**Female stem cells could be better for heart repair, disease treatment**



Above is a pig heart, which has been stripped of all its cells, leaving only the scaffolding to grow a new heart with human stem cells. This approach may be used in the future to repair heart damage or even generate new hearts for transplantation. Pig hearts are used because they are of a similar size and complexity to human hearts.

Some of the most prominent diseases that older people have to fight -- heart disease, diabetes, age-related degenerative diseases and other disorders -- may meet their match in the coming decade with the development of stem cell therapies. And when it comes time to enter the ring, research shows you may want to place your bets on female stem cells to pack the stronger punch.

“We always knew women were awesome,” said Doris Taylor, director of  Regenerative Medicine Research at the Texas Heart Institute. “Now we have the science to back it up.”

Johnny Huard, a University of Pittsburgh researcher who heads the local Stem Cell Research Center, was one of the first to make the discovery in 2007. His team found that female stem cells, derived from animal muscle tissue, generated more muscle fiber and survived better when repairing injured muscle than male cells. Mr. Huard and his team are investigating possibilities but have theorized that because women are smaller and typically have smaller muscles than men, they may have a larger reserve of stem cells.

A study conducted by Ms. Taylor and her team, published last year in the Texas Heat Institute Journal, pointed again to the strength of female stem cells in animals. The team broadened research to humans ages 20 to 70, harvesting stem cells from the blood and bone marrow. The same is true in people; female stem cells were “stronger” than their male counterparts.

Female stem cell strength refers to their number and the fact that “they are more potent than cells derived from males the same age," said Ms. Taylor. “At a given age women will have more stem cells present, in the blood at least, and as we age, women retain more potent stem cells for a longer period of time.”

The team's current theory points to the need for reduced blood levels of inflammation during pregnancy as one reason why female stem cells may have an advantage.

**The quality and quantity of female stem cells may bring a new dimension of efficacy to stem cell therapies to treat disease. “The data on stem cells is very hopeful,” said Paula Johnson, director of the Mary Connors Center for Women’s Health and Gender Biology at Brigham and Women’s Hospital. “This may help us understand sex differences on a cellular level.”**

Stem cell therapies use stem cells’ inherent ability to differentiate into other specialized cells, such as skin, bone or muscle. They can be used to treat a wide variety of disorders because they are “capable of moving through all developmental stages to become functional tissue,” said Justin Brown, assistant professor of biomedical engineering at Penn State.

However, their ability to repair damaged organs eventually diminishes because they “are limited in the number of times they can divide and the rate at which they divide slows as we age,” he said.

This inhibits stem cells’ natural ability to replace or rejuvenate specialized cells damaged by the wear and tear on internal organs. The basic premises of stem cell therapies is to counteract this by harvesting stem cells from bone marrow, fat or heart muscle and then injecting them at the sight of injury to repair and replace damaged cells.

“And if endogenous stem cell repair works a lot better in women, why not figure out what that is and make it available for male colleagues,” said Ms. Taylor. “In theory, if someone had a heart attack and we wanted to do cell therapy, we would want to give them the most potent cells available. We could give them female stem cells or figure out what is in the cells that makes them better.”

Research in the field of cardiovascular disease, the No. 1 killer of men and women in the country, may benefit from using and understanding the differences between male and female stem cells. The clinical manifestation of heart disease differs between the sexes. Women on average develop heart disease 10 to 20 years later than men.

“Men seem to have fewer stem cells in their blood but more inflammatory cells,” Ms. Taylor said. “At the same age men are not going to have the same number of stem cells as women, so in a situation where women repair, men are instead likely to end up with more damage.”

She also noted that in animal studies, stem cell number went down earlier in the blood of males than females. As cell number dropped, plaque build-up increased, potentially explaining the timing gap in the development of heart disease.

“Doris Taylor’s work with cardiac stem cells and looking at stem cells by sex may give us insight into the different behaviors of male and female hearts,” said Dr. Johnson of Brigham and Women’s Hospital.

Multiple international trials are exploring the effectiveness of stem cell therapy to treat heart disease. While clinical trials that would give definitive results regarding differences in strength of stem cells by sex have yet to start in the U.S., David Owen, program director in the Repair and Plasticity Cluster at the National Institute of Neurological Disorders and Stroke, noted that researchers have begun a deeper exploration of sex differences in the established practice of bone marrow transplants.

During transplants, stem cells are taken from the bone marrow of a healthy donor and are injected to give rise to new, healthy blood cells in the recipient.

A team at the Children’s Medical Center Research Institute at University of Texas Southwestern and Baylor College discovered that higher levels of estrogen in females result in more frequent division and enhanced self-renewal of blood-forming stem cells. While the study, published in 2014 in Nature, used mice, researchers hope that the results will open the possibility of increased effectiveness of treatment.

“It is critically important to understand where and what the differences are,” said Dr. Johnson, “and figure out how we better understand those differences to create improved outcomes in both women and men."

Even though it has been 20 years since legislation first required NIH phase 3 trials to include women and minorities, many gaps still remain, Dr. Johnson said.

“Why are younger women getting lung cancer more often? Why is it that aspirin protects heart attacks in men but strokes in women? Is it the same disease in men and women? This an area we still don't really understand,” she said. “When we look for sex differences and find them, we can extrapolate those differences to better understand implications of health and disease.”

“The NIH is now looking at policies that are going to require applicants to report use of male and female in pre-clinical research,” said Dr. Owen, “Sex differences in research are a variable you want to be aware of, however it is important to also look case-by-case -- there can be exceptions to the rule.”

He emphasized the importance of never overgeneralizing results in regard to stem cells due to their variability in terms of derivation and complexity.

Mr. Huard, who holds an endowed chair in orthopaedic surgery research at Pitt, also noted that stem cell number and potency can be affected by environmental factors such as smoking and exercise. While his lab now almost exclusively uses female stem cells for skeletal muscle repair, Mr. Huard believes that their strength can’t be overgeneralized because in the cases of bone and articular cartilage repair, male stem cells appear to be better.

Although there is still a big jump between the results of research and established medical procedures, Ms. Taylor still hopes her research, and others like it, will impact the future of health care.

“I’m lucky to be surrounded by a team of visionary individuals who work hard -- none of us believe we should be moving forward in ways that aren’t transparent. If we have an opportunity to make a difference in the world of medicine and someone’s life, we have an obligation to do so.”