

SEPTEMBER 22, 1999

Stem Cells May Be Powerful Gene Shuttle

Stem cells may prove to be a better shuttle than viruses for delivering corrective genes to tissues throughout the body, say researchers from the Howard Hughes Medical Institute (HHMI) at Children's Hospital in Boston and Harvard Medical School.

Stem cells are immature cells that have the unique capacity to give rise to populations of mature, functioning cells. Using stem cells derived either from the bone marrow or from specific organs to carry therapeutic genes back to sites of disease might prove advantageous because it may "remodel" genetically defective organs and tissues, allowing them to permanently carry the corrective gene, say HHMI investigators Richard Mulligan and Louis Kunkel of Children's Hospital and Harvard Medical School, whose laboratories collaborated on this study.

Virus-based gene therapies for muscular dystrophy, for example, must be injected directly into the muscle, and they only correct the altered tissue locally, said Kunkel. "If the virus doesn't reach stem cells, the therapeutic effect is lost when the muscle degenerates naturally. Stem cell therapy has the potential to fundamentally remodel the tissue itself," said Kunkel, an expert on the molecular basis and treatment of muscular dystrophies. More importantly, said Mulligan, "the use of stem cells for transplantation appears to result in the disseminated delivery of cells, a critical requirement for the effective treatment of a disease such as muscular dystrophy, where the afflicted cells are found throughout the body."

In an article in the September 23, 1999, issue of *Nature*, Mulligan's and Kunkel's laboratories describe the development and testing of their approach in a mouse model of the human disease Duchenne muscular dystrophy (DMD). Like patients with DMD, the mice do not produce the protein dystrophin, the absence of which causes rapid and life-threatening deterioration of muscles.

The researchers first irradiated female mice to eliminate any blood-related, or hematopoietic, stem cells, which are normally found in bone marrow. The

scientists then injected into the female mice, dystrophin-positive stem cells isolated from the bone marrow or muscle tissue of male mice.

To their surprise, the scientists found that the injected hematopoietic stem cells and the muscle stem cells were both able to give rise to blood cells and also provided for the engraftment of diseased muscle with healthy muscle cells expressing dystrophin.

While the researchers caution that their results are still preliminary, their findings hint that adults may harbor stem cells from a variety of organs and tissues that might be manipulated to heal genetic defects in organs and tissues throughout the body.

The scientists say, however, that the restorative effects were well below what would be required if the technique were to be used for clinical treatment. But they believe there are ways to improve the method.

The discovery of similarities in hematopoietic and muscle stem cells also raises important questions about the origin of stem cells and their therapeutic potential, said Mulligan, an expert in the development of gene transfer technology and leader of the gene therapy efforts at Harvard.

"The muscle-derived stem cells might originate from the hematopoietic compartment or they might be present in muscle as a consequence of the natural process of development," said Mulligan. "However, it might make sense for hematopoietic stem cells to communicate with organs and tissues, since they have the capacity to traffic throughout the body," he added. "The hematopoietic system might be able to sense the need for replenishment of cells and organs or tissues," and provide the cells necessary for tissue or organ repair.

Mulligan said that it will be important to compare the properties of the adult stem cells they have isolated to embryonic stem cells, which are known to be able to give rise to a broad range of tissues. Embryonic stem cells are now being studied for use in tissue transplantation

"Perhaps such breadth is not necessary," Mulligan noted. "It might be that different adult stem cell populations will still have the capacity to give rise to cells from the organ in which they originated."

If the existence of organ-specific stem cells is confirmed, and if researchers can determine the cellular signals that control their differentiation, it might be possible to use the cells to genetically "remodel" heart, liver, pancreas or brain tissue, theorize the scientists. And if hematopoietic stem cells can be

manipulated to produce organ-specific cells, they may one day prove to be a better source of therapeutic cells than the damaged organs.

Mulligan's and Kunkel's collaborators on the *Nature* paper were postdoctoral fellows Emanuela Gussoni and Yuko Soneoka, Corinne Strickland, Elizabeth Buzney, Mohamed Khan and Alan Flint.