Science Abstracts

Biomaterials

B. J. Jank et al., **Engineered Composite Tissue as a Bioartificial Limb Graft**, *Biomaterials* 61 (August 2015): 246–256 • The loss of an extremity is a disastrous injury with tremendous impact on a patient's life. Current mechanical prostheses are technically highly sophisticated, but only partially replace physiologic function and aesthetic appearance. As a biologic alternative, approximately 70 patients have undergone allogeneic hand transplantation to date worldwide. While outcomes are favorable, risks and side effects of transplantation and long-term immunosuppression pose a significant ethical dilemma. An autologous, bio-artificial graft based on native extracellular matrix and patient derived cells could be produced on demand and would not require immunosuppression after transplantation. To create such a graft, we decellularized rat and primate forearms by detergent perfusion and yielded acellular scaffolds with preserved composite architecture. We then repopulated muscle and vasculature with cells of appropriate phenotypes, and matured the composite tissue in a perfusion bioreactor under electrical stimulation in vitro. After confirmation of composite tissue formation, we transplanted the resulting biocomposite grafts to confirm perfusion in vivo.

Brain

A. Mackay-Sim et al., **Autologous Olfactory Ensheathing Cell Transplantation in Human Paraplegia: A 3-Year Clinical Trial**, *Brain* 131.9 (September 2008): 2376–2386 • Olfactory ensheathing cells show promise in preclinical animal models as a cell transplantation therapy for repair of the injured spinal cord. This is a report of a clinical trial of autologous transplantation of olfactory ensheathing cells into the spinal cord in six patients with complete, thoracic paraplegia. We previously reported on the methods of surgery and transplantation and the safety aspects of the trial 1 year after transplantation. Here we address the overall design of the trial and the safety of the procedure, assessed during a period of 3 years following the transplantation surgery. All patients were assessed at entry into the trial and regularly during the period of the trial. Clinical assessments included medical, psychosocial, radiological and neurological, as well as specialized tests of neurological and functional deficits (standard American Spinal Injury Association and Functional Independence Measure assessments). Quantitative test included neurophysiological tests of sensory and motor function below the level of injury. The trial was a Phase I/IIa design whose main aim was to test the feasibility and safety of transplantation of autologous olfactory ensheathing cells into the injured spinal cord in human paraplegia. The design included a control group who did not receive surgery, otherwise closely matched to the transplant recipient group. This group acted as a control for the assessors, who were blind to the treatment status of the patients. The control group also provided the opportunity for preliminary assessment of the efficacy of the transplantation. There were no adverse findings 3 years after autologous transplantation of olfactory ensheathing cells into spinal cords injured at least 2 years prior to transplantation. The magnetic resonance images (MRIs) at 3 years showed no change from preoperative MRIs or intervening MRIs at 1 and 2 years, with no evidence of any tumour of introduced cells and no development of post-traumatic syringomyelia or other adverse radiological findings. There were no significant functional changes in any patients and no neuropathic pain. In one transplant recipient, there was an improvement over 3 segments in light touch and pin prick sensitivity bilaterally, anteriorly and posteriorly. We

conclude that transplantation of autologous olfactory ensheathing cells into the injured spinal cord is feasible and is safe up to 3 years of post-implantation, however, this conclusion should be considered preliminary because of the small number of trial patients.

Cell Transplantation

D. Jarocha et al., **Continuous Improvement after Multiple Mesenchymal Stem Cell Transplantations in a Patient with Complete Spinal Cord Injury**, *Cell Transplant* 24.4 (April 2015): 661–672 • Interruption of spinal cord (SC) continuity leads to functional loss below the lesion level. The purpose of this study was to evaluate the safety and efficacy of bone marrow nucleated cell (BMNC) and multiple mesenchymal stem cell (MSC) transplantations in spinal cord injury (SCI). A patient with total SC interruption at the Th2-3 level underwent experimental therapy with BMNC and MSC transplantations followed with intensive neurorehabilitation treatment. At admission, 6 h after SCI, the patient was scored ASIA A, had a Th1 sensation level, paraplegia with sphincter palsy, and was without the ability to control trunk movement. Neurophysiology examination showed bilateral axonal damage to the motor and sensory neural fibers with no motor unit potentials or peripheral motor nerve conduction in the lower extremities. The standard therapy had been applied and had not produced any positive results. The patient was treated with autologous BMNCs injected intravenously (3.2×10^9) and intrathecally (0.5×10^9) 10 weeks after the SCI and with five rounds of MSCs every 3-4 months ($1.3\text{-}3.65 \times 10^7$) administered via lumbar puncture. Total number of transplanted MSC cells during the course of treatment was 1.54×10^8. There were no complications related to transplantations and no side effects related to the therapy during 2 years of treatment. The ASIA score improved from A to C/D (from 112 to 231 points). The sensation level expanded from Th1 to L3-4, and the patient's ability to control the body trunk was fully restored. Bladder filling sensation, bladder control, and anal sensation were also restored. Muscle strength in the left lower extremities improved from plegia to deep paresis (1 on the Lovett scale). The patient's ability to move lower extremities against gravity supported by the movements in quadriceps was restored. The patient gained the ability to stand in a standing frame and was able to walk with the support of hip and knee ortheses. Magnetic resonance imaging (MRI) revealed that at the Th2/Th3 level, where the hemorrhagic necrosis was initially observed, small tissue structures appeared. Our results suggest that repeated intrathecal infusions of MSCs might have the potential to produce clinically meaningful improvements for SCI patients.

P. Tabakow et al., **Transplantation of Autologous Olfactory Ensheathing Cells in Complete Human Spinal Cord Injury**, *Cell Transplant* 22.9 (September 2013): 1591–1612 • Numerous studies in animals have shown the unique property of olfactory ensheathing cells to stimulate regeneration of lesioned axons in the spinal cord. In a Phase I clinical trial, we assessed the safety and feasibility of transplantation of autologous mucosal olfactory ensheathing cells and olfactory nerve fibroblasts in patients with complete spinal cord injury. Six patients with chronic thoracic paraplegia (American Spinal Injury Association class A-ASIA A) were enrolled for the study. Three patients were operated, and three served as a control group. The trial protocol consisted of pre- and postoperative neurorehabilitation, olfactory mucosal biopsy, culture of olfactory ensheathing cells, and intraspinal cell grafting. Patient's clinical state was evaluated by clinical, neurophysiological, and radiological tests. There were no adverse findings related to olfactory mucosa biopsy or transplantation of olfactory ensheathing cells at 1 year after surgery. There was no evidence of neurological deterioration, neuropathic pain, neuroinfection, or tumorigenesis. In one cell-grafted patient, an asymptomatic syringomyelia was observed. Neurological improvement was observed only in transplant recipients. The first two operated patients improved from ASIA A to ASIA C and ASIA B. Diffusion tensor imaging showed restitution of continuity of some white matter

tracts throughout the focus of spinal cord injury in these patients. The third operated patient, although remaining ASIA A, showed improved motor and sensory function of the first spinal cords segments below the level of injury. Neurophysiological examinations showed improvement in spinal cord transmission and activity of lower extremity muscles in surgically treated patients but not in patients receiving only neurorehabilitation. Observations at 1 year indicate that the obtaining, culture, and intraspinal transplantation of autologous olfactory ensheathing cells were safe and feasible. The significance of the neurological improvement in the transplant recipients and the extent to which the cell transplants contributed to it will require larger numbers of patients.

S. Wang et al., **Autologous Olfactory Lamina Propria Transplantation for Chronic Spinal Cord Injury: Three-Year Follow-Up Outcomes from a Prospective Double Blinded Clinical Trial**, *Cell Transplant*, e-pub April 22, 2015, doi: 10.3727/096368915X688065 • We did a clinical trial to determine whether olfactory mucosa lamina propria (OLP) transplants promote regeneration and functional recovery in chronic human spinal cord injury (SCI). The trial randomized 12 subjects to OLP transplants (n=8) or control sham surgery (n=4). The subjects received magnetic resonance imaging (MRI), electromyography (EMG), urodynamic study (UDS), American Spinal Injury Association impairment scale (AIS) and other functional assessments. OLP-transplanted subjects recovered more motor, sensory, and bladder function compared to sham operated subjects. At three years after OLP transplant, one patient improved from AIS A to C and another recovered from AIS A to B, two recovered more than three segmental sensory levels, two had less spasticity, two had altered H-reflexes and SSEP, two regained bladder and anorectal sensation and had improved bladder compliance on UDS. OLP-treated patients had partial or complete tissue bridges at the injury site compared to cavitary gaps in sham-operated patients. The limited recovery suggests that OLP transplants alone do not have significant benefits but may provide a rationale for larger randomized trials or combination therapies.

eLife

S. Goksan et al., **fMRI Reveals Neural Activity Overlap between Adult and Infant Pain**, *ELife* 4 (April 21, 2015): e06356 • Limited understanding of infant pain has led to its lack of recognition in clinical practice. While the network of brain regions that encode the affective and sensory aspects of adult pain are well described, the brain structures involved in infant nociceptive processing are less well known, meaning little can be inferred about the nature of the infant pain experience. Using fMRI we identified the network of brain regions that are active following acute noxious stimulation in newborn infants, and compared the activity to that observed in adults. Significant infant brain activity was observed in 18 of the 20 active adult brain regions but not in the infant amygdala or orbitofrontal cortex. Brain regions that encode sensory and affective components of pain are active in infants, suggesting that the infant pain experience closely resembles that seen in adults. This highlights the importance of developing effective pain management strategies in this vulnerable population.

Lancet

O. C. Aszmann et al., **Bionic Reconstruction to Restore Hand Function after Brachial Plexus Injury: A Case Series of Three Patients**, *Lancet* 385.9983 (May 30, 2015): 2183–2189 • *Background:* Brachial plexus injuries can permanently impair hand function, yet present surgical reconstruction provides only poor results. Here, we present for the first time bionic reconstruction; a combined technique of selective nerve and muscle transfers, elective amputation, and prosthetic rehabilitation to regain hand function. *Methods:* Between April 2011, and May 2014, three patients with global brachial plexus injury including lower root avulsions underwent bionic reconstruction. Treatment occurred in two stages; first, to identify and create useful electromyographic signals for

prosthetic control, and second, to amputate the hand and replace it with a mechatronic prosthesis. Before amputation, the patients had a specifically tailored rehabilitation programme to enhance electromyographic signals and cognitive control of the prosthesis. Final prosthetic fitting was applied as early as 6 weeks after amputation. *Findings:* Bionic reconstruction successfully enabled prosthetic hand use in all three patients. After 3 months, mean Action Research Arm Test score increased from 5·3 (SD 4·73) to 30·7 (14·0). Mean Southampton Hand Assessment Procedure score improved from 9·3 (SD 1·5) to 65·3 (SD 19·4). Mean Disabilities of Arm, Shoulder and Hand score improved from 46·5 (SD 18·7) to 11·7 (SD 8·42). *Interpretation:* For patients with global brachial plexus injury with lower root avulsions, who have no alternative treatment, bionic reconstruction offers a means to restore hand function.

Lancet Haematology

A. Gratwohl et al., **One Million Haemopoietic Stem-Cell Transplants: A Retrospective Observational Study**, *Lancet Haematol* 2.3 (March 2015): e91–e100 • *Background:* The transplantation of cells, tissues, and organs has been recognised by WHO as an important medical task for its member states; however, information about how to best organise transplantation is scarce. We aimed to document the activity worldwide from the beginning of transplantation and search for region adapted indications and associations between transplant rates and macroeconomics. *Methods:* Between Jan 1, 2006, and Dec 31, 2014, the Worldwide Network for Blood and Marrow Transplantation collected data for the evolution of haemopoietic stem-cell transplantation (HSCT) activity and volunteer donors in the 194 WHO member states. *Findings:* 953 651 HSCTs (553 350 [58%] autologous and 400 301 [42%] allogeneic) were reported by 1516 transplant centres from 75 countries. No transplants were done in countries with fewer than 300 000 inhabitants, a surface area less than 700 km^2, and a gross national income per person of US$1260 or lower. Use of HSCT increased from the first transplant in 1957 to almost 10 000 by 1985. We recorded a cumulative total of about 100 000 transplants by 1995, and an estimated 1 million by December, 2012. Unrelated donor registries contributed 22·3 million typed volunteer donors and 645 646 cord blood products by 2012. Numbers of allogeneic HSCTs increased in the past 35 years with no signs of saturation (R^2=0·989). Transplant rates were higher in countries with more resources, more transplant teams, and an unrelated donor infrastructure. *Interpretation:* Our findings show achievements and high unmet needs and give guidance for decisions; to grant access for patients, to provide a donor infrastructure, and to limit overuse by defining risk and region adapted indications for HSCT as an efficient and cost-effective approach for life-threatening, potentially curable diseases.

Neurorehabilitation and Neural Repair

C. Lima et al., **Olfactory mucosal autografts and rehabilitation for chronic traumatic spinal cord injury**, *Neurorehabil Neural Repair* 24.1 (January 2010): 10–22 • *Background/Objective:* Basic science advances in spinal cord injury (SCI) are leading to novel clinical approaches. The authors report a prospective, uncontrolled pilot study of the safety and outcomes of implanting olfactory mucosal autografts (OMA) in 20 patients with chronic, sensorimotor complete or motor complete SCI. *Methods:* Seven paraplegic and 13 tetraplegic subjects (17 men and 3 women; 19–37 years old) who sustained a traumatic SCI 18 to 189 months previously (mean = 49 months) were enrolled. Preoperative rehabilitation that emphasized lower extremity stepping using either overground walking training or a robotic weight-supported treadmill training was provided for 25 to 39 hours per week for a median of 4 months at 3 sites. No change in ASIA Impairment Scale (AIS) motor scores for the lower extremities or AIS grades of completeness was found. OMAs were transplanted into 1.3- to 4-cm lesions at C4-T12 neurological levels after partial scar removal. Therapy was continued postoperatively. Preoperative and postoperative assessments included AIS

scores and classification, electromyography (EMG) of attempted voluntary contractions, somatosensory evoked potentials (SSEP), urodynamic studies with sphincter EMG, spinal cord magnetic resonance imaging (MRI), and otolaryngology and psychology evaluations. The Functional Independence Measure (FIM) and Walking Index for Spinal Cord Injury (WISCI) were obtained in 13 patients. *Results:* All patients survived and recovered olfaction. One patient was rehospitalized for aseptic meningitis. Minor adverse events occurred in 4 others. The mean duration of follow-up was 27.7 months (range = 12–45 months). By MRI, the lesion site was filled in all patients with no neoplastic overgrowth or syringomyelia. AIS grades improved in 11 of 20 patients, 6 (A --> C), 3 (B --> C), and 2 (A --> B), and declined in 1 (B --> A). Improvements included new voluntary EMG responses (15 patients) and SSEPs (4 patients). Scores improved in the FIM and WISCI (13/13 tested), and urodynamic responses improved in 5 patients. *Conclusion:* OMA is feasible, relatively safe, and possibly beneficial in people with chronic SCI when combined with postoperative rehabilitation. Future controlled trials may need to include a lengthy and intensive rehabilitation arm as a control.

New England Journal of Medicine

M.A. Rysavy et al., **Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants**, *N Engl J Med* 372.19 (May 7, 2015): 1801–1811 • *Background:* Between-hospital variation in outcomes among extremely preterm infants is largely unexplained and may reflect differences in hospital practices regarding the initiation of active lifesaving treatment as compared with comfort care after birth. *Methods:* We studied infants born between April 2006 and March 2011 at 24 hospitals included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Data were collected for 4987 infants born before 27 weeks of gestation without congenital anomalies. Active treatment was defined as any potentially lifesaving intervention administered after birth. Survival and neurodevelopmental impairment at 18 to 22 months of corrected age were assessed in 4704 children (94.3%). *Results:* Overall rates of active treatment ranged from 22.1% (interquartile range [IQR], 7.7 to 100) among infants born at 22 weeks of gestation to 99.8% (IQR, 100 to 100) among those born at 26 weeks of gestation. Overall rates of survival and survival without severe impairment ranged from 5.1% (IQR, 0 to 10.6) and 3.4% (IQR, 0 to 6.9), respectively, among children born at 22 weeks of gestation to 81.4% (IQR, 78.2 to 84.0) and 75.6% (IQR, 69.5 to 80.0), respectively, among those born at 26 weeks of gestation. Hospital rates of active treatment accounted for 78% and 75% of the between-hospital variation in survival and survival without severe impairment, respectively, among children born at 22 or 23 weeks of gestation, and accounted for 22% and 16%, respectively, among those born at 24 weeks of gestation, but the rates did not account for any of the variation in outcomes among those born at 25 or 26 weeks of gestation. *Conclusions:* Differences in hospital practices regarding the initiation of active treatment in infants born at 22, 23, or 24 weeks of gestation explain some of the between-hospital variation in survival and survival without impairment among such patients.

J.E. Wagner et al., **Bone Marrow Transplantation for Recessive Dystrophic Epidermolysis Bullosa**, *N Engl J Med* 363.7 (August 12, 2010): 629–639 • *Background:* Recessive dystrophic epidermolysis bullosa is an incurable, often fatal mucocutaneous blistering disease caused by mutations in COL7A1, the gene encoding type VII collagen (C7). On the basis of preclinical data showing biochemical correction and prolonged survival in col7 −/− mice, we hypothesized that allogeneic marrow contains stem cells capable of ameliorating the manifestations of recessive dystrophic epidermolysis bullosa in humans. *Methods:* Between October 2007 and August 2009, we treated seven children who had recessive dystrophic epidermolysis bullosa with immunomyeloablative chemotherapy and

allogeneic stem-cell transplantation. We assessed C7 expression by means of immunofluorescence staining and used transmission electron microscopy to visualize anchoring fibrils. We measured chimerism by means of competitive polymerase-chain-reaction assay, and documented blister formation and wound healing with the use of digital photography. *Results:* One patient died of cardiomyopathy before transplantation. Of the remaining six patients, one had severe regimen-related cutaneous toxicity, with all having improved wound healing and a reduction in blister formation between 30 and 130 days after transplantation. We observed increased C7 deposition at the dermal–epidermal junction in five of the six recipients, albeit without normalization of anchoring fibrils. Five recipients were alive 130 to 799 days after transplantation; one died at 183 days as a consequence of graft rejection and infection. The six recipients had substantial proportions of donor cells in the skin, and none had detectable anti-C7 antibodies. *Conclusions:* Increased C7 deposition and a sustained presence of donor cells were found in the skin of children with recessive dystrophic epidermolysis bullosa after allogeneic bone marrow transplantation. Further studies are needed to assess the long-term risks and benefits of such therapy in patients with this disorder.

Protein Cell

P. Liang et al., **CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes**, *Protein Cell* 6.5 (May 2015): 363–372 • Genome editing tools such as the clustered regularly interspaced short palindromic repeat (CRISPR)-associated system (Cas) have been widely used to modify genes in model systems including animal zygotes and human cells, and hold tremendous promise for both basic research and clinical applications. To date, a serious knowledge gap remains in our understanding of DNA repair mechanisms in human early embryos, and in the efficiency and potential off-target effects of using technologies such as CRISPR/Cas9 in human pre-implantation embryos. In this report, we used tripronuclear (3PN) zygotes to further investigate CRISPR/Cas9-mediated gene editing in human cells. We found that CRISPR/Cas9 could effectively cleave the endogenous β-globin gene (HBB). However, the efficiency of homologous recombination directed repair (HDR) of HBB was low and the edited embryos were mosaic. Off-target cleavage was also apparent in these 3PN zygotes as revealed by the T7E1 assay and whole-exome sequencing. Furthermore, the endogenous delta-globin gene (HBD), which is homologous to HBB, competed with exogenous donor oligos to act as the repair template, leading to untoward mutations. Our data also indicated that repair of the HBB locus in these embryos occurred preferentially through the non-crossover HDR pathway. Taken together, our work highlights the pressing need to further improve the fidelity and specificity of the CRISPR/Cas9 platform, a prerequisite for any clinical applications of CRSIPR/Cas9-mediated editing.

Science

I. G. Cohen, Julian Savulescu, and E. Y. Adashi, **Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy**, *Science* 348.6231 (April 2015): 178–180 • Mutant mitochondrial DNA (mtDNA) gives rise to a broad range of heritable clinical syndromes (1). A cure for those affected remains out of reach (1). However, recently developed mitochondrial replacement therapy (MRT) has raised the prospect of disease-free progeny for women carriers (2–4). Moreover, the feasibility of replacing mutant oocytic or zygotic mtDNA with a donated wild-type counterpart in humans has now been firmly established (2–4). In the United Kingdom, legislation regulating the clinical application of MRT, now 10 years in the making, has recently been approved by the House of Commons (5) and the House of Lords (6). The regulatory vetting of MRT in the United States, under way for a year, remains a work in progress (7). Here, we compare and contrast the regulatory history of MRT in the United Kingdom and the United States and examine potential lessons learned.

J.A. Doudna and E. Charpentier, **The New Frontier of Genome Engineering with CRISPR-Cas9**, *Science* 346.6213 (November 28, 2014): 1–9 • The advent of facile genome engineering using the bacterial RNA-guided CRISPR-Cas9 system in animals and plants is transforming biology. We review the history of CRISPR (clustered regularly interspaced palindromic repeat) biology from its initial discovery through the elucidation of the CRISPR-Cas9 enzyme mechanism, which has set the stage for remarkable developments using this technology to modify, regulate, or mark genomic loci in a wide variety of cells and organisms from all three domains of life. These results highlight a new era in which genomic manipulation is no longer a bottleneck to experiments, paving the way toward fundamental discoveries in biology, with applications in all branches of biotechnology, as well as strategies for human therapeutics.

Stem Cells Translational Medicine

W. Liao et al., **Direct Conversion of Cord Blood CD34+ Cells into Neural Stem Cells by OCT4**, *Stem Cells Transl Med* 4.7 (July 2015): 755–763 • Cellular reprogramming or conversion is a promising strategy to generate desired stem cell types from somatic cells. Neural stem cells (NSCs) have the potential to regenerate central nervous system tissue and repair damage in response to injury. However, NSCs are difficult to isolate from human tissues and expand in sufficient quantities for therapy. Here, we report a method to generate neural stem cells from cord blood CD34-positive cells by ectopic expression of OCT4 in a feeder-free system. The induced cells (iNSCs) show a characteristic NSC-like morphology and can be expanded in vitro for more than 20 passages. In addition, the iNSCs are positive for neural stem cell-specific markers such as Nestin and Musashi-1 and are similar in gene expression patterns to a human neural stem cell line. The iNSCs express distinct transcriptional factors for forebrain, hindbrain, and spinal cord regions. Upon differentiation, the iNSCs are able to commit into multilineage mature neural cells. Following in vivo introduction into NOD/SCID mice, iNSCs can survive and differentiate in the mouse brain 3 months post-transplantation. Alternatively, we were also able to derive iNSCs with an episomal vector expressing OCT4. Our results suggest a novel, efficient approach to generate neural precursor cells that can be potentially used in drug discovery or regenerative medicine for neurological disease and injury.

K.W. Oh et al., **Phase I Trial of Repeated Intrathecal Autologous Bone Marrow-Derived Mesenchymal Stromal Cells in Amyotrophic Lateral Sclerosis**, *Stem Cells Transl Med* 4.6 (June 2015): 590–597 • Stem cell therapy is an emerging alternative therapeutic or disease-modifying strategy for amyotrophic lateral sclerosis (ALS). The aim of this open-label phase I clinical trial was to evaluate the safety of two repeated intrathecal injections of autologous bone marrow (BM)-derived mesenchymal stromal cells (MSCs) in ALS patients. Eight patients with definite or probable ALS were enrolled. After a 3-month lead-in period, autologous MSCs were isolated two times from the BM at an interval of 26 days and were then expanded in vitro for 28 days and suspended in autologous cerebrospinal fluid. Of the 8 patients, 7 received 2 intrathecal injections of autologous MSCs (1 × 10(6) cells per kg) 26 days apart. Clinical or laboratory measurements were recorded to evaluate the safety 12 months after the first MSC injection. The ALS Functional Rating Scale-Revised (ALSFRS-R), the Appel ALS score, and forced vital capacity were used to evaluate the patients' disease status. One patient died before treatment and was withdrawn from the study. With the exception of that patient, no serious adverse events were observed during the 12-month follow-up period. Most of the adverse events were self-limited or subsided after supportive treatment within 4 days. Decline in the ALSFRS-R score was not accelerated during the 6-month follow-up period. Two repeated intrathecal injections of autologous MSCs were safe and feasible throughout the duration of the 12-month follow-up period.

R.P. Salewski et al., **Transplantation of Induced Pluripotent Stem Cell-Derived Neural Stem Cells Mediate Functional**

Recovery following Thoracic Spinal Cord Injury through Remyelination of Axons, *Stem Cells Transl Med* 4.7 (July 2015): 743–754 • Neural stem cells (NSCs) from embryonic or fetal/adult tissue sources have shown considerable promise in regenerative strategies for traumatic spinal cord injury (SCI). However, there are limitations with their use related to the availability, immunogenicity, and uncertainty of the mechanisms involved. To address these issues, definitive NSCs derived from induced pluripotent stem (iPS) cells generated using a nonviral, piggyBac transposon approach, were investigated. Committed NSCs were generated from iPS cells using a free-floating neurosphere methodology previously described by our laboratory. To delineate the mechanism of action, specifically the role of exogenous myelination, NSCs derived from wildtype (wt) and nonmyelinating Shiverer (shi) iPS cell lines were used following thoracic SCI with subacute intraspinal transplantation. Behavioral, histological, and electrophysiological outcomes were analyzed to assess the effectiveness of this treatment. The wt- and shi-iPS-NSCs were validated and shown to be equivalent except in myelination capacity. Both iPS-NSC lines successfully integrated into the injured spinal cord and predominantly differentiated to oligodendrocytes, but only the wt-iPS-NSC treatment resulted in a functional benefit. The wt-iPS-dNSCs, which exhibited the capacity for remyelination, significantly improved neurobehavioral function (Basso Mouse Scale and CatWalk), histological outcomes, and electrophysiological measures of axonal function (sucrose gap analysis) compared with the nonmyelinating iPS-dNSCs and cell-free controls. In summary, we demonstrated that iPS cells can generate translationally relevant NSCs for applications in SCI. Although NSCs have a diverse range of functions in the injured spinal cord, remyelination is the predominant mechanism of recovery following thoracic SCI.

Trends in Molecular Medicine

T. Ishii, **Germline Genome-Editing Research and Its Socioethical Implications**, *Trends Mol Med*, e-pub June 12, 2015, doi: 10.1016/j.molmed.2015.05.006 • Genetically modifying eggs, sperm, and zygotes ("germline" modification) can impact on the entire body of the resulting individual and on subsequent generations. With the advent of genome-editing technology, human germline gene modification is no longer theoretical. Owing to increasing concerns about human germline gene modification, a voluntary moratorium on human genome-editing research and/or the clinical application of human germline genome editing has recently been called for. However, whether such research should be suspended or encouraged warrants careful consideration. The present article reviews recent research on mammalian germline genome editing, discusses the importance of public dialogue on the socioethical implications of human germline genome-editing research, and considers the relevant guidelines and legislation in different countries.