

SMOKE OUT: By July 2008, DHMC will be totally free of smoking—outdoors as well as in. A small but growing cadre of medical centers is concluding that allowing any smoking is simply inconsistent with their missions to improve health.



THEN & NOW

A reminder of the pace of change, and of timeless truths, from an article about national “firsts” in the Fall 1991 issue of this magazine:

“The first continuous infusion pump to deliver drugs for the management of intractable pain was implanted in a patient at DHMC in 1981. Dr. Dennis Coombs, the Garth Professor of Anesthesiology at DMS, developed a technique by which low doses of narcotics can be continuously infused into the spinal area. . . . Such pumps are now widely used for alleviating pain in patients with cancer and other disorders.”



2007

Year the American Pain Society established national pain management awards

2007

Year DHMC was chosen for honorable mention in those awards

Getting to the root of stem cell science

If it weren't for limitations on human embryonic stem cell research, “I think that there could be children being cured of type 1 diabetes today,” says Dartmouth's Ronald M. Green, Ph.D. “I think that there could be cardiac patients being brought back to functioning. And I think Christopher Reeve may not have had to die.”

Many scientists and physicians hope that human embryonic stem cells (hESCs)—which can develop into any of the 200-plus types of cells that make up the body—may one day be used to treat such diseases as Parkinson's, Alzheimer's, heart disease, and type 1 diabetes, as well as spinal-cord injuries like Reeve's. Some even hope they could be grown into new organs. But the political and ethical controversy swirling around hESCs has led to limits on federal funding for such research and thus the amount of it being conducted in the U.S. So scientists have begun exploring alternative approaches to deriving hESCs.

Panel: Green, the director of Dartmouth's Ethics Institute and an adjunct professor at DMS, served on a 1994 National Institutes of Health panel on human embryo research and has studied stem cell ethics for many years. In the June issue of *Nature Reviews Genetics*, he explored the ethical and scientific aspects of six current alternatives—single-blastomere biopsy, parthenogenesis, somatic-cell dedifferentia-

tion, altered nuclear transfer, dead embryos, and chromosomally abnormal embryos.

The source of hESCs is typically eggs discarded or unused after *in vitro* fertilization. When an egg is allowed to develop, by day three it's an 8- to 16-cell ball called a morula. By day five or six it's a blastocyst, which is about the size of a period. Embryonic stem cells form the inner cell layer of a blastocyst, which becomes an embryo only if it implants in the uterine wall 7 to 10 days after fertilization.

Lines: While hESC research is not prohibited in the U.S., federal funding is allowed only for studies on cell lines in existence prior to August 2001. But the 21 approved lines have been contaminated with nonhuman molecules. So scientists have been seeking expanded federal funding—as well as corporate, foundation, and state monies—to support the development of new stem cell lines and to explore alternatives.

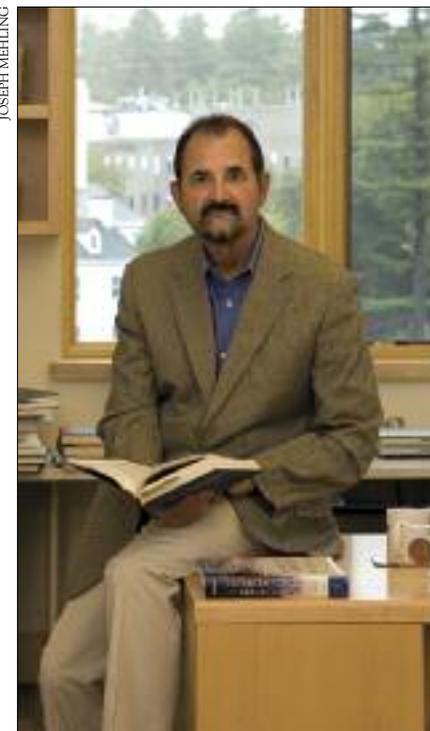
The most promising alternative, Green says, is single-cell blastomere biopsy (SBB). SBB is an adaptation of preimplantation genetic diagnosis (PGD), in which a single blastomere is removed from the morula and allowed to divide into two cells. One cell can be used for genetic diagnosis and the other for the creation of the hESC line. Scientists at a biotech firm called Advanced Cell Technologies (ACT) reported in *Nature* in

2006 that they had successfully derived hESCs from SBBs using donated human embryos. Green chairs ACT's ethics advisory board but has no financial interest in nor is paid by ACT.

Embryo: SBB and PGD do not harm embryos, says Green, citing a 2004 report indicating that more than 1,000 children born as a result of PGD had suffered no ill effects. But there is debate on the matter; others point to studies showing an embryo survival rate after PGD of only around 3%. With SBB, “you just can't know that you're not bringing harm to the embryo,” feels Father Thomas Berg, executive director of the Westchester Institute for Ethics and the Human Person, a Catholic think tank.

“I think Christopher Reeve may not have had to die,” says Ron Green.

JOSEPH MEHLING



Dartmouth ethicist Ron Green has a high profile on the issue of stem cells.

But Berg does agree with Green that parthenogenesis and somatic-cell dedifferentiation merit more investigation. The former involves deriving stem cells from an embryo that has developed from an unfertilized egg, while the latter involves reprogramming body cells to an embryonic-stem-cell-like stage.

Remote: Several stem-cell scientists reported success this summer in reprogramming mouse cells to act like embryonic stem cells. But Green cautions that “in terms of clinical application, cellular reprogramming . . . is really the most remote of all the possibilities.” And he feels the three other alternatives—altered nuclear transfer, dead embryos, and chromosomally abnormal embryos—are least likely to be ethically acceptable.

Many are frustrated that resources—money and scientific brainpower—are being devoted to the search for alternatives, says Anthony Mazzaschi, a senior associate vice president at the Association of American Medical Colleges. He predicts that interest in alternatives may wane quickly once there is a new administration in Washington and federal limitations are lifted. “Researchers are more likely to want to use well-defined stem-cell sources,” he says.

In the meantime, although Green argues for putting funding into developing alternatives, he agrees that none of the options “should be regarded as an alternative in the sense of being a replacement for existing methods of generating hESC lines.”

Laura Stephenson Carter

INVESTIGATOR INSIGHT



In this section, we highlight the human side of biomedical investigation, putting a few questions to a researcher at DMS-DHMC.

Yolanda Sanchez, Ph.D.

Associate Professor of Pharmacology and Toxicology

Sanchez studies signaling pathways that regulate cell division, DNA repair, and cell death and their role in the etiology and treatment of cancer.

If you weren't a scientist, what would you like to be?

I love what I do, and I would not change it. But I have thought that as Plan B, I'd like to own a restaurant. I find that I can make people happy the occasional times that I cook up a storm.

What is the greatest frustration in your work?

Currently, a big one for me (and many others) is the state of funding for research. When I see patients, especially children, who are afflicted with a disease that we're trying to find a therapy for, I feel frustrated with the pace of the work.

And the greatest joy?

When we make a discovery, it's like finding the piece that allows you to solve the rest of a puzzle. This may date me, but it's analogous to the feeling you get when you score in pinball—or, for today's audience, in a video game. Then you're hooked and want to get to the next level. The greatest joy is when I see the curiosity and the high of making a discovery in people I've played a role in training.



Are there misconceptions people have about your field?

The public is led to believe that all research has to be close to the clinic or it does not serve the public health. It is our duty to engage in a conversation with the public on the process of discovery and the urgent need for basic research—the foundation on which biomedical discoveries

are made. Many drugs being developed today target proteins that were first identified using model organisms such as yeast, flies, worms, and frogs.

What famous person would you like to meet?

Charles Darwin and Gregor Mendel. When I teach basic genetics, I am always amazed by the fact that in the 1800s, long before we knew what the genetic material was, Gregor Mendel came up with the principles of hereditary transmission that are still in place today. Outside of science, I would like to meet Nelson Mandela.

What do you admire most in other people?

Patience and honesty in leadership.

What's the hardest lesson you ever had to learn?

Patience, and I am still working on it.

What's your favorite nonwork activity?

Traveling with my husband and discovering new places, cultures, people, and cuisines.

If you could travel anywhere that you've never been, where would it be?

That's a tough one. I'd like to go to Greece, Turkey, and Thailand, to name a few places. To be alone with nature, I'd like to go to Idaho and Montana; my husband has been trying to convince me these states should move up on our list.

What about you would surprise most people?

I wanted to be a nun when I was young and have wanted to ride a motorcycle for many years. When I finally had a motorcycle, I fell while taking a rider's course and we moved to New Hampshire shortly after that. I am now trying to make time to obtain my motorcycle license, but the warm-weather season is short here so I may have to wait another year.

What kinds of music do you enjoy?

I like classical, jazz, and blues and the music from Mexico that I grew up with.

What is a talent you wish you had?

I wish I had musical talent to play the cello.