

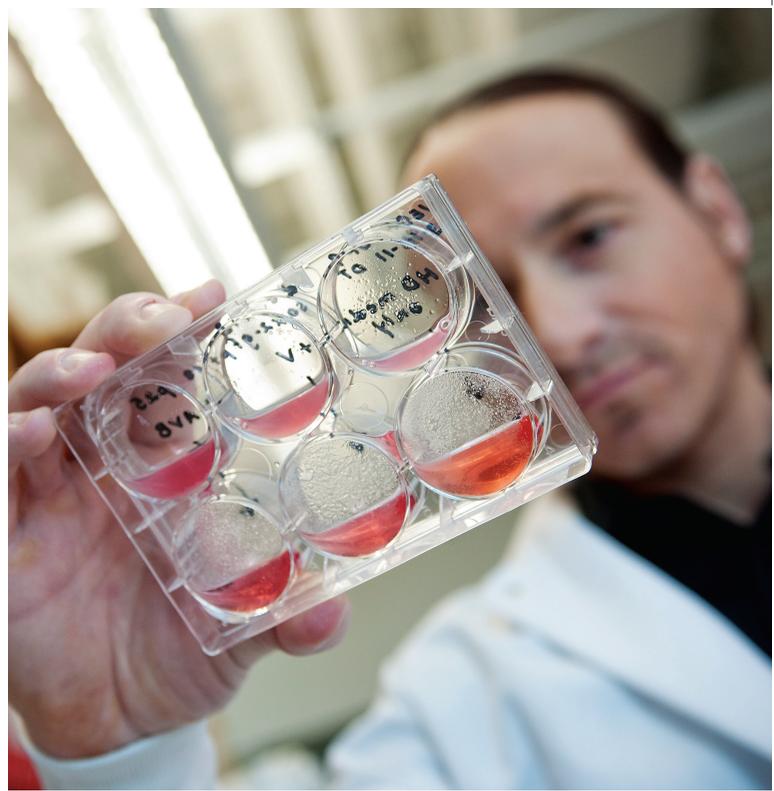
**MED CENTER TRANSFORMS SKIN CELLS INTO STEM CELLS**  
 BY CALEB DANILOFF

# More Than Just Skin Deep

DARRELL KOTTON, GEORGE MURPHY, and Gustavo Mostoslavsky roll up their sleeves and proudly display small oval marks on their forearms. Biopsies from which the medical researchers harvested their own skin cells to create—well, actually, the sky may be the limit.

“Pretty much all the biology books are wrong now,” says Murphy, a School of Medicine assistant professor of medicine, who specializes in hematology. “Because they all say that your skin cells, your skin fibroblasts are always going to be fibroblasts. Turns out now they can become cells like an embryonic stem cell, which can then differentiate into any kind of cell it wants.”

Murphy is talking about human induced pluripotent stem cells, or iPSC, which form the core of the work at BU’s Center for Regenerative Medicine (CRoM), a research facility

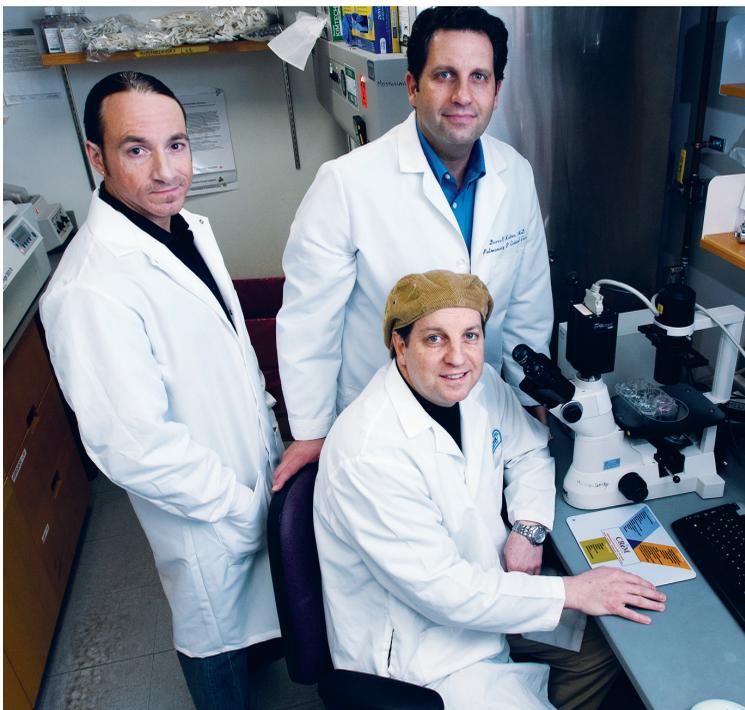


» You can look at cells in the context of a patient’s genetic background. It’s patient-specific medicine.

he codirects with Kotton and Mostoslavsky that seeks to advance stem cell research. The collaborative effort among scientists on the Medical and Charles River campuses unites teams of stem cell biologists, physician-researchers, and biomedical engineers. CRoM focuses on developing new treatments for diseases commonly seen at Boston Medical Center, such as cystic fibrosis, sickle cell anemia, emphysema, amyloidosis, and inflammatory bowel disease. The use of iPSCs, first developed in 2006 at the University of Kyoto, reduces dependence on the controversial, and federally limited, embryonic stem cell lines.

Last fall, the three CRoM codirectors announced the creation of a bank of more than 100 lung disease-specific stem cell lines from patients with inherited diseases, including cystic fibrosis, alpha 1 antitrypsin deficiency emphysema, and sickle cell anemia. The lines mark the first time lung disease-specific iPSC have been created in a lab. The research was funded by the National Institutes of Health, the Cystic Fibrosis Foundation, and an ARC award from BU’s Evans Center for Interdisciplinary Research.

Led by pulmonary specialist Kotton, a MED associate professor of medicine, the team took tissue samples from patients with the diseases. Using a tool that Mostoslavsky, a MED assistant professor of medicine specializing in gastroenterology, engineered in 2008, called the stem cell cassette, the team was able to reprogram adult skin cells into



↑ **MEDICAL RESEARCHERS** George Murphy (from left), Darrell Kotton, and Gustavo Mostoslavsky, codirectors of BU’s Center for Regenerative Medicine, have created 100 new lung disease-specific cell lines that could lead to new treatments for diseases such as emphysema and cystic fibrosis.

clinical-grade pluripotent stem cells. Mostoslavsky's design, which BU has since patented, is now used by hundreds of labs around the world and is considered the industry standard.

"Our dream was to make a better tool, a viral vector to pop these genes into cells and do the equivalent of the University of Kyoto experiment that was better, safer, more efficient, and allowed translation to human beings in a way that was very simple and elegant," Kotton says.

Many scientists believe that stem cells will play a crucial part in the fight against Parkinson's, Alzheimer's, and a range of genetic diseases, but in the United States, because of the use of human embryos, government injunctions against their use have been issued and lifted and issued again. Even with the high-quality iPSC lines CReM has developed, embryonic stem cells are still necessary to serve as a positive control: "a roadmap for developmental biology," as Kotton puts it.

#### FROM LAB TO BEDSIDE

Murphy often uses a "flight recorder" analogy when he explains his work.

"When there's a plane crash, investigators look for the flight recorder so they can determine each event that led up to the catastrophic event," he says. "In much the same way, we can take skin cells from sick patients and differentiate those cells into the affected tissue type and go through all the molecular events that led up to the disease and that catastrophic event. It creates the ability to intervene early."

Human induced pluripotent cells also allow drug developers and scientists more precision, offering a quality even embryonic cells don't offer. The use of a person's own skin or blood to create embryonic-like stem cells means the patient's body won't reject them, thereby eliminating the need for immunosuppressive drugs.

"You're looking at cells and the disease in the context of the exact genetic background of that patient," Murphy says. "So it becomes possible to test therapeutic drugs in the test tube before using them on patients. It's patient-specific medicine."

A seminal CReM project, which got under way in 2009, involves an infant in New York City with inherited long QT syndrome, which causes a serious heart arrhythmia. Kotton and his team took skin cells from the baby, as well as from the parents, and generated iPSC, which in turn were programmed to differentiate into heart muscle cells, or cardiomyocytes. CReM researchers are coordinating with laboratories in New York and Toronto to test available pharmaceuticals on those cardiomyocytes, which in essence act as the disease in miniature, to determine how best to treat the sick child.

The Boston University team has also collaborated with researchers at Massachusetts General Hospital to engineer a bioartificial rat lung that allowed a living rat to breathe for six hours, and they've developed a gene therapy that offers lifetime protection against an inherited form of emphysema in mice.

## DIGEST | BU research in brief

### ARE THE DEAF AN ETHNIC GROUP?



Deaf Americans who sign know that they share much more than a language; they comprise a common culture with its own ancestry, art, and humor. Now a book titled *The People of the Eye: Deaf Ethnicity and Ancestry*, coauthored by Richard C. Pillard, a School of Medicine professor of psychiatry, goes further, arguing that the deaf should be recognized as a distinct ethnic group.

The authors say that beyond being a means of communication for the deaf, American Sign Language has a rich literature.

They argue that being identified as an ethnic group would afford the deaf not just a greater respect, and in some cases the protections of the law, but could finally dispel the assumption that deaf people consider themselves handicapped or as failing to meet an accepted physical ideal of wholeness and health.

SUSAN SELIGSON

### YOU ARE WHAT YOU EAT



In one of the first studies undertaken at BU's new Center for Molecular Discovery, monoglycerides—commonly used in small quantities in dozens of commercial food products, including beverages, bakery items, and margarine—were shown to stimulate the production of insulin in beta cells.

"Human beings are constantly being exposed to new drugs and food additives, and these drugs and additives have never been tested for chronic effects on systems such as metabolic health," says Barbara Corkey, a MED professor of gastroenterology.

The Center for Molecular Discovery gives BU researchers access to high-throughput screening, a process used by the pharmaceutical industry in which thousands of small molecule compounds can be screened for physiological effect (e.g., normalization of insulin secretion) using cell-based or biochemical assays. The rapid process can identify active compounds that change a particular biomolecular pathway.

MAGGIE BUCHOLT

### THE HIGH COST OF HAIR REPLACEMENT DRUGS



A paper principally authored by Abdulmageed Traish, a

MED professor of urology and biochemistry, reports that men who use certain drugs to battle baldness or reduce enlarged prostates may torpedo their sex lives in the bargain.

The drugs are finasteride (made by Merck and sold generically as Proscar and Propecia) and dutasteride (made by GlaxoSmithKline and sold generically as Avodart). Finasteride is approved for both baldness and benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate. Dutasteride is used to treat BPH.

In the study, published in the March *Journal of Sexual Medicine*, the researchers pored over all the published scientific literature about the drugs' side effects, including data from Merck. They found that, depending on the study, 3 percent to 22 percent of patients reported problems such as erectile dysfunction or diminished sex drive, and the problems persisted for some even after they discontinued the drugs. The paper acknowledges that the number of men affected long-term is small, perhaps 7 percent of all patients using the drugs.

RICH BARLOW