Stem Cells Get Real

STEM CELLS ARE THE FOUNTAIN OF YOUTH—OR THE TOOLS OF SATAN. IT DEPENDS ON WHOM YOU ASK. SOMEWHERE IN BETWEEN ARE PIONEERING COMPANIES MAKING INCREDIBLE STRIDES IN MEDICINE.

BY ROBERT LANGRETH AND MATTHEW HERPER

IT WAS ONLY TEN YEARS AGO THAT JAMES THOMSON, AN UNASSUMING BIOLOGIST AT THE UNIVERSITY OF Wisconsin, grew the first human embryonic stem cells in a lab. Few discoveries before or since have inspired more hype (they regrow spines!) or rancor (it's murder of unborn babies!).

The controversy isn’t going away, but it is obscuring the fact that the science is finally hitting its stride. Stem cells are dormant cells behind growth and healing in the body. Most can create only a specific body part such as blood, bone, brain or heart. Embryonic stem cells can become any kind of cell you want them to be. The problem was you had to destroy an embryo to create them.

Last year brought the sudden discovery that human adult skin cells can be reprogrammed into cells just as potent as embryonic stem cells, with no embryos harmed. This embryo-free approach still needs a lot more time
Fixing Pharma

STEM CELLS COULD LEAD TO BETTER, SAFER DRUGS

Drug discovery is a cruel business. A hundred thousand people die every year because of adverse drug side effects. Millions die too young because drugs just aren’t good enough.

The problem is that scientists invent medicines to treat people, but they have to use animal or tumor cells to do it. Heart cells, brain cells and liver cells all die when you try to keep them in a petri dish. So over decades researchers have come up with jury-rigged tests. They use preserved kidney cells extracted from a human fetus 30 years ago to see if an experimental drug will disrupt the rhythm of the heart. They use cells from a rat’s digestive tract with human receptors stuck in. They force

to mature, but it has the potential to end the ethics debate.

It may be decades before an injection of neurons grown from embryonic stem cells will be able to repair a damaged spine. But stem cells are advancing medicine in other ways right now. “These cells suddenly give us access to all the bits of the human body we’ve never had access to,” says Thomson.

Over the next few years we’ll see stem cells used to speed drug development for all sorts of dread diseases, eliminate unsafe medicines and create better diagnostic tests. California is pushing ahead with its $3 billion stem cell research funding program. All three presidential candidates have favored a lessening of the restrictions on stem cell science. Drug firms such as GlaxoSmithKline, Roche, AstraZeneca and Novartis are tiptoeing into the field. Pfizer has started a new research division to focus on stem cell therapies.

“There is a lot of opportunity here and a lot of ignorance,” says Martin Evans, who won the Nobel Prize for discovering stem cells in mice three decades ago, leading directly to Thomson’s work. “We don’t know half of what we need to know.”

The key now, says Thomson, is “getting on with it.”

Gabriela Cezar of biotech startup Stemina is unraveling the chemistry of autism.
MEDICAL TECHNOLOGY

huge doses of every potential medicine down the throats of rodents. "The system is failing," says Gabriela Cezar, who left Pfizer to study stem cells at the University of Wisconsin-Madison.

It's a testament to the ingenuity of pharmaceutical researchers that the system works at all. Nine out of ten drugs studied in humans turn out not to work or to be too toxic. Sanofi-Aventis, Pfizer and AstraZeneca have all had promising compounds go up in flames because of dangerous side effects. One solution may be to use embryonic stem cells to test drugs for safety and efficacy. "You should be able to get rid of some of the nasty drugs before they even hit clinical trials," says UW-Madison stem cell pioneer James Thomson. "And we're able to do that today."

Two years ago Thomson founded Cellular Dynamics International, a biotech firm that uses embryonic stem cells to make beating human heart cells, something that's never before been available to drug companies. Thomson has avoided the business world as long as possible but now says it is time for his cells to go commercial. Roche is the first announced customer. Earlier this year it began tests with Thomson's heart cells to catch cancer drugs that are toxic to the heart. A rival company, Sweden's Cellartis, is developing ways to test drugs for liver toxicity (with AstraZeneca) and for birth defects (Pfizer).

Even bigger, but further off, is the potential that being able to study neurons in a dish will allow researchers to understand what causes Parkinson's or Lou Gehrig's disease. It could be that in 20 years almost every medical researcher is going to use embryonic stem cells as basic tools. "That is going to profoundly change medicine," says Thomson.

Catapulting this work forward is the discovery of ways to create cells that act like embryonic stem cells but without ever using embryos. Last year Japan's Shinya Yamanaka and Thomson simultaneously showed that adult human cells could be transformed into embryolike stem cells by activating only four genes using viruses. "That has galvanized the field," says Alexander Rod MacKenzie, head of basic research at Pfizer.

UC, San Diego researcher Lawrence Goldstein is using these so-called induced pluripotent stem cells to make neurons that are "genetically identical" to those of Alzheimer's patients. He is collecting 50 skin samples from Alzheimer's patients in order to hunt for new drugs.

Wisconsin's Cezar has started a biotech called Stemina that is using stem cells to get to the roots of autism. Autism appears in a tenth of the children born to mothers who take the epilepsy drug valproate. Valproate is known to injure neurons, so Cezar is converting embryonic stem cells into live neurons and adding valproate to the sample. The neurons gush chemicals that she is comparing to those found in brain cells of people with autism. If there's a match, Cezar could be on a path toward diagnostic tests or drugs. Stemina is using a similar strategy for a range of potential drugs. "[Autism] is an epidemic," she says, "and we have no idea about the cause."

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The Ultimate Turn-On
FIGHTING DISEASE BY ACTIVATING CELLS IN THE BODY

NEUROSCIENTIST CARROLEE BARLOW QUIT A CUSHY RESEARCH JOB AT MERCK BECAUSE SHE thinks everything you've heard about antidepressants is wrong.

The idea that Prozac, Zoloft and their ilk work by fixing an imbalance in the chemical serotonin is so mainstream that drug companies use it in their ads. But in 2003 Columbia University neuroscientist René Hen showed that the drugs' most important function may be to spur the growth of new neurons in the brain. Block the growth of new brain cells in mice, and Prozac and other antidepressants don't work, he discovered.

Barlow is now chief scientific officer of BrainCells, Inc., a fledgling San Diego firm founded on this
work and backed with $77 million in funding from AstraZeneca and other investors. Barlow hopes to create antidepressants designed specifically to spur brain cell growth, with the thought that they'll be more effective and safer than existing drugs. The company mixes experimental drugs with neural stem cells in the test tube, searching for the rare chemicals that make the stem cells form neurons faster. The firm already has one neuron-boosting drug in trial for depression, with two others close behind. "This opens up whole new possibilities for mood disorders," says Barlow.

One of the most startling prospects to emerge from stem cell research is the idea of combating disease with medicines that turn dormant stem cells inside the body. A stunning 2005 experiment by Thomas Rando of Stanford University proved that stem cell boosting substances exist. His lab bathed the tissue of decrepit mice in a mixture of young and old blood, and then injured the hind leg muscles of the old mice. The young blood vastly enhanced the ability of the mice to regenerate their muscles by activating dormant muscle progenitor cells. The experiment showed that unidentified hormones or proteins in the blood were spurring these cells into action.

Figuring out how to turn all those cells on and off with pills is the mission of another company, Fate Therapeutics, founded seven months ago and backed by $23 million from Arch Venture Partners, Polaris, Venrock and other firms. The goal is to make cells go backward and forward in time, turning old, sick cells into young ones that can heal the body, says Fate Chairman John Mendlein, who sold his last company to Bristol-Myers Squibb for $500 million.

One stem cell stimulator that might make a good drug target is a protein called WNT. Fate cofounder Randall Moon discovered its role in embryonic development 20 years ago when he accidentally created two-headed tadpoles at the University of Washington. WNT appears to be crucial for bone growth, heart repair and wound healing, and may be impaired in Alzheimer's.

Another cofounder, Philip Beachy of Stanford University, is studying a set of key signaling proteins called hedgehog that tells developing cells in a fetus how to grow; a misfire can lead to one-eyed sheep or babies with underdeveloped brains. Beachy has evidence that disruptions in hedgehog may be one way the extra chromosome in Down syndrome retards brain development. It might be possible to limit the damage from Down syndrome by giving newborns a drug that boosts hedgehog activity.

In the near term Fate is testing drugs in clinical trials that could make bone marrow transplants more effective for patients with blood cancers. Says Fate research chief Thomas St. John: "This is one of those moments where you wake up and realize the world's about to change."
Clarke is pioneering a radical theory of how cancer grows. He argues that a handful of aberrant stem cells drive the growth and spread of most cancers. Chemo drugs may fail, the theory goes, because they spare some tumor stem cells. But if you kill these cancer stem cells, the tumor will be rendered benign.

“If we can make this work, it will be a fundamental step forward in cancer treatment,” says GlaxoSmithKline Vice President Barbara Weber. Last December her company agreed to pay OncoMed up to $1.4 billion for four of its drugs targeting cancer stem cells. Genentech and Pfizer are working on similar approaches.

Clarke was inspired to search for cancer stems in 1996 after puzzling over a slide of a testicular cancer patient. The patient was essentially cured, even though he still had a few mature cancer cells left. Suddenly Clarke had an epiphany: “I said, ‘Cancer is a stem cell disease.’”

In 2003 he shocked researchers by isolating stem cells inside breast tumors, the first time such cells had been found in a solid tumor. These stem cells formed 5% of the cells inside the tumor, but if just a couple hundred of them were implanted in mice, new tumors took hold. When he implanted tens of thousands of regular breast cancer cells in mice, nothing happened. The finding was so radical, “most people thought I was nuts,” he recalls.

But since then cancer stem cells have been found in brain, colon, head and neck, pancreatic and skin tumors. “At least now we know the face of the true enemy,” says renowned cancer biologist Robert Weinberg at the Massachusetts Institute of Technology.

The commercial implications were so obvious that Clarke and collaborator Max Wicha sent their breast cancer data to venture investors at the same time they sent it out to be published. The proposal eventually landed on the desk of former Genentech biologist Laurence Lasky, now a partner at U.S. Venture Partners. He was stunned by the data and felt it was
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Paths to a Person

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EMBRYONIC STEM CELL

ENDODERM
FOREGUT
MIDGUT
HINDGUT

ECTODERM
HAIR STEM CELL
SKIN PROGENITOR CELL

MESODERM
HEMATOPOIETIC STEM CELL

HUMAN Cells

SKIN
HAIR
BLOOD
BONE
MUSCLE

NERVE INSULATION
THYROID

HEART
STOMACH
LIVER
PANCREAS
SMALL INTESTINE
BLADDER
COLON

MOTOR NERVES
Cell Factories
TRAINING STEM CELLS TO PRODUCE WHAT THE BODY IS MISSING

EMMANUEL (ED) BAETGE, CHIEF SCIENTIFIC OFFICER AT SAN Diego biotech Novocell, may be closer than anyone else to using embryonic stem cells to cure Type 1 diabetes. His work shows the immense promise of stem cell transplants—and the huge hurdles that stand in the way of their becoming a medical reality.

Diabetic patients with the worst form of the disease must take four or more shots of insulin a day because their insulin-producing cells have been killed by a haywire immune system. Novocell's plan is to turn embryonic stem cells into these missing insulin producers and inject them into the bodies of diabetics to put their disease into remission. Medical giants J&J and Becton Dickinson are backing the firm. It has raised $60 million to date. "We are doing something no one has done before," Baetge says.

In February Novocell researchers stunned diabetes experts when they reported they could convert human stem cells into insulin-producing cells that staved off diabetes in mice. Novocell won't be ready for human trials for another three years, and it must figure out how to purify its cells so that no immature ones remain that can cause tumors. It is also working on a way of encapsulating the cells so the immune system won't reject them.

Other ailments such as spinal cord injury and Parkinson's disease will be tougher targets for cell therapy than diabetes. Researchers don't know how to regrow entire nerves so they make the proper connections. A more likely strategy is to use the cells as factories to make proteins or hormones the body is not making. To treat Parkinson's, Clive Svendsen at UW-Madison has engineered fetal neurons so they churn out growth-promoting proteins that help preserve the dopamine-producing cells that die off in the disease. Evan Snyder at the Burnham Institute for Medical Research in La Jolla, Calif. has shown in mice that stem cells may be able to supply missing enzymes to babies with Tay-Sachs disease. A human trial could begin next year.

Osiris Therapeutics, whose $430 million market value is largest among stem-cell companies, is implanting so-called mesenchymal stem cells from bone marrow in patients with heart disease and Crohn's disease. They produce anti-inflammatory proteins that may limit scar tissue after a heart attack or damage to the intestine from Crohn's.

Martin Friedlander of the Scripps Research Institute has found blood and bone marrow stem cells that help repair damaged vessels in the eye. In China, Rutgers University neuroscientist Wise Young is testing umbilical cord cells as a treatment for spinal cord injuries. Cytori Therapeutics has a device to spot stem cells in fat it says might heal lots of body parts. The first use: breast reconstruction after lumpectomy. The device is on the market in Europe. Says Baetge, "The field is taking off."