Carnegie Mellon researchers to develop new drug delivery system

November 2 2007

Carnegie Mellon University's Stefan F. Zappe is using adult neural stem cells to develop a new stem cell-based drug delivery therapy that may ultimately help treat a variety of inherited genetic disorders like Hunter syndrome.

Zappe, an assistant professor of biomedical engineering at Carnegie Mellon, and his graduate student Sasha Bakhru, are creating genetically engineered adult neural stem cells for delivery to patients' brains, where they will be programmed to produce an essential missing protein. In Hunter syndrome, for example, patients are lacking the enzyme iduronate-2-sulfatase that helps cells break down certain waste products. One in every 130,000 boys is born with the rare but deadly genetic disorder.

Zappe, who is working with Dr. Raymond Sekula, a neurosurgeon at Allegheny General Hospital, said he selected adult neural stem cells for his work because they can be harvested from a patient's brain, have the potential to be multiplied outside of the body, can be genetically engineered, can disperse within the brain once re-implanted and can replace all major cell types of the brain.

To support their therapeutic goals, Zappe and his team have developed cell-instructive microcapsules that contain neural stem cells. These microcapsules efficiently control whether stem cells proliferate (multiply), differentiate into more specialized cell types like neurons and to what extent implanted stem cells will be allowed to migrate to the host

tissue.

Zappe will be using these caviar-sized capsules specifically for rapid manipulation of stem cells outside the body and for reliable delivery of stem cells to the brain. The acute inflammatory response that usually occurs from implantation would normally cause implanted neural stem cells to differentiate into mature cell types that are not able to migrate extensively. Encapsulated stem cells will be protected from such premature differentiation.

Once the brain has healed from the initial implant of the encapsulated stem cells, the stem cells are genetically engineered to produce an enzyme that eats the microcapsule, freeing the neural stem cells. The stem cells can then migrate deep into the surrounding brain tissue where they provide the missing enzyme.

“We are particularly interested in targeting the brain because this area of the body is protected by the so-called blood-brain barrier that has been very difficult to penetrate with therapeutic enzymes that are usually injected into the patient’s bloodstream,” Zappe said. Zappe and Sekula are working to develop technologies that will ultimately enable clinicians to harvest neural stem cells from a patient, genetically engineer them from outside the body and then re-implant them and remotely control their actions in non-invasive ways.

“By using inducible gene expression, we hope to provide physicians with external control over capsule degradation and the amount of therapeutic enzyme released into the brain by engineered cells as determined by the dose of drugs that are given to the patient in pill form,” Zappe said.

“Hunter syndrome is a devastating illness affecting more than 500 children in the U.S. alone. Over time, toxic waste products accumulate in the cells of the body, and, although progression of the disease varies, the

majority of children die in their teens. If we can reliably provide the missing enzyme iduronate-2-sulfatase to the central nervous system of these children, we may change the course of this disease. Our technology and methodology also will likely have far-reaching implications for hundreds of other diseases of the central nervous system," Sekula said.

Source: Carnegie Mellon University