Stem cells are chock full of therapeutic promise. Armed with the capacity to almost limitless copy themselves and grow into many types of cells in the body, they function as the body’s cellular repair shop. While embryonic stem cells have been the focus of heated nationwide debate since 1998, many scientists have been quietly examining the potential therapeutic possibilities of two controversy-free and very promising alternatives — adult bone marrow-derived stem cells and umbilical cord blood stem cells.

According to the National Institutes of Health, adult stem cells, whose main function is to maintain and repair tissue, have been studied since the 1960s. Bone marrow-derived adult stem cell transplants have been used for over 30 years and umbilical cord blood stem cell transplants have been used for over 20 years to treat patients with blood cancers. Recent discoveries have shown that these stem cells also have the potential to repair damaged tissue cells in several organs, generating new hope and excitement for researchers seeking better treatment options for a host of illnesses.

A group of researchers in the Department of Medicine has gained wide recognition for their work with adult stem cells in treating lung and cardiac diseases.

by JENNIFER NACHBUR

photography by RAJ CHAWLA
For the past several years, a small group of researchers in the Pulmonary and Critical Care Division of the Department of Medicine at the University of Vermont have been gaining momentum as well as international recognition for their work in the area of adult stem cells’ potential role in treating lung diseases. Benjamin Suratt, M.D., assistant professor of medicine, and his colleagues were the first to find evidence that adult human stem cell transplantation resulted in spontaneous cellular regeneration in damaged lung tissue. News generated by their August 2003 publication in the American Journal of Respiratory and Critical Care Medicine continues to prompt queries from lung disease patients hoping for a cure. Though that cure is still far off in the future, Suratt and colleague Daniel Weiss, M.D., Ph.D., associate professor of medicine, are working diligently to understand how adult stem cells might offer a therapeutic approach for several lung diseases.

“A number of papers show that adult bone marrow-derived stem cells can be induced to turn into heart, liver or brain or more importantly for us, the lung,” says Weiss, whose research takes place in the Vermont Lung Center lab in the Health Science Research Facility on the medical campus. “We’ve been able to follow the lead of these papers and do some pretty amazing things.” In the lab, his team has successfully isolated adult stem cells from the bone marrow of adult mice and begun to turn them into lung cells. “We’ve been able to transplant stem cells from donor mice into recipient mice and get them to go to the lung and insert themselves into the airway and express the normal CF protein. “What we’re doing is taking these two, sophisticated, high-tech techniques and combining them in a rational way for a disease that’s the result of a genetic defect,” says Weiss. Results of this research made the cover of the American Journal of Respiratory and Critical Care Medicine in January 2006.

Though they have the capacity to turn into a variety of cells and tissues, adult stem cells are not as versatile as embryonic stem cells. A viable and legal alternative is using stem cells found in umbilical cord blood. Through a program run in collaboration with obstetrician Ira Bernstein, M.D., a new instructor in the pulmonary and critical care division, to take this research one step further — to collect cord blood from babies who have CF. Administered through the CF Foundation’s Therapeutics Development Network, a consortium of about 30 medical centers around the country that collaborate on CF-related clinical trials, the goal of this cutting-edge research will be to isolate the cord blood stem cells and use gene transfer/therapy techniques to correct the CF defect. According to Weiss, who receives funding from the National Institutes of Health, the CF Foundation, American Lung Association and the Tulane Primate Research Center for his stem cell research, his group is also actively pursuing this approach for emphysema. Among the few major diseases that are increasing in prevalence and predominantly seen in older people, emphysema is a disease that has no cure. For this population, Weiss and his team are interested in using stem cells to grow new lung tissue to replace the destroyed lung. Preliminary results using several mouse models of emphysema are promising.

Weiss explains that his current adult stem cell research is an outgrowth of cystic fibrosis gene therapy work he’s done in the past. Weiss and his colleagues have noted promising results from combining the two therapies. In a mouse model of CF, which has the defective protein (CFTR) responsible for CF’s symptoms, Weiss’ team has been able to replace the defective airway epithelial cells with epithelium derived from marrow cells from a normal adult mouse.

“What we’re hoping is that by using bone marrow transplantation, CF patients could essentially use their own bone marrow to correct their lungs,” says Weiss. His theory maintains that stem cells isolated from the bone marrow could be corrected in a Petri dish — manipulated to express the normal CF protein using a gene transfer technique. Then, Weiss, the corrected stem cells could be administered back into the CF patient and coaxed to go to the lung and insert themselves into the airway and express the normal CF protein. “What we’re doing is taking these two, sophisticated, high-tech techniques and combining them in a rational way for a disease that’s the result of a genetic defect,” says Weiss.

On the horizon for Weiss is a newly-approved protocol with the Cystic Fibrosis Foundation that will allow him and his colleagues, including Viraunoi Sushildevong, M.D., a new instructor in the pulmonary and critical care division, to take this research one step further — to collect cord blood from babies who have CF. Administered through the CF Foundation’s Therapeutics Development Network, a consortium of about 30 medical centers around the country that collaborate on CF-related clinical trials, the goal of this cutting-edge research will be to isolate the cord blood stem cells and use gene transfer/therapy techniques to correct the CF defect. According to Weiss, who receives funding from the National Institutes of Health, the CF Foundation, American Lung Association and the Tulane Primate Research Center for his stem cell research, his group is also actively pursuing this approach for emphysema. Among the few major diseases that are increasing in prevalence and predominantly seen in older people, emphysema is a disease that has no cure. For this population, Weiss and his team are interested in using stem cells to grow new lung tissue to replace the destroyed lung. Preliminary results using several mouse models of emphysema are promising.

Focusing less on regeneration and more on repair, Suratt’s specialty areas include acute lung injury (ALI) and its most severe form, adult respiratory distress syndrome (ARDS), which may develop in the setting of such insults as infection, shock and trauma. ALI/ARDS affects over 150,000 Americans each year and is characterized by injury to the membrane that separates the lung’s blood vessels from the air sacs or alveoli. This injury allows fluid to leak into the air sacs, resulting in fluid build-up and lung failure. For the past two years, his work has centered on examining the molecular activity involved in the development and repair of acute lung injury, especially the inflammatory signaling process.

On May 1, Suratt received a $1.9 million, five-year Research Project Grant (RO1) award from the National Heart Lung and Blood Institute (NHLBI) to look specifically at several cytokines — proteins that function as intracellular communicators and are involved in immune response — and their role in both the development of acute lung injury and recruitment of inflammatory cells and reparative cells.

What’s most interesting about this area of research, explains Suratt, is an apparent “overlap” between the path of the monocytic cell and the path of the neutrophil cell. Though they have the capacity to turn into a variety of inflammatory cells and reparative cells. A viable and legal alternative is using stem cells found in umbilical cord blood. Through a program run in collaboration with obstetrician Ira Bernstein, M.D., a new instructor in the pulmonary and critical care division, to take this research one step further — to collect cord blood from babies who have CF. Administered through the CF Foundation’s Therapeutics Development Network, a consortium of about 30 medical centers around the country that collaborate on CF-related clinical trials, the goal of this cutting-edge research will be to isolate the cord blood stem cells and use gene transfer/therapy techniques to correct the CF defect. According to Weiss, who receives funding from the National Institutes of Health, the CF Foundation, American Lung Association and the Tulane Primate Research Center for his stem cell research, his group is also actively pursuing this approach for emphysema. Among the few major diseases that are increasing in prevalence and predominantly seen in older people, emphysema is a disease that has no cure. For this population, Weiss and his team are interested in using stem cells to grow new lung tissue to replace the destroyed lung. Preliminary results using several mouse models of emphysema are promising.

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Associate Professor of medicine Dan Weiss, M.D., in his lab in the Health Science Research Facility.

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phases of acute lung injury,” notes Suratt. “It’s also widely believed that SDF1 is responsible for the trafficking of a number of different cell types to the lung. The new grant is directed specifically at examining the role of these cytokines — both SDF1 and another cytokine called Granulocyte Colony-Stimulating Factor or GCSF — in the inflammatory cell trafficking that overlaps with the stem cell trafficking.”

According to Suratt, the same cytokine response seems to play a role in a lot of different events beyond what is currently obvious. Originally, SDF1 was described as the co-receptor of HIV; after further research, it was shown that the cytokine really did not have as much of a role in HIV, but it greatly increased white blood cell counts in the people who received it. The key discovery was that SDF1 was mobilizing cells from the bone marrow; now, a drug based on this finding, designed to mobilize bone marrow-derived stem cells, is in phase 2 trials.

In the future, Suratt hopes to more closely examine how cytokine signaling influences the reparative response. “Understanding cytokines is going to be critical to understanding what we can do with any kind of therapy, because they play a role in inflammation, the repair and the reparative response, so the answers are not that simple,” he cautions.

With what Weiss refers to as “a critical mass” of faculty members devoted to stem cell research, the group — including newest faculty member Jeffrey Spees, Ph.D., assistant professor of medicine — is working to lay the groundwork to create a fully fledged stem cell center at UVM. In addition to conducting his own stem cell research, Spees’ role is to direct a new Stem Cell Core facility that provides expertise in stem cell biology as well as isolating, culturing, characterizing and providing the stem cells that the group uses in their research. Spees is already providing isolated cells to a number of College of Medicine investigators, as well as national and international researchers. To date, these include neural stem cells for neuroscience researchers and umbilical cord blood-derived stem cells for Weiss’ research. Spees reports that the new Stem Cell Core will be running at full capacity by the end of summer 2006.

Since arriving at UVM from Tulane University nearly a year ago, Spees has been closely collaborating with Weiss, as well as with David Schneider, M.D., associate professor of medicine and director of cardiology, and Burton Sobel, M.D., professor of medicine, regarding the role of adult bone marrow progenitor cells in stimulating cardiac repair.

Spees arrived at UVM with an NIH grant to study the role of non-blood-forming bone marrow stem cells in the repair and remodeling of the lung and heart during pulmonary hypertension. While at Tulane’s Center for Gene Therapy, he and colleagues were the first to show that human stem cells could fuse with lung epithelial cells during the repair process. They also discovered that intercellular material called mitochondria could be transferred from adult stem cells to rescue epithelial cells with non-functional mitochondria.

In his lab in the Starbuck Family wing of UVM’s Colchester Research Facility, Spees has continued to work on cell fusion and is also examining the effects of factors secreted by bone marrow stem cells on the growth and support of native adult cardiac stem cells with the goal of finding out whether or not they will initiate repair in the heart. With Sobel and Schneider, he uses a mouse model of heart attack, which partially blocks the blood supply to the left ventricle of the heart. In their experiments, which focus on injecting adult bone marrow intravenously into immunodeficient mice, they have observed improved heart function in the treated mice. “We don’t actually know what the most important effects or mechanisms are,” says Spees, “but you generally have improved heart function and reduced fibrosis. Cardiac fibrosis usually occurs about one week after cardiac muscle fiber cells called myocytes have died. If there’s less fibrosis, it typically means there is less injury to myocytes.”

Spees has set up an incubator that creates a hypoxic environment — an atmosphere containing only one percent oxygen — in which he observes how the factors produced by bone marrow stem cells can protect the adult cardiac stem cells.

UVM’s rising status in the field of adult stem cells and lung biology research was clearly marked in July 2005 when the University hosted a meeting co-chaired by Weiss and sponsored by the National Heart Lung and Blood Institute (NHLBI) and the Cystic Fibrosis Foundation. Over 120 biomedical researchers from around the world convened on the College of Medicine campus to discuss research discoveries, roadblocks, methods and goals. The meeting’s sponsors have already requested to return to Burlington in 2007.

The group’s collective hope is to recruit additional stem cell researchers and to continue to broaden the scope of their research in the near future. Weiss looks forward to interacting with two additional UVM scientists who currently collaborate with Spees — Dinendar Kumar, Ph.D., assistant professor of medicine, who is working on cardiac development and repair, and Ying-Mao Draayer, M.D., research assistant in pathology, who is examining neuronal stem cells in the lab of Felix Eckenstein, Ph.D., professor of neurology. Of course, admin Weiss, continued funding is key to their future success. However, with their current research efforts, available funding and proven track record in pushing forward, this new venture is becoming a reality. Stem cell researchers, like the cells themselves, are well-situated to grow into new structures.