The Promise of Stem Cells
Stem cells are the body’s “master” cells. They have two unique abilities: They can proliferate virtually without limit to produce an essentially infinite supply of their unspecialized cellular selves, and they can differentiate to produce any other cell types that can be used to repair or replace worn-out or damaged tissues. Combine those two superpowers, and you’ve got the proverbial medical magic bullet — somewhat like having a box of elastic bandages in your medicine cabinet that always replenishes itself, always comes in exactly the right size for your needs and doesn’t just cover a cut but can regrow the injured skin.

At the Eli & Edythe Broad Center of Regenerative Medicine & Stem Cell Research at UCLA, more than 200 faculty members are working to translate the promise of stem cells into viable treatments for some of society’s most vexing medical conditions, including cancer, heart disease, immune disorders, Alzheimer’s and Parkinson’s diseases, autism, blindness, diabetes and more. Much of the work being done is supported by both private and institutional sources, including grants approaching $190 million from the California Institute for Regenerative Medicine (CIRM). CIRM was established in 2004 to fund translational stem-cell research at institutions throughout California with the goal of developing new therapies for deadly diseases and disorders. Here are just a few examples of that work being done at the center.

**EYEING EMBRYONIC THERAPY**

Stem cells come in two forms, adult and embryonic. Whereas adult stem cells, which are found in particular organs of the mature body — the bone marrow, for example, or the brain — can only produce the specialized cells for that particular tissue type, embryonic stem cells derive from a far earlier point in development and thus have the potential to differentiate into every type of cell in the body. For that reason, human embryonic stem cells (hESC) are considered ideal tools for regenerative medicine.

Their promise is finally beginning to be realized; in January 2012, UCLA retinal specialist Steven Schwartz, MD, and colleagues reported the first safe clinical use of hESC-derived cells in two legally blind patients. Both patients — a woman with dry-age-related macular degeneration, the No. 1 cause of blindness in the developed world, and a woman with Stargardt’s macular dystrophy, a progressive vision disorder that can lead to blindness by the third or fourth decade of life — received relatively low doses of hESC-derived retinal pigment epithelial (RPE) cells transplanted into the space beneath the retina of one eye each.

RPE cells, which form a supportive layer beneath the retina, “are 100-percent critical for vision. When those cells go, vision goes,” says Dr. Schwartz. Ahmanson Professor of Ophthalmology and chief of the Retina Division at UCLA’s Jules Stein Eye Institute. “Both of these diseases have, as a final common pathway, the death of the RPE.” The RPE had been considered “low-hanging fruit” for an embryonic-stem-cell trial, he notes, in part because the cells are terminally differentiated, can be accessed surgically and they have no synaptic connections.

Four months after the injections, both patients felt they saw more clearly; the woman with macular degeneration, for example, went from being unable to read any letters on a visual-acute chart to discerning five letters. Neither woman suffered side effects such as retinal detachment, eye inflammation or abnormal cell growth.

As a result of that early success, Dr. Schwartz and colleagues have transplanted RPE cells in 18 more patients and have expanded the trial to include four other top eye institutes. “Our results have been so positive in terms of safety, that the Food and Drug Administra-
tion (FDA) granted us permission to open up another cohort in the study: those with better vision," Dr. Schwartz says. "My hope is that this can be a meaningful first step toward regenerative medicine for the eye.

BURSTING THE BUBBLE
Children born with severe combined immunodeficiency (SCID) – also known as “Bubble Boy” disease – have no functioning immune system and thus cannot fight off even the mildest of infections. If not treated, the disease is invariably fatal within the first year of life.

One common form of SCID is caused by a mutation in both copies, maternal and paternal, of the gene for an essential metabolic enzyme called adenosine deaminase (ADA). Regular injections of the enzyme can restore some immune function in these individuals, but the therapy is both expensive and far from a cure. For that, Donald Kohn, MD, is turning to stem cells.

Two decades ago, Dr. Kohn, then at Children's Hospital Los Angeles, performed the world’s first gene therapy on newborns with ADA-deficient SCID. He and his colleagues isolated stem cells from the umbilical-cord blood of three newborns diagnosed with the disease before birth. Their cells were cultured with viral vectors, which transferred a normal copy of the ADA gene into the stem cells. The modified cells were then infused back into the babies to help restore their immune systems.

Last fall, Dr. Kohn, director of the UCLA Human Gene Medicine Program, reported the results of what he calls Version 2.0 of the therapy. In the first phase of the study, begun in 2001, four children with ADA-deficient SCID were infused with their own genetically modified bone marrow. The treatment, however, "really didn’t do anything," he says. "It didn’t hurt them, but it didn’t help them, either."

The next six patients, treated between 2005 and 2006, were given chemotherapy before getting back their bone marrow. This modification of the gene-therapy protocol mimics one first used with some success by a separate group of European researchers.

"The chemotherapy eliminates some of the patients’ residual bone marrow and makes space for the gene-corrected cell to go back," Dr. Kohn explains. Indeed, half of this second group of children “have good immune recovery,” he says. The patients who benefitted the most were also the youngest – including a baby boy who was diagnosed with ADA-deficient SCID at 10 months old after significant illness and his younger sister, who was diagnosed shortly after birth. Both are now doing well.

The results suggest that the optimal time for the therapy is when children with ADA deficiency are

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around 3-to-6 months of age. Dr. Kohn and his colleagues have just received FDA approval for Version 3.0 of their ADA gene-therapy protocol. The two-to-three-year, 10-patient trial will employ an improved gene-delivery virus that uses components of HIV, but which cannot transmit the disease, instead of the mouse-virus-based delivery used previously. "Because it is a human virus," he says, "it gets into the bone-marrow stem cells more efficiently. That means we only have to have the cells in culture for one or two days instead of about week, better preserving the stem cells."

Ultimately, Dr. Kohn hopes, the therapy will be approved as an orphan drug and made available to all future patients with this disease — providing that long-sought cure. "So far, in the patients in which the treatment has been successful, it has lasted for as long as we have looked" — 10-to-12 years. "We hope it is forever, but we won't know that until 30, 40, 50 years from now," says Dr. Kohn, who will soon begin a clinical trial using a similar gene-therapy approach to treat sickle-cell anemia, a genetic disorder characterized by abnormally shaped red blood cells. His clinical trial for sickle-cell disease was developed with support of a $10 million CIRM grant. "That's the beauty of stem cells. If we can get the gene into a long-lasting stem cell, it will be there for the rest of the person's life, making gene-corrected blood cells."

**CULTIVATING KILLER CELLS**

**Immunotherapy** is an established treatment for melanoma, with several drugs already approved for treatment. The drugs work by stimulating an immune response that causes T cells — the workhorse cells of the immune system — to attack and kill cancerous cells. One problem with the therapy, however, is that relatively few of those melanoma-destroying cells are actually produced. Now, Antoni Ribas, MD, PhD, and his team, with support from a $20-million CIRM grant, are developing new methods to boost the numbers of cells.

In recent work, Dr. Ribas, professor of hematology/oncology, and colleagues were able to dramatically reduce the size of melanoma tumors by isolating and then genetically modifying the patients' T cells so that they would specifically attack tumor cells.

One downside to the treatment, however, was that although the altered T cells were initially very active, "with time they lost their antitumor activity," Dr. Ribas says. "This results in a high rate of initial tumor responses, but as the T cells decrease their killer functions for melanoma, then the cancer starts to regrow."

The researchers are now investigating a number of different techniques to preserve that cancer-destroying ability, including changes to the method by which the cells are grown in the lab and enhancing a phenomenon known as "antigen spreading." In antigen spreading, T cells that are genetically engineered to attack particular cancer-cell lines transfer that immune response to other types of T cells that can attack the tumor via different types of antigens (the substances, such as proteins, that trigger immune responses).

But the ultimate solution, Dr. Ribas says, is to genetically engineer stem cells to target tumors — creating a group of cells that would continuously repopulate the body with their cancer-killing progeny. "With this research, we want to create a large army of activated and fully functional T cells with the main aim of providing higher rates of responses," Dr. Ribas says. Furthermore, adds Dr. Ribas, who hopes to begin a clinical trial using these sorts of engineered stem cells in approximately two years, "what we learn from melanoma can be transferred to other cancers."

**TESTING FOR AUTISM**

In just the past few years, hundreds of genes have been identified that are linked to autism-spectrum disorder (ASD). The puzzling neurodevelopmental condition estimated to affect 1-in-100 children in the United States. Although scientists haven't yet determined just what those genes do to produce the unique suite of symptoms experienced by autism patients, "knowing these genetic mutations gives us an incredible toehold to begin to move to mechanistic therapy," says Daniel Geschwind, MD, PhD, Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and director of UCLA's Center for Autism Research and Treatment. "It's very analogous to
targeted cancer therapy. You look for certain mutations, and you pick the drug focused on those.”

Dr. Geschwind and his team are working to develop a large-scale, rapid, efficient and cost-effective “screening system in a dish” to do just that. Their work is being funded, in part, by a Broad Stem Cell Research Center Innovation Grant – a $4-million pool from philanthropic sources that to date has been instrumental in helping to generate some $40 million in extramural funding from such resources as the National Institutes of Health, CIRM and the National Science Foundation.

Because autism is a disorder that affects the brain, “We start with fetal human neurons from primary human neural stem cells and manipulate their genome to recreate the mutations that are causing autism in patients,” Dr. Geschwind explains.

Separate cell lines have been reprogrammed to express each of 24 different mutations associated with autism. In some cases, mutations are produced by knocking out a specific stretch of DNA, in others, by overexpressing it. Each mutation is created using several different methods, and duplicate cultures are produced of each of those cell lines, “so you can see that we’re talking about a very large-scale project,” Dr. Geschwind says.

Although all of the tested mutations are rare – no known autism mutation occurs in more than 1 percent of patients – they could reveal vital information about the disorder and its causes. “We want to find areas of convergence in these genes that might provide a more global treatment or global view of the disorder,” he says.

Among other factors, the researchers will assay the RNA complement of each cell line. “The notion is that the RNA is a readout of how the genome is being turned on and off, so that gives us a first hint as to what pathways are actually being rearranged,” he says. “By correlating that with other functional phenotypes, like the cells’ morphology and kinds of synapses, we can triangulate in on the mechanism.”

For example, Dr. Geschwind says, “If we identify that the genes that code for proteins that make neuronal synapses are down-regulated in a bunch of these different mutations and then find morphological evidence of changes by looking at the cells themselves and physiological evidence that there is low synaptic signaling, that may lead us to a pathway that we can use to try to correct that problem. If we identify pathways for which there are already drugs developed,” he adds, “we can immediately start to test those drugs.”

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- DR. GAY CROOKS
FINDING THE MISSING LINK

It's long been known that the body's immune system is generated through a regimented series of steps called lymphoid differentiation that starts with blood-forming stem cells, known as hematopoietic stem cells, in the bone marrow. Gay Crooks, MD, co-director of the Broad Center, and his colleagues have now identified a crucial early stage in this process: the so-called lymphoid-primed progenitor cell. The cell represents the "missing link" between hematopoietic stem cells and the rest of the human lymphoid system.

"With the knowledge gained on how to isolate these lymphoid progenitors, we are now conducting detailed gene-expression analyses to understand how the stem-cell program gets turned off and the lymphoid program is initiated," says Dr. Crooks, professor of pathology and laboratory medicine and of pediatrics. "By studying these lymphoid progenitors, we can understand the key genes that control how stem cells first enter the pathway that leads to the generation of the entire immune system. That will give us targets through which we can manipulate the process."

Discovering those targets could lead to new therapeutic methods to treat blood diseases, which is an area of particular interest to Dr. Crooks. "A major problem that plagues bone-marrow transplant patients, young and old, is that the immune system takes several months or years to be remade from the transplanted stem cells. This makes our patients at high-risk for serious infections. One reason for studying the lymphoid progenitors in bone marrow is to understand how the stem cells might be encouraged to differentiate into lymphoid cells faster and more efficiently."

There is no current medication or cell therapy to hasten the recovery of the lymphocytes, she adds. "That is what makes it such an exciting and important area of research."

CONTROLLING PROSTATE CANCER

Hundreds of thousands of men receive therapy every year for prostate cancer, and although those treatments work well when the disease is confined within the prostate gland itself, they are ineffective once the cancer metastasizes. "In that case," says noted cancer researcher Owen Witte, MD, President's Chair in Developmental Immunology and the center's founding director, "we have a really limited set of therapeutic options, all of which alter the efficiency or production of androgen, or male steroid, used by the cancer as part of its growth control." Unfortunately, the cancer invariably becomes resistant to this therapy as well, with tragic consequences.

Stem cells may be the solution, Dr. Witte says. His lab is working to characterize the biochemical pathways through which normal prostate stem cells self-renew—mechanisms that may be corrupted in advanced, aggressive forms of prostate cancer.

Recently, for example, Dr. Witte and his colleagues found that damage to the gene for a protein called Bmi-1, which is crucial for cellular repair, causes prostate stem cells to grow abnormally; blocking the expression of the protein, the team discovered, prevents that out-of-control behavior. "If we can enumerate the mechanisms that are used in prostate cells to maintain their normal growth and how those mechanisms are exploited as the cells turn into a cancer, that becomes the target for therapeutic intervention," says Dr. Witte.

Indeed, through similar efforts over the past 35 years, his lab has contributed to the development of three different cancer drugs, including Gleevec, the world's first drug to specifically target cancer cells. In the 1990s, he and his colleagues identified the gene for an enzyme called Bruton's tyrosine kinase (BTK) that, when mutated, causes an inherited immunodeficiency disease. "We showed that the enzyme can also be a target for treating cancers of the immune system, including lymphomas and certain kinds of leukemia, leading to a new pharmaceutical," he says.

"My hope is that this work on prostate cancer will ultimately lead to precisely the same point: new therapies to help patients with this disease and related diseases. The message that I think is most important is that this type of basic work—understanding cells and pathways—leads to targets, which leads to treatments."

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