ES cell lines to produce "hepatocyte-like" cells. They first exposed the cells to sodium butyrate, a chemical known to promote cell differentiation. Many of the cells died, Carpenter said, but when the team cultured the survivors in media designed for growing hepatocytes, many of them began to store glycogen and express proteins typical of liver cells. Although the results are promising, Thomson cautions that liverlike cell markers appear on other cell types as well: "If they're really hepatocytes, it would be good. It's not yet clear to me that they are."



First step. Differentiating human embryonic stem cells express nestin (red), a marker for neural precursor cells. Cell nuclei are stained blue.

CREDIT: SU-CHUN ZHANG/UNIVERSITY OF WISCONSIN

Meanwhile, Thomson and his colleagues have found an efficient way to transform human ES cells into neural epithelial cells—precursors of more mature cell types in the brain. The team allowed the ES cells to cluster into balls of cells called embryoid bodies and then exposed them to media designed for neural cells. Next they isolated a partially differentiated cell type from the embryoid bodies and cultured those cells with basic fibroblast growth factor. Ninety-six percent of the resulting cells expressed neural markers, Su-Chun Zhang and Thomson reported. When transplanted into the brains of newborn mice, the cells migrated to several brain regions and showed signs of developing into mature neurons and glia, the neuronal supporting cells.

Stem cell researchers would like to create immune-neutral stem cells that wouldn't trigger rejection when transplanted into a patient. But that would require genetically altering ES cells. So far, that has proved far trickier in human cells than in their mouse counterparts. At the meeting, Joseph Gold of Geron said that he and his colleagues have genetically altered cell lines to express green fluorescent protein (GFP)—making them easier to track in animal transplantation experiments. And in a paper now in press, Nissim Benvenisty of the Hebrew University in Jerusalem, Joseph Itskovitz-Eldor of Rambam Medical Center in Haifa, Israel, and their colleagues report that they have created cells that express GFP only when they are undifferentiated. This would enable the scientists to weed out cells that have already chosen a developmental path.

Ultimately, researchers hope to devise a way to target genetic changes precisely. Several teams are working to adapt so-called homologous recombination—the technique that has made mouse ES cells such a valuable tool for geneticists—to human cells. So far none has reported success. **–GRETCHEN VOGEL**

* "Pluripotent Stem Cells: Biology and Applications," 6–11 February.