A 15-year-old boy has cancer. With treatment, he is likely to survive (75 percent of children with cancer are cured), but there is a 7 to 15 percent chance that the treatment will leave him infertile. Because the boy is past puberty, he could provide a semen sample before the
treatment begins. The sperm could be frozen and later used to conceive a child through assisted reproductive technology. But often the treatment must start immediately, within a day or two of the diagnosis, and saving a semen sample means visiting another specialist, which can be logistically complicated. Sometimes, the devastated parents are overwhelmed, unable to think of anything but saving their son’s life. Under the stress of facing the disease and the prospect of a difficult treatment regimen, the boy may not even be able to produce a semen sample. Or because of religious or other beliefs, the parents may not want to ask their child to provide one. For any number of reasons, the boy may not give a sample, and his fertility may be lost.

Of course, if a boy has not reached puberty, providing a semen sample is not even a possibility. Currently, there is no option for safeguarding the fertility of pubescent boys during treatment. However, research by Kyle Orwig, a PhD assistant professor of obstetrics, gynecology, and reproductive sciences, and of molecular genetics and biochemistry, and Stefan Schlatt, a PhD assistant professor of cell biology and physiology, may offer new options to help boys facing cancer, whether they’ve reached puberty or not. Their research may also help men with cancer, including those facing testicular cancer (the most common cancer in men ages 15 to 40).

Chemotherapy or radiation can kill the stem cells in the testes, and it is these cells that normally give rise to sperm. But what if before the cancer treatment started, the physician was able to take a biopsy from a testicle, a procedure that is not much more complicated than drawing blood, and later use the tissue sample to restore fertility?

Researchers are exploring this strategy. In experiments with mice, they take a testicular biopsy, then manipulate the tissue to derive a solution of cells with a high concentration of sperm-producing (spermatogonial) stem cells. They irradiate the mouse, then put the solution of cells back into its testicle. The mouse becomes fertile again.

Schlatt was the first to use this technique in monkeys—he showed that injection of stem cells enhanced the recovery of the monkey testis following irradiation, though it did not result in normal sperm counts.

A clinical trial is currently under way in England to study the use of this technique in humans. Seven adult male patients received a transplant of spermatogonial stem cells following cancer treatment. Although Schlatt is not a clinician, he was in the operating room for the first two transplants, guiding the doctors as they performed the procedure.

“The primate testis is quite different from that of mice and other rodents,” explains Schlatt. The techniques researchers had developed for performing the transplant in mice did not work in larger animals. Schlatt was the first to show that it was possible to inject the cells into the proper place in the primate testis (by using ultrasound). The expertise Schlatt developed through primate studies was invaluable as the clinicians performed the first transplants in humans.

From each of the study participants, the researchers will take periodic biopsies to compare the testicle that received the stem cell injection to the one that didn’t, monitoring their ability to produce sperm.

Although the stem cell transplant technique is promising, it does have risks. “We take cells from a tumorigenic organism. If we put those cells back into the organism, we may be reintroducing cancer,” says Schlatt. In one Swedish study, researchers took testicular biopsies from rats with leukemia. Cells from the biopsies were transplanted into the testes of healthy rats who’d been made infertile; they all developed leukemia. The researchers further showed that injecting as few as 20 leukemic cells into the testicle of a healthy rat caused it to develop leukemia. (In the English clinical trial, the patients were selected to minimize the risk of reintroducing their disease—they had cancers that were unlikely to have affected the testes.)

One way to overcome the risk of cancer would be to transplant back into the patient a pure population of stem cells. But how do you ensure that there are no cancer cells mixed in? Orwig has identified rat gonocytes, the primitive embryonic cells that later become sperm-forming adult stem cells. He showed that they have distinctive characteristics, including an arm-like appendage. If such a ready-made marker also exists in adult stem cells, it could
help researchers create cancer-cell free populations of stem cells.

Because of the problems associated with the transplantation technique, Schlatt is also pursuing an alternative approach. A few years ago, he took a testicular biopsy from a pig. He placed a small piece of the testicular tissue underneath the skin on the back of a mouse. The mouse had been bred not to reject tissue from other species. Inside the mouse, new blood vessels grew into the tissue, nourishing it with mouse blood. The testicular tissue eventually formed normal pig sperm. His paper describing the success of this technique in generating mouse, pig, and goat sperm was published in *Nature* in 2002. He has since used the same process to generate monkey sperm.

Schlatt has also performed studies implanting human testicular tissue into the backs of mice. The tissue was obtained from male-to-female transsexual patients who had their testes removed. While the tissue survived in the mouse, it never produced sperm—because, Schlatt believes, the patients had received treatment with estrogen prior to surgery, and estrogen badly damages the testes. In the next year, Schlatt and Orwig will do the same experiment with human tissue that has not been compromised by estrogen.

By using the mouse as a “bioincubator” for generating sperm, doctors would avoid any possibility of reintroducing cancer into a patient, but the technique raises other concerns. For example, a virus from the animal could move into the sperm.

Although his studies are preclinical, Schlatt believes they show enough promise that physicians should take action now. “I believe we should ask doctors to freeze tissue, whenever it is available, to keep these possible options open,” he says.

---

Cancer mortality among Blacks is nearly 10 percent higher than in Whites, yet African American cancer researchers are rare. Richard Steinman, an MD/PhD assistant professor of medicine and pharmacology, wanted to do something to increase the number of African American scientists. So Steinman approached Hampton University, in Virginia, which has among the highest number of biology majors of any historically Black college or university. Together with Cecile ANDRAOS-SELIM, an associate professor of biology at Hampton, Steinman obtained a $750,000 National Cancer Institute grant. They forged a plan for making Hampton’s biology curriculum more lab based. They wanted to improve students’ chances of getting into medical or graduate school and encourage them to consider careers in cancer research.

As part of the program, which started last year, three Hampton students spent 10 weeks at the University of Pittsburgh Cancer Institute this summer. For Dakisha Felder, a 21-year-old biology major from Detroit, it was the first time she’d ever helped staff a lab. She’d taken Hampton’s new Cancer Biology course. (Steinman helped develop the curriculum for the course and taught some of the lectures on the Web and through videoconferencing.) Before coming to work in Steinman’s lab, Felder thought she’d be given a protocol to follow—*Do this, do that.* “It was 100 percent better than that,” she says. She found that Steinman encouraged her to think of experiments she could do to answer her questions and let her know that her work was vital to the efforts of the lab.

While in Pittsburgh, Felder presented her work weekly, took part in an ethics forum, interviewed a cancer survivor, shadowed an otolaryngologist, got advice on interviewing for medical and graduate school—she also went whitewater rafting with the two other Hampton students. Now a senior, Felder is applying to MD/PhD programs. “This program sealed it for me,” she says. “I want to be a physician-scientist.”
As a medical student, Tao Cheng shared a dorm room with seven others from Shanghai Second Military Medical University. His bunkmate was Bin Zhong Hui, a young man who loved to read and sing traditional songs. By their second year in school, Hui and Cheng had become close. One late afternoon, they'd returned from playing a game of soccer, and Hui told Cheng he wasn't feeling well. His body temperature had spiked, so Cheng went with him to the emergency room. A half hour later, the diagnosis came: Leukemia. A month later, Cheng’s good friend was dead. This was the first time Cheng “so deeply felt the great danger of such a blood cancer,” he says.

Cheng knew he wanted to be a hematologist before he even took his general medicine rotation. And as a doctor in Shanghai, he saw the same story play out again and again. Leukemia patients died all the time at the hospital. It came to the point where he couldn't bear to be in the clinic; he knew there was no worse setting than to tell a patient that you have the ability to cure this disease but don’t have enough cells,” says Scadden.

Adult stem cells repair and maintain tissue and organs as needed. But as we age, they start to take it easy. Scientists would love to “wake them up” on demand when the body is in decay or when its repair system has shut down. They’ve imagined a role for awakened adult stem cells for every part of the body: more blood cells for leukemia and lymphoma patients, more neurons to cure Parkinson’s, more cartilage to cure arthritis… But how do we get enough healthy stem cells to keep up with the imagination?

Funding Tao Cheng seems like a good step in this direction. Cheng has identified molecules that regulate key mechanisms of the stem cell cycle. By targeting a molecule known as p21, which normally inhibits replication, Cheng is able to “wake up” blood-forming stem cells so they’ll proliferate in knockout mice. But afterward, the stem cells become exhausted and can no longer do their job. Inhibiting another molecule, p18, doesn’t seem to affect the rate of the cycle but keeps the stem cells healthy after replication. And when Cheng deletes a molecule known as p27 from the cell cycle, stem cell progeny are increased. The stem cell becomes more efficient.

Cheng suspects he’ll find the family of molecules he has identified will work similarly in other adult stem cells as well. They do in stem cells that build neurons.

He envisions therapies for leukemia and other diseases: Doctors would temporarily shut down these molecules until the patient has a healthy and sufficient stable of stem cells. Cheng is now silencing the expression of p18 in human stem cells that have been placed in immunodeficient mice. The success of such a study would be noteworthy. It would be a persuasive piece of testimony to present FDA officials one day, to allow investigators to pursue clinical trials.