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Center for Stem Cell Biology and Regenerative Medicine

By Robyn Fieser

Curt Civin, MD, discovered a groundbreaking way to isolate stem cells. His work revolutionized the treatment of leukemia and dozens of other diseases.

But for the better part of the past decade, politics kept Civin out of the laboratory more than he would have liked. He was splitting time finding new treatments for cancer, while advocating for Maryland to fund embryonic stem cell research amid a ban on the use of federal dollars on the practice.

With the political question answered, Civin is back in the lab full time, where he plans to complete his next major achievement: Leading University of Maryland, Baltimore scientists to build a world-class stem cell research center where scientists from scores of disciplines work together to discover treatments and prevention for countless diseases.

"The stars are aligned right now and it is a propitious time to start the center," says Civin. We have incredible research tools available. For example, based on the latest discoveries, we can re-program almost any body cell type into cells that have most of the attributes of stem cells-- easily accessible skin or blood cells can be made into "induced pluripotent stem" (iPS) cells that appear to be able to generate every cell type in the body. In addition, we have powerful new model systems in animals such as flies, worms, frogs, and fish. Using these simpler models, we can identify molecules including drugs that will allow us to control the behavior of stem cells. The Center has already begun interactions with scientists studying zebrafish at the University of Maryland's Columbus Center, a downtown Baltimore marine biology research center. Such molecules can then be tested on mouse and human stem cells, for example to grow them for research studies or hopefully someday for transplantation or transfusion therapies.

The mission of the University of Maryland School of Medicine Center for Stem Cell Biology and Regenerative Medicine is to encourage collaboration in stem cell research among faculty members across the University of Maryland System and beyond. Our Stem Cell Center will foster synergistic biomedical interactions in Maryland between public and private institutions using all kinds of stem cells, multiple species models and basic and translational research to enhance the diagnosis, treatment, and prevention of multiple human diseases. We will cultivate a broad range of interdisciplinary research in a highly collaborative environment while encouraging the translation of these discoveries into new commercial products to maximize the impact on human health and disease.

After 30 years at the Johns Hopkins University School of Medicine where he led active projects totaling more than $20 million in research funding, Civin joined the university to become the founding director of the new University of Maryland School of Medicine Center for Stem Cell Biology and Regenerative Medicine, bringing his research projects with him as well as his entire research team.

**Starting Small**

The December opening of the center was an important step in making the university a national leader in stem cell research, says Ricardo A. Feldman, PhD, associate professor in the School of Medicine's department of microbiology and immunology. Feldman, a core member of the university's renowned team of stem cell researchers, recently won a large grant from the state's Stem Cell Research Fund to grow stem cells to study future treatments of Gaucher's disease.

“We have the seeds of a great enterprise at the University of Maryland. And under the lead of Dr. Civin, who is already bringing people together who wouldn’t otherwise have the opportunity, I think we can become a very important player.”

In its current state, the center is merely a glimpse into what Civin hopes the future holds. His office -- the same in size and in finishes as that of his fellows -- sits in front of the three adjoining labs that are strung together in an unremarkable corner suite on the 1st floor of a medical school research building. This is the nucleus of the new Center.

“All major centers like this have started in just a couple of labs,” Civin says. “In California, in Boston [leaders in the field], it was the same way. There is a line of faculty wanting to join the Center, and addition of the first 30 or so Founding Members is now in progress.”

From this beginning, Civin, who was also named the Associate Dean of Research in the School of Medicine, envisions the development of a dedicated center where, in the next step, two core facilities will act in tandem to fuel stem cell research.

The first will grow stem cells of all kinds -- including embryonic and iPS cells, both of which are in high demand from researchers. The facility will act as a hub that can fuel research throughout the region, which encompasses Johns Hopkins University, the National Institutes of Health, and a myriad of biotechnology companies.

Scientists working on treatments for Diabetes or Parkinson’s disease, for instance, could order stem cells differentiated with those diseases from the Center.

Creating such a facility will require highly skilled scientists, Civin says. “It’s hard to grow enough of these induced pluripotent cells or human embryonic stem cells. And it is very laborious. You need real skilled artisans, not just average scientists or technicians,” he says. Research has been slowed by the lack of available these pluripotent stem cells due to the extreme technical difficulty in growing them.

In the second core facility, stem cells will be modified genetically, providing scientists models of how cells function in diseases. “It’s like a temperature control thermostat concept: we can dial a ‘thermostat’ we put in the cell so that the cell the cell makes a lot or a little of a certain natural molecule,” Civin says. “If the cell is making 100 units of a certain protein, we can turn it up higher. Or we can lower its expression down to zero.” By doing so, researchers can study how such changes affect the cell’s abilities to carry out its functions.

Modifying the cells “takes a lot of intellectual skill and intricate experience and again, some art,” Civin says. By taking that painstaking process out of the hands of individual researchers, it can speed their science. “It might take one year for a lab new to the techniques to make a set of vectors. This core lab would allow the researcher to, instead, just order them up. This will make a lot of people’s science more efficient and shorten the time to discovery.”

**Drawing on experience**

To build the Center, Civin is drawing on decades of experience in stem cell research and the relationships he has developed over the course of his 30+ year career in science and medicine.

Civin, a graduate of Harvard Medical School, began his career at Johns Hopkins University in 1979, following a research stint with the National Cancer Institute from 1976-79. As a pediatric oncology physician who saw children dying of leukemia more often than they survived, he became convinced that stem cells were key to unlocking cures for the disease.

But this was the early 1980s and a major obstacle remained: isolating stem cells. The common treatment for leukemia was—and still is—chemotherapy. Intensive chemotherapy can destroy the bone marrow. Transplants saved in the freezer from the patient's own bone marrow to regenerate the patient's bone marrow after intensive chemotherapy often proved unsuccessful because that marrow contained cancer cells.

Civin's goal was to isolate bone marrow stem cells so only stem cells –without any cancer cells--would be transplanted back into the patient's body. By transplanting only the normal marrow stem cells, free of cancer cells, patients could receive the benefits of high-dose chemotherapy and bone marrow transplant less risk of recurring cancer. At the time many researchers understood the importance of stem cells, but isolating them was impossible.

But in 1984, Civin solved the problem. He invented an antibody that bound itself to stem cell antigens — allowing researchers to harvest isolated stem cells. The antibody called CD34, Civin explains, acts as "a tiny hook for stem cells," pulling only the stem cells from the mass of other bone marrow cells. The purified stem cells can then be transplanted to the patient. The Food and Drug Administration approved the use of Civin's antibody in 1996. Since then it has become the standard practice for isolating bone marrow cells used in cancer therapy for leukemia, lymphoma and myeloma, as well as several other blood diseases . Civin holds nine U.S. patents for biomedical inventions related to his stem cell work, which won him several honors, including the National Inventor of the Year Award in 1999 and the Landsteiner Award in 2009. Thousands of patients have been treated across the globe, and nearly 20,000 scientific articles have involved CD34 in the research .

Today, Civin and the 15-members of his own lab research team are studying the inner workings of blood-forming stem cells to learn not only how to manipulate them to optimize therapeutics but also why they malfunction and cause cancers such as leukemia.

"By learning how normal stem cells develop, we also can learn where and how they errors are made in their DNA code and in which genes are turned on and off," explains Civin. "Then we can find cracks in their armor."

If researchers learn why cells malfunction, they can develop cures aimed directly at the causes. "We can develop a targeted therapy. This gives us a rational basis for treating leukemia," he says.

Using millions of dollars of annual research grant funding from the National Institutes of Health, the State of Maryland, philanthropic foundations, and the University of Maryland, Civin's lab has focused on several molecules which play critical roles both in normal blood-forming stem cells and in leukemias. We recently published the first study to systematically examine the expression and actions of microRNAs in human stem-progenitor cells. Until recently, microRNAs were thought to be junk like sawdust from the messenger RNAs which were thought to be the only real "lumber". However, in the past few years, certain microRNAs have emerged as powerful new class of master regulatory molecules that can serve as "master multi-switches" to regulate large networks of target molecules and thus potently control complex processes such as normal mammalian development and cancer. We discovered that microRNAs appear to play "master multi-switch" roles in normal blood formation and in leukemias. We will extend this groundwork to learn the precise roles of these microRNAs in regulation of normal blood cell formation and in leukemias. Recent exciting results suggest that 2 microRNAs may function in normal blood cells to suppress the development of leukemias. We are concentrating our major efforts to understand basic mechanisms as well as to exploit the clinical potential of these microRNAs.

**Away from the lab**

Civin spent a good part of the last decade on the "politics" of stem cell science.

In 2000, he found himself at the epicenter of a national debate over federal funding for embryonic stem cell research, a practice that was almost halted by Former President George W. Bush. Proponents of stem cell research pointed out that embryonic stem cells are an important research tool because they can morph into any cell in the body and, therefore, hold promise for treating a variety of diseases from Parkinson's to Alzheimer's. Opponents argued that harvesting embryonic stem cells was morally wrong.

Civin took a public stance on the debate, lobbying to end the policies limiting public funding of stem cell research to already-existing lines of embryonic stem cells. He was called to Washington numerous times to make the case that the President Bush's policy would hold the field of stem cell research back because existing stem cell lines were flawed. He took a personal role in educating US Senators and Congressmen on the details of stem cell science. President Bush's bans were not removed until President Obama reversed them. But Civin's role proved good practice for his next fight: Convincing legislators in Maryland to create a state fund to support embryonic stem cell research. President Bush's ban only affected federal funding.

Civin was convinced the state needed to play a pivotal role in stemming the flow of scientists to places like California which passed its own $3 billion fund to finance such research. A Maryland fund, Civin argued, would help the state secure its spot as a biotechnology hub. He joined with Baltimore City delegate Sandy Rosenberg to campaign for the Maryland Stem Cell Research fund, testifying at legislative hearings and speaking to media outlets across the state.

The work paid off. The fund was launched in 2006. Since then, School of Medicine researchers have earned 31 grants from the State of Maryland. Among these, Civin just won another grant for a joint project with Johns Hopkins to determine if, via a novel genetic manipulation, blood-forming stem cells can be made to multiply and expand in a lab and then shrunk down to be placed back in the body. This uncharted research has potential to break ground in disease treatment. But such untried research normally is not funded by the National Institutes of Health, underscoring the importance of the state fund. This State-funded research will tell us if we are on the right track with this new idea. If so, we will apply for larger Federal grants to take the work to the next stage. President Barak Obama's lifting of the ban on federal funding of embryonic stem cell research in March, will make NIH funding more available for stem cell science. "And Maryland's stem cell biologists, like us, will be at a competitive advantage in bringing increased federal dollars to support research in Maryland, because we will be able to show the results of the State-supported research validating our concepts. This is important because research is big business and a large source of good jobs in Maryland."

Civin applauds Obama's decision, but worries that with federal funding in place states, like Maryland, will cut back their role. State funds, he says, support research into ideas not yet fully developed, providing a key first step in the research process. After completing research on the state level, Maryland scientists often secure federal funding for their work, which creates jobs and keeps the state competitive.

"We have turned all of this into support from the feds as well," he says. "So the money has created jobs in Maryland and helped us become more competitive."

Part of his job at the Center will be to continue to push for state funding. That means not only educating the public about the benefits of stem cell research, but also encouraging young doctors and scientists to join the field.

Civin "is well-known so he attracts a high level of people to his lab," says Kara Scheibner, PhD, assistant professor in the Department of Pediatrics and one of the team of scientists who followed Civin from Johns Hopkins to the center. "We have a lot of people from a lot of backgrounds: molecular biology, immunology, cellular biology. It's an incredibly well-rounded lab."

Scheibner, a pharmacologist, says one of Civin's greatest strengths is his ability to cultivate collaboration. "He encourages a cooperative environment within the lab, in the University of Maryland and even in the state," she says. "He has a lot of close colleagues so we have several open collaboration efforts still going

on with John Hopkins and with NIH."

Civin sees the new Center as a key piece of a regional "quartet" where cutting-edge stem cell research is conducted. That includes Johns Hopkins' center, the NIH in Bethesda, and host of biotech companies.

Baltimore was chosen to host the 2009 World Stem Cell Summit in September. The University of Maryland, Baltimore and the Johns Hopkins University will co-host the event, which is expected to bring 1,500 researchers, funders, policy-makers and educators from around the globe to discuss the future of stem cell research and regenerative medicine.

"We have a critical mass of scientists and resources equalling anyplace else," he says. "But in the end, this is really about helping and curing people, not about the numbers of scientists, research articles, or money."