# Team Discovers Specialized, Rare Heart Stem Cells In Newborns, With Potential for Replacing Damaged Tissue

February 9, 2005

Sue Pondrom

The first evidence of cardiac progenitor cells - rare, specialized stem cells located in the newborn heart of rats, mice and humans - has been shown by researchers at the UCSD School of Medicine. The cells are capable of differentiation into fully mature heart tissue.

Called isl1+ cells, these cardiac progenitor cells are stem cells that have been programmed to form heart muscle during fetal growth. Until this new discovery, the cells were thought to be absent after birth. However, the UCSD team discovered a small number of the specialized stem cells remained embedded in a region of the newborn heart called the atrium. They also determined that the cells could be expanded into millions of progenitor cells by growing them on a layer of neighboring heart cells called fibroblasts.

Published in the February 10, 2005 issue of the journal *Nature*, the research identified the isl1+ progenitor cells in the tissue of newborn rats and mice, and then in heart tissue taken from five newborn human babies undergoing surgery for congenital heart defects.

Study author Sylvia Evans, Ph.D., a member of the UCSD Institute of Molecular Medicine (IMM) and professor of pharmacology, and co-first author Alessandra Moretti, Ph.D., IMM member, explained that the cells are programmed to become spontaneously beating cardiac muscle cells simply by exposure to other neighboring heart cells.

And, since these rare cardiac progenitor cells are found in regions of the atrium that are normally discarded during routine cardiac surgery, the discovery raises the possibility that an individual could receive their own cardiac stem cells to correct a wide spectrum of pediatric cardiac diseases, according to co-first authors Moretti and Karl-Ludwig Laugwitz, M.D., a Heisenberg-Scholar of the German Research Foundation.

"Conceptually, these cells could provide a cell-therapy based approach to pediatric cardiac disease, which is new for cardiology," said the study's senior author, Kenneth Chien, M.D., Ph.D., director of the UCSD Institute of Molecular Medicine. "Traditionally, pediatric cardiologists and cardiac surgeons have relied on mechanical devices, human and synthetic tissue grafts, and artificial and animal derived valves to surgically repair heart defects. While progenitor cells won't grow a whole new heart, our research has shown that they can spontaneously become cells from specific parts of the heart by simple co-exposure to other heart cells, which could augment existing surgical procedures. If the cells maintain pacemaker function when placed in the intact heart, they might serve as biological pacemakers for infants born with heart block, which could also be valuable."

After the isl1+ cells were found in newborn rats, the UCSD team used sophisticated genetic methods to tag the progenitor cells in living embryonic tissue and in the newborn heart of mice. With these techniques, they were able to show that the isl1+ progenitor cells were spontaneously able to form cardiac muscle tissue.

"Furthermore, the cardiac muscle cells formed were totally mature and had the complete array of function that one would expect in completely differentiated heart tissue," said the study's co-first author Jason Lam,

Ph.D. candidate in the IMM. The cells exhibited contractility, pumping ability, the correct electrical physiology and normal heart structure. In addition, the progenitor cells coupled with neighboring cardiac muscle cells with resulting normal electrical heart beats.

"Another important discovery was the ability to expand the few cells found in a newborn heart, into millions of cells in lab culture dishes," Laugwitz said. "This implies that the isl1+ cells potentially could be harvested from an individual's heart tissue, multiplied in a laboratory setting, then re-implanted into the patient. Furthermore, the developmental lineage marker which identifies undifferentiated cardiogenic precursors suggests the feasibility of isolating isl1+ cardiac progenitors from mouse and human embryonic stem cell systems during cardiogenesis."

"We think that these cells normally play an important role in the remodeling of the heart after birth, when the newborn heart no longer relies upon the mother's circulation and oxygenation," Chien said. "We believe the isl1+ progenitor cells are left over from fetal development so that they can insure the closure of any existing small heart defects and the formation of a completely mature heart in newborns."

The UCSD team noted in the Nature paper that the next research steps with the isl1+ cells will be cellular transplantation in living animals to study their role in endogenous repair after cardiac injury.

In addition to Chien, Evans, Lauagwitz, Moretti and Lam, study authors included Peter Gruber, M.D., Ph.D., Children's Hospital of Philadelphia; Yinhong Chen, M.D., Ph.D., Sarah Woodard, B.S., Lizhu Lin, Ph.D., and Chen-Leng Cai, Ph.D., UCSD Institute of Molecular Medicine; Min Min Lu, Ph.D., Department of Medicine, University of Pennsylvania; and Michael Reth, Ph.D., Max-Planck Institut fur Immunbiologie, Universitat Freiburg, Freiburg, Germany.

The research was supported by the National Institutes of Health, the Fondation Leducq, and the German Research Foundation.

Media Contact: Sue Pondrom (619) 543-6163