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Press Room, Oct. 13–17: (504) 670-4630

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REALIZING THE POTENTIAL OF STEM CELL THERAPY: STUDIES REPORT PROGRESS IN DEVELOPING TREATMENTS FOR DISEASES AND INJURIES

Animal research shows promise for treating Alzheimer's disease, brain damage, and heart problems resulting from spinal cord injuries

NEW ORLEANS — New animal studies provide additional support for investigating stem cell treatments for Parkinson's disease, head trauma, and dangerous heart problems that accompany spinal cord injury, according to research findings released today. The work, presented at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health, shows scientists making progress toward using stem cell therapies to repair neurological damage.

The studies focused on using stem cells to produce neurons — essential, message-carrying cells in the brain and spinal cord. The loss of neurons and the connections they make for controlling critical bodily functions are the chief hallmarks of brain and spinal cord injuries and of neurodegenerative afflictions such as Parkinson's disease and ALS (amyotrophic lateral sclerosis), also known as Lou Gehrig's disease.

Today's new findings show that:

- Neurons derived from human embryonic stem cells implanted in monkeys displaying symptoms of Parkinson's disease appear to have matured into healthy, dopamine-producing neurons without causing any adverse effects (Dustin Wakeman, PhD, abstract 314.11, see attached summary).
- Life-threatening heart problems caused by spinal cord injury were partially remedied in rats treated with stem cells derived from the fetal brainstem. The findings suggest new avenues of research for repairing cardiovascular damage in human patients with spinal cord injuries (Armin Blesch, PhD, abstract 637.10, see attached summary).
- Experiments in mice indicate it may be possible to activate dormant stem cells in the adult prompting the production of new neurons that might help repair damage caused by injury (Nathaniel Hartman, PhD, abstract 823.07, see attached summary).

Other recent findings discussed show that:

- Scientists believe they have isolated a protein that can signal the adult brain to produce more neurons, raising the possibility that boosting production of the protein could help patients recover neurons lost to degenerative diseases like Parkinson's and ALS, or to trauma, such as spinal cord injury (Anthony Conway, abstract 823.04, see attached speaker's summary).

"As the fields of developmental and regenerative neuroscience mature, important progress is being made to begin to translate the promise of stem cell therapy into meaningful treatments for a range of well-defined neurological problems," said press conference moderator Jeffrey Macklis, MD, of Harvard University and the Harvard Stem Cell Institute, an expert on development and regeneration of the mammalian central nervous system. "Solid, rigorous, and well-defined pre-clinical work in animals can set the stage toward human clinical trials and effective future therapies."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 314.11 Summary

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Potential Advance for Parkinson's: Neurons from Embryonic Stem Cells Mature in Brains of Monkeys

Researchers see no side effects in work that could provide evidence to support human trials

Neurons derived from human embryonic stem cells and implanted in monkeys exhibiting symptoms of Parkinson's disease appear to fully mature into the same type of dopamine-producing neurons destroyed by the affliction — without causing tumors or other adverse effects, according to a new study. The findings were presented today at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Challenges related to cell survival, maturation, and tumor risk have stymied early efforts to realize the potential of human embryonic stem cells to provide new treatments for Parkinson's disease, which is characterized by tremors and movement problems caused by the loss of dopamine-producing neurons in the brain.

Dustin Wakeman, PhD, of Rush University Medical Center, and his colleagues had previously shown that the dopamine-producing neurons they had developed from human embryonic stem cells were capable of surviving in the brains of "parkinsonian" monkeys — a long-standing primate model of the disease. But a missing piece of the puzzle was evidence that the transplanted human cells could fully mature in animals without causing problems.

"We ended up with excellent stem cell graft survival and the development of true, mature dopamine cells in the parkinsonian monkeys, with no evidence of tumors," Wakeman said. "This is significant because rigorous testing of stem cells in parkinsonian monkeys is essential to providing data to justify a Phase 1 clinical trial in humans."

Research was supported by the National Institutes of Health, the Consolidated Anti-Aging Foundation, and the Castle Foundation.

Scientific Presentation: Wednesday, Oct. 15, 8–11:15 a.m., Room 277

314.11, Dopamine neurons derived from human ES cells retain midbrain phenotype in aged MPTP monkeys.
***D. R. WAKEMAN**, S. KRIKS, H. B. DODIYA, L. STUDER, J. H. KORDOWER; Neurolog. Sci., Rush Univ., Chicago, IL; Mem. Sloan-Kettering Cancer Ctr., New York, NY

TECHNICAL ABSTRACT: Human pluripotent stem cells remain a promising alternative substrate for transplantation in Parkinson's disease (PD). Efficient differentiation of embryonic and induced pluripotent stem cells into functional midbrain dopamine neurons was demonstrated utilizing a unique floor-plate induction strategy (Kriks et al., Nature 2011). In vivo survival and function of transplanted cells were shown in 6-hydroxy-dopamine-lesioned mice and rats verifying robust survival of FOXA2+ midbrain DA neurons derived from human embryonic stem cells (hESC), including restoration of amphetamine-induced rotation behavior and improvements in tests of akinesia and forelimb use. While these results were extremely promising, the clinical translational value remained untested at longer time points. Therefore, we tested the scalability and short-term potential (up to 3 months) of hESC derived midbrain dopaminergic neurons in parkinsonian non-human primates. Midbrain floor-plate precursors were derived from WA-09 hESC (H9) utilizing dual SMAD inhibition in combination with small molecule activators of sonic hedgehog and canonical WNT signaling. FOXA2+ midbrain DA neuroblasts were transplanted bilaterally into the striatum of aged, MPTP-lesioned Rhesus monkeys (10-12kg). After 1-month (N=2) and 3-months (N=2) post-transplantation, robust donor derived grafts were located within the graft zone. Immunohistochemical analysis using a human cytoplasm specific antibody (STEM-121) revealed extensive outgrowth of fibers from donor cells, specifically along endogenous white matter tracks. Maintenance of the midbrain dopaminergic lineage was confirmed by co-expression of FOXA2 and tyrosine hydroxylase (TH) in combination with human cytoplasm. By 3-months, grafted cells matured into highly arborized, mature TH+ dopaminergic neurons reminiscent of fetal ventral mesencephalic nigral neuron grafts in human clinical patients. The results demonstrate excellent graft survival, maintenance of the midbrain dopaminergic phenotype, and lack of neural overgrowth in aged parkinsonian monkeys as well as indicate considerable promise for the development of pluripotent cell-based therapies in PD.

Abstract 637.10 Summary

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Stem Cells Have Potential to Treat Heart Problems Caused by Spinal Cord Injuries

Study in rats shows stem cells may restore damaged nerve connections that control blood pressure and heart rate

Spinal cord injuries frequently cause life-threatening heart conditions, but new research suggests a potential role for stem cells in addressing the problem. In a study of rats with cardiovascular problems resulting from spinal cord damage, scientists found the condition was partially relieved by transplanting stem cells derived from the fetal rat brainstem. The research was presented today at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Injuries to the upper level of the spinal cord can disrupt nerve fibers connecting the brainstem and the spinal cord, causing blood pressure to drop and heart rate to increase. Also, when patients experience certain painful stimuli below the level of the injury, a potentially life-threatening situation called autonomic dysreflexia can develop, a condition characterized by a sudden increase in blood pressure and a decrease in heart rate.

Armin Blesch, PhD, of the Spinal Cord Injury Center at Heidelberg University Hospital, and his colleagues from the University of California, San Diego, tested a way to deal with these challenges. They isolated neural stem cells from the fetal brainstem and transplanted them into the spinal cords of injured rats. The response to the treatment was then compared with that of two other groups: injured rats that had received stem cells taken from the fetal spinal cord (not the brainstem), and injured rats that had received no transplant at all. Blood pressure and heart rate were recorded eight weeks later.

"Only the animals that received transplants of fetal cells derived from the brainstem had a resting heart rate and blood pressure that was similar to normal values," Blesch said. "When we looked at their spinal cords, we found evidence that the transplanted cells may be serving as nerve relays to reconnect the brain with centers of control for cardiovascular function."

Research was supported with funds from the National Institute of Neurological Disorders and Stroke and the Craig H. Neilsen Foundation.

Scientific Presentation: Tuesday, Oct. 16, 2–3 p.m., Hall F-J

637.10, Partial restoration of cardiovascular dysfunction by fetal brainstem grafts after spinal cord transection.
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TECHNICAL ABSTRACT: High thoracic and cervical spinal cord injury (SCI) usually results in cardiovascular dysfunction. The disruption of supraspinal vasomotor pathways (SVPs) to sympathetic preganglionic neurons (SPNs) in the spinal cord leads to hypotension and compensatory tachycardia at rest. Episodic autonomic dysreflexia can develop upon sensory stimulation below the level of injury. To restore input to and supraspinal control of SPNs, fetal tissue dissected from embryonic day 14 brainstem (E14BS) of GFP transgenic rats was transplanted into a T4 complete spinal cord transection in adult rats. Control animals received E14 spinal cord tissue (E14SC) or just a lesion without graft. Biotinylated dextran amine (BDA) was injected bilaterally into the rostral ventrolateral medulla to anterogradely label SVPs and fluorogold was injected intraperitoneally to retrogradely label SPNs in the spinal cord. Mean arterial pressure (MAP) and heart rate (HR) were recorded 8 weeks later using a telemetric system. Hypotension and tachycardia were evident at rest in injured animals without graft (MAP 109 ± 2 mmHg, HR 457 ± 8 bpm) or E14SC transplants (MAP 109 ± 3 mmHg, HR 462 ± 11 bpm), whereas resting MAP (118 ± 2 mmHg) and HR (422 ± 11 bpm) approached normal values after E14BS grafts. Although colorectal distension resulted in autonomic dysreflexia in all groups, the extent of MAP increases was significantly ($p<0.05$) lower in animals that received E14BS grafts (34 ± 4 mmHg) than in animals with lesion alone (50 ± 6 mmHg). No significant difference was detected between animals grafted with E14SC (36 ± 4 mmHg) and animals without graft. Spinal re-transection above E14BS transplants abolished hemodynamic recovery, suggesting that cardiovascular parameters were influenced by inputs from neurons above the graft. Immunohistochemistry revealed that E14BS grafts contained a large number of catecholaminergic (TH-labeled) and serotonergic (5HT-labeled) neurons that extended a remarkable number of axons into the intermediolateral cell column below the injury where they closely associated and formed synapses with SPNs. In contrast, no or only very few TH- and 5HT-labeled fibers were detected below the lesion in animals without graft or E14SC transplants, respectively. BDA-labeled vasomotor pathways extended into E14BS implants and displayed synapse-like boutons that were closely associated with brainstem neurons. Thus, grafted embryonic brainstem neurons may serve as functional relays to restore signals from higher autonomic centers to denervated SPNs, thereby contributing to cardiovascular improvement after SCI.

Abstract 823.07 Summary

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Researchers Seek to Send Wake-Up Call to Stem Cell that Could Help Repair Brain Damage

Scientists focus on activating neural stem cells that are hard at work in development, but dormant in adults

New research in mice reveals that it may eventually be possible to awaken a slumbering stem cell in the adult brain and prompt it to produce neurons, which in turn could help repair damage caused by head injuries. The findings were presented today at Neuroscience 2012, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"In the very young human brain, neural stem cells are hard at work producing neurons, but in adults, they are mostly dormant, which contributes to the body's limited capacity to replace neurons lost to head trauma or diseases," said Nathaniel Hartman, PhD, of Yale University, and the study's lead author. "Our early results in mice suggest there may be a way to activate neural stem cells so they can generate replacement neurons and help repair damage that occurs when we suffer sharp blows or other insults to the brain."

Hartman and his colleagues tested their approach by injecting a region deep inside the brains of mice with a specially formulated strand of DNA. The DNA carried a set of specific genetic instructions for activating a molecule called mammalian target of rapamycin complex 1 (mTOR) inside neural stem cells that is believed to be essential for stem cell activation and neuron production. In newborn and young adult mice treated in this fashion, the researchers found increased cell proliferation, suggesting that previously dormant, or "quiescent," neural stem cells had commenced production of neurons.

Research was supported with funds from Connecticut Stem Cell Research Grants Program and the Department of Defense.

Scientific Presentation: Wednesday, Oct. 17, 1–3:15 p.m., Room 391

823.07, mTOR acts as a molecular switch for lineage expansion in the neonatal subventricular zone.
***N. W. HARTMAN**, D. M. FELICIANO, T. LIN, C. M. BARTLEY, A. BORDEY; Neurosurg., Yale Univ. Sch. of Med., New Haven, CT

TECHNICAL ABSTRACT: Activation of dormant neural stem/progenitor cells (NPCs) is a critical step for neuron production. This step requires the integration of many extrinsic signaling pathways, including growth factor and glucose signaling. The mammalian target of rapamycin complex 1 (mTORC1, noted mTOR) is a convergence point for many of these processes, and mTOR plays a crucial role in cell growth and proliferation. Here, we found that proliferative neural progenitor cells (NPCs) and Mash1+ transit amplifying cells (TAC) in the neonatal subventricular zone (SVZ) display active mTOR signaling. Using a targeted genetic approach, we manipulated mTOR activity by electroporating plasmids encoding a constitutively active form of Rheb (Rheb-CA) into the postnatal SVZ. Introduction of Rheb-CA to SVZ cells increased mTOR activity and phosphorylation of S6 ribosomal protein. This increase in neonatal NPCs also led to NPC cell proliferation and the expansion of the Mash1+ cell population. Reducing mTOR activity by systemic administration of rapamycin during the first week of life decreases the TAC population and the overall number of proliferative cells in the SVZ. Consistent with this finding, short hairpin RNA (shRNA) against Rheb decreased the pool of Mash1+ cells, and led to a reduction in newborn neurons. Collectively, these data show that mTOR activity titers the degree of NPC proliferation and lineage expansion in a postnatal neurogenic zone. Deviation from an optimal mTOR activity, which occurs in several neurodevelopmental disorders such a tuberous sclerosis complex and neurofibromatosis, should alter cell production.

Speaker's Summary

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Astrocytes Regulate Adult Hippocampal Neurogenesis through Ephrin-B Signaling (823.04)

Nanosymposium: Proliferation: Molecular Mechanisms II
Wednesday, Oct. 17, 1–3:15 p.m., Room 391

Neurogenesis in the adult hippocampus involves activation of quiescent neural stem cells (NSCs) to yield transiently amplifying NSCs and ultimately neurons that affect learning and memory. This process is tightly regulated by microenvironmental cues, though few endogenous factors are known to regulate neuronal differentiation. While astrocytes have been implicated, their role in juxtacrine (i.e. cell-cell contact-dependent) signaling within NSC niches has not been investigated. We show that ephrin-B2 presented from hippocampal astrocytes regulates neurogenesis in vitro and in vivo. Furthermore, clonal analysis in NSC fate-mapping studies reveals a novel role for ephrin-B2 in instructing neuronal differentiation. Additionally, ephrin-B2 signaling, transduced by EphB4 receptors on NSCs, activates β-catenin in vitro and in vivo independent of Wnt signaling and upregulates proneural transcription factors. Ephrin-B2+ astrocytes thus promote neuronal differentiation of adult NSCs through juxtacrine signaling, findings that advance our understanding of adult neurogenesis and may have future regenerative medicine implications.