

## Stem Cell Overview

Stem cells make the cover of national magazines and newspapers. They're debated in the halls of Congress and state capitols. And yet they are widely misunderstood and shrouded in mystery, even in many of the scientific laboratories that are working on them.

In an attempt to demystify stem cells and bring some light to the debate over the science and ethics surrounding these vital microscopic units of life, Dominican University of California and Zero Breast Cancer sponsored a dynamic all-day conference on The Promise of Stem Cell Research in Human Health on Feb. 9 at Dominican's San Rafael campus.

"In labs world-wide, scientists are turning to stem cells to help with the development of treatments of ailments, including heart disease, diabetes and cancer," said Dr. Sibdas Ghosh, chair of Dominican's Department of Natural Sciences and Mathematics. "The public still knows little of this vital field of research, which holds great promise for therapies and cures. Stem cells are still so new that few people even learn about it in school."

More than 300 people attended the conference, from Dominican students to senior citizens active with the Buck Institute for Age Research.

The conference helped demystify stem cells, telling the difference between embryonic stem cells and adult stem cells, and spelling out some of the ethical issues that researchers wrestle with. A range of speakers touched on various aspects of the research. Dr. Mary Helen Barcellos-Hoff, PhD, a senior scientist and deputy director of the Life Sciences Division at Lawrence Berkeley National Laboratory, told how knowledge about stem cells is informing research into how breast cancer develops in the mammary gland, while Dr. Mary Devereaux, PhD, a bioethicist in the Research Ethics Program at the University of California, San Diego, explored the ethical debate, which touches on the question of when human life actually begins.

Dr. Mohammed El Majdoubi, an assistant professor of biology at Dominican, spoke of his work with Dominican students in solving the mysteries of certain hormone-secreting neurons, while Dr. Warren Hoeffler, the founder of Xgene Corporation, a company commercializing discoveries in tissue engineering, spoke of the role of private enterprise in stem cell research.

And delving into the complex world of embryonic stem cells were Dr. Xianmim Zeng, assistant professor and director of the North Bay CIRM Shared Research Laboratory for Stem Cells and Aging at the Buck Institute for Age Research, and Dr. Renee Reijo Pera, professor and director of the Center for Human Embryonic Stem Cell Research and Education within the Stanford Institute for Stem Cell Biology and Regenerative Medicine at Stanford University School of Medicine.

At the Buck Institute, Zeng said, embryonic stem cell research focuses on four areas:

- Developing cell therapy strategies for neurodegenerative disorders.
- Developing drug screening.
- Studying aging-related processes. "You can find some clues for why we age," she said.

- Modeling human diseases.

In the conference's keynote presentation, Dr. Gilberto R. Sambrano, PhD, the senior officer in charge of peer review for the California Institute for Regenerative Medicine, spoke of the state of stem cell research in California. The institute was established by a 2004 ballot measure that provided \$3 billion for stem cell research, in part a reaction to federal restrictions on such research.

Sambrano started the discussion at the simplest level: What is a stem cell? "It's important that we are all on the same page," he said.

"A stem cell has two very basic characteristics," he said. "It is a cell that can mature and specialize into other cell types that have very specific functions, and it can renew itself."

Embryonic stem cells, like human embryos themselves, have the potential to grow into something much larger. "Stem cells have the potential to each grow into your entire body," he said. "As we grow, that potential slowly, progressively begins to decline. Adult stem cells have a limited capacity to renew themselves and to produce all the different cell types."

That's why researchers find the embryonic stem cells so attractive, he said. Stem cell research received a major boost in 1998 when Dr. James Thomson at the University of Wisconsin announced the ability to culture stem cells in a laboratory. "This was a tremendous finding," Sambrano said. "For the first time, we could take human embryonic stem cells, in a dish, and culture them. Under specific conditions those cells can be specialized to create different tissues."

Scientists had typically used embryos from *in vitro* fertilization, in which a sperm and an egg are put together in a laboratory, and allowed to grow into a ball of cells called a blastocyst. The blastocyst contains cells that can produce stem cell lines, and "once you have a stem cell line, those cells can propagate indefinitely," Sambrano said, "and you have the potential to produce in a lab all the different cells in the body."

"This is a very young field," he said. "Scientists are currently trying to understand the mechanisms that allow a human embryonic stem cell to become a nerve cell, or a pancreatic cell, or a blood cell, or a heart muscle cell. There are still many questions that need to be addressed in terms of the science."

Even with the questions, however, stem cells hold great promise for new therapies.

"Stem cell research really is an enabling technology," he said. "It might enable us to replace tissues that are diseased, or to deliver drugs to specific areas of the body."

If a scientist had a diseased cell in a culture dish, he or she could test hundreds or thousands different drugs. Such research would be difficult if not impossible in living humans, but the same results could come from stem cells.

Yet Sambrano acknowledged that the discussion is not purely scientific, but is layered with issues of politics and religion. The development of the controversial technique known as Somatic Cell Nuclear Transfer (SCNT), in which the nucleus is removed from an egg and another nucleus is inserted, marked the dawn of a "very powerful technique," Sambrano said. "It gave us the ability to create cells that are specific to a patient."

"This very basic technique, although powerful, was also used to clone Dolly the sheep (by taking the SCNT blastocyst and implanting in the uterus of a surrogate sheep),"

he said. “Will scientists be interested in wanting to clone people? That is not the interest of scientists. It’s not something that scientists want to do. But it did ruffle feathers.”

A common concern in the public mind is the necessary use of an embryo to derive stem cells, in part augmented by a not-so-clear idea of what a blastocyst-stage embryo is. Some might imagine a blastocyst embryo as one that begins to demonstrate recognizable features like an arm or leg. In fact, a blastocyst-stage embryo has not begun to distinguish itself beyond a small cluster of cells. He showed a dramatic slide, showing the size of a blastocyst-stage embryo used for derivation of stem cells next to a penny. Pointing to the letter “R” in the word liberty on the front of the penny, Sambrano said the embryo could nestle in the little crevice inside the R.

Neither the blastocyst created in a dish, nor the stem cells derived from it, can actually develop into a full organism on their own. The development of an organism from an SCNT blastocyst would require at the very least implantation of the blastocyst into a uterus; a step that scientists have no desire or reason to take.

“Nevertheless,” he said, “in 2001, there was an executive order by the president that affected human embryonic stem cell research quite deeply. In his mind it was a compromise. It prohibits using federal funds on embryonic stem cell lines that were derived prior to the date of the decree, Aug. 9, 2001.”

Scientists moved quickly to find alternate funding so that the research could move forward. Several states stepped into the breach, with California the first and the largest, but Illinois, Connecticut, Maryland, Massachusetts, Maine, New Jersey, New York and Ohio all following suit.

California’s Proposition 71 passed in 2004 with 59 percent of the vote, authorizing \$3 billion for stem cell research over a 10 year period. The measure affirmed the right to conduct research that was not supported by federal funding, and it banned reproductive cloning, which the federal government has not yet done.

The measure created two entities, the California Institute for Regenerative Medicine, or CIRM, which is charged with disbursing the \$3 billion to researchers, and the Independent Citizens Oversight Committee, a 29-member governing board for CIRM. CIRM’s mission is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies and diagnostic tools.

“It’s basically turning stem cells into cures,” Sambrano said, citing patient advocate Roman Reed’s phrase. “That is the goal of the institute.”

CIRM faced some big challenges from the start. It had to build a granting agency from the ground up, Sambrano said, and scientists already felt that time was being lost due to the federal funding restrictions. It had to meet many state laws that dictate how the public’s money can be spent. It needed to set up a grants management system, so that it could make sure it tracked its grantees’ accomplishments.

And it faced a major legal challenge. As soon as Prop. 71 passed, two lawsuits “challenged our constitutional authority to spend state money,” Sambrano said. “If you can’t spend state money, you can’t fund scientific research.”

A third suit, which said that CIRM was depriving frozen embryos of their constitutional rights, was dismissed.

CIRM’s chairman of the board, Robert Klein, was able to assemble some interim funding in the form of bond anticipation notes to get CIRM off the ground while the legal

system sorted out the controversy. In May 2007, the California Supreme Court freed CIRM to start funding research.

CIRM then established a 10-year plan for spending the money, involving 200 people, including scientists, ethicists, clinicians, patient advocates and public interest groups. While it also aspires to make California the worldwide leader in stem cell research, it also includes doses of realism.

“Therapeutic drug development is expensive,” Sambrano said. “It takes time, and it fails more often than it succeeds. It typically takes seven to nine years to bring a drug to patients, and we’re only developing a 10-year plan.”

And in many cases, stem cell research could lead to cellular therapies – replacing diseased cells in the body with healthy ones – a new field that will require close discussion with the federal Food and Drug Administration to get therapies approved. One of CIRM’s goals is to achieve clinical proof of the principle that cells can be used to restore function for at least one disease, Sambrano said.

According to the CIRM Web site, the CIRM governing board has approved 156 research grants totaling almost \$260 million, making CIRM the largest source of funding for human embryonic stem cell research in the world. Sambrano said it is moving forward quickly to move research forward, both in the nonprofit and for-profit sectors.

Many audience members peppered Sambrano with questions. Sambrano assured one woman that CIRM is working with international colleagues on stem cell research. “Even though Proposition 71 is about California, the institute realizes that this effort is worldwide and should not be restricted to California,” he said.

Another questioner wanted to know where current presidential candidates stand on stem cell research, and while Sambrano said they have not clearly outlined their positions, he believes no matter who is elected will ease the restrictions that President Bush has placed on the research. A greater challenge, he said, will be finding the money, as the National Institutes of Health has been cutting its budget every year.

In response to another question, Sambrano said that the institute is not merely funding embryonic stem cell research. It is very interested in other developments – from Japan and from Thompson’s lab in Wisconsin, for instance – indicating that some adult cells, such as skin cells, can behave like embryonic stem cells in the laboratory. If that works, that could help change the entire debate, but the technique is still unproven.

“There’s a lot we can learn, and we won’t learn if we only focus on one thing,” he said. “We need to reach out and look at new technologies that come into play.”

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