Review

Disease and Stem Cell-Based Analysis of the 2013 ASNTR Meeting

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A wide diversity of subjects are presented at the annual American Society of Neural Therapy and Repair meeting every year, and 2013 was no exception. An insight into the current research trends in regenerative medicine was provided, including studies to elucidate disease mechanisms and the means to treat them. Different methods featured in 2013 included stem cell and tissue transplantation, gene therapy, dietary supplementation, and hydrogels as scaffold systems for the growth of stem cells. Diseases ranged from Parkinson's disease, spinal cord injury, and stroke to traumatic brain injury, pain, and epilepsy. Traumatic brain injury was an increasingly popular topic, highlighting the concerns of soldiers returning from duty overseas. A number of studies looked at ways to treat or elucidate mechanisms for more than one disorder. The studies including stem cells predominantly involved human-derived cells being transplanted, and the most common recipient of stem cells were rodents. Only one autologous transplant study, which featured mouse bone marrow cells being transplanted into mice for the treatment of stroke, was presented this year. The most popular stem cell studied was the neural stem cell, which in some instances was predifferentiated from induced pluripotent stem cells or embryonic stem cells. Other stem cells included the mesenchymal stem cell and adipose, amniotic fluid, and umbilical cord blood-derived cells. Many studies also looked at more than one stem cell type. Combinational studies, such as gene therapy and transplantation, were also commonly explored as well as studies using fetal ventral mesencephalon or spinal cord tissue rather than stem cells. Numerous studies also featured the use of "drugs"—some naturally derived or naturally occurring as well as drug cocktails. A number of possible treatments, including physical therapy and socialization, were explored for a number of different diseases, as well as reports on the current status of four gene therapy clinical trials for the treatment of Parkinson's disease. Other studies assessed possible causes of specific disorders. In this way, the ASNTR provides an important snapshot of developments in the field of regenerative medicine.

Key words: Regenerative medicine; Neurodegenerative diseases; Stem cell therapies;
Combinational studies/therapies

INTRODUCTION

The annual American Society of Neural Therapy and Repair (ASNTR) meeting provides an insight into the current research trends in the field of regenerative medicine. Numerous diseases and a myriad of different techniques, including model characterization, cell and tissue transplantation, dietary supplementation, and elucidation of disease mechanisms, are reported on. This summary gives readers an overview of the 2013 meeting at which 85 diverse abstracts were presented. The abstracts for the 2013 ASNTR were published in Issue 22(5) on pages 893–920 and Issue 22(7) on pages 1307 and 1308 of the journal *Cell Transplantation*.

The Myriad of Diseases Studied

As in previous years, numerous diseases were investigated (Table 1), and again, Parkinson's disease (PD) was the most popular, followed by spinal cord injury (SCI) and stroke. The increased prominence of traumatic brain injury (TBI) highlights a field that is at the forefront of research due to the number of soldiers returning from combat with TBIs. A special session on TBI was presented at the meeting in which translational challenges, biomarkers, rehabilitation (Scott), genetic resiliency, and an eyewitness account of TBI in military service were discussed.

Alzheimer's disease (AD) by itself appears to be less studied this year, while Down syndrome (DS), epilepsy,

Table 1. Disease Distribution at the 2013 ASNTR

Disease	No. (First Author)
Parkinson's disease	13 (Bankiewicz et al.; Bye et al.; Heiss; Kordower; Kousik et al.; Leveque et al.; Manfredsson et al.; Palfi et al.; Paumier et al.; Rumpel et al.; Shahaduzzaman et al.; Stromberg et al.; Zhang et al.)
Spinal cord injury	12 (An et al.; Arias et al.; Cerreta et al.; Choi et al.; Jendelova et al.; Little et al.; Menon et al.; Mercier et al.; Minor et al.; Rombola et al.; Spruance et al.; Yu et al.)
Stroke	11 (Antonucci; Cui and Zhao; DuChamp et al.; de C. Lima et al.; Parsha et al.; Schaar et al.; Shinozuka et al.; Staples et al.; Tamboli et al.; Vasconcellos et al.; Yang et al.)
Traumatic brain injury	10 (Acosta et al.; Borlongan et al.; Chao et al.; Chiang et al.; Das et al.; Febinger et al.; Hernandez-Ontiveros et al.; Pabon et al.; Scott; Sharma HS et al.)
Down syndrome	3 (Cuello et al.; Iulita et al.; Kelley et al.)
Huntington's disease	3 (Crane et al.; Fink et al.; Smith GA et al.)
Pain	3 (Gordon et al.; Perez et al.; Priddy et al.)
Alzheimer's disease	2 (Blair et al.; Darlington et al.)
Epilepsy	2 (Dailey et al.; Tajiri et al.)
Amyotrophic lateral sclerosis	1 (Garbuzova-Davis and Sanberg)
Cognitive dysfunction	1 (Acharya et al.)
Other disorders	5 (Lee et al.; Muresanu et al.; Portis et al.; Sharma A et al.; Willing et al.)
Multiple disorders	4 (Bjugstad et al.; Granholm et al.; Granic and Potter; Kim DW et al.)
Non-disease	15 (Andrzejewska et al.; Aurand et al.; Braun et al.; Chou and Modo; Denham et al.; Eve; Garcia et al.; Gonzalez-Rothi et al.; Hsu et al.; Kim SW et al.; Porz et al.; Roholt et al.; Rossetti et al.; Smith AJ et al.; Vorobyeva et al.)
Total	85

and the number of studies that apply to more than one disorder, for example, exploration of changes to the extracellular matrix in various diseases (Bjugstad et al.), have increased. Three of the four latter studies explore DS, while two of them also focus on AD, demonstrating the potential overlap between these two disorders and highlighting their relevance as shown by their increased prominence when the multiple disorder studies are taken into account.

Other disorders included sleep deprivation (Sharma A et al.) and lysosomal storage disorders, such as Sandhoff disease (Lee et al.) and Sanfilippo Type 3B (Willing et al.), while non-disease-specific studies touched on subjects such as neurodevelopment (Braun et al.), interneuron innervation (Gonzalez-Rothi et al.), and an electron microscope-based method to assess myelination (Roholt et al.). Several of the non-disease-specific studies do highlight topics that could have a bearing on a specific disease with further study. For instance, two studies could eventually have some bearing on PD, as Braun et al.'s study of neurodevelopment in the marmoset monkey is necessary before the primates could be used to model PD [via 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment], and Garcia et al.'s study explores whether enteric neurons can be transduced by viral vectors since they may be one of the earliest sites to actually be affected in PD. The studies of Denham et al. on white matter tracts, Gonzalez-Rothi et al. on interneuron innervation within the spinal cord, and Roholt's method of assessing remyelination could also all be expanded on to investigate spinal cord injuries/diseases and/or multiple sclerosis.

The Non-Stem Cell Studies

The studies can be split into those that involve stem cells and those that do not. Examining the latter first (Table 2), many of these studies focused on furthering our understanding of different diseases and their animal models. For instance, four studies looked at how SCI affects respiration (Arias et al.), bladder muscle (Cerreta et al.), phrenic motor neurons (Little et al.), and the forelimbs (Romboa et al.). The potential benefit of Schwann cell transplantation on respiration (diaphragm recovery) following SCI was also explored by Mercier et al. Garbuzova-Davis and Sanberg, Muresanu et al., and both of the Sharma et al. as well as the Das et al. studies explored the role of the blood-brain barrier in ALS, heatstroke, sleep deprivation, and concussive or TBI, respectively. The Muresanu et al. study actually looked at whether cerebrolysin was neuroprotective toward blood-brain barrier dysfunction and so has been classified under drug treatments rather than disease models in Table 2. Das et al. attempted to deliver DNA using magnetic micelle nanoparticles following disruption of the blood-brain barrier after TBI and so has been classified under gene therapy rather than disease models in Table 2. Two studies investigated the role of nerve growth factor

Table 2. Non-Stem Cell Studies at the 2013 ASNTR

Type	No. (First Author)
Disease models	19 (Arias et al.; Bjugstad et al.; Blair et al.; Cerreta et al.; Cuello et al.; Febinger et al.; Garbuzova-Davis and Sanberg; Granholm et al.; Granic and Potter; Hernandez-Ontiveros et al.; Iulita et al.; Little et al.; Pabon et al.; Rombola et al.; Sharma A et al.; Sharma HS et al.; Smith GA et al.; Vasconcellas et al.; Zhang et al.)
Drugs	14 (Chao et al.; Chiang et al.; Cui and Zhao; DuChamp et al.; Kousik et al.; de C. Lima et al.; Menon et al.; Minor et al.; Muresanu et al.; Paumier et al.; Perez et al.; Portis et al.; Smith AJ et al.; Yu et al.)
Gene therapy	9 (Bankiewicz et al.; Das et al.; Garcia et al.; Gordon et al.; Heiss; Kordower; Manfredsson et al.; Palfi et al.; Priddy et al.)
Tissue	4 (Bye et al.; Rumpel et al.; Spruance et al.; Vorobyeva et al.)
Diet	2 (Kelley et al.; Stromberg et al.)
Methodology	2 (Roholt et al.; Staples et al.)
Other therapies	6 (Borlongan et al.; Mercier et al.; Schaar et al.; Scott; Shahaduzzaman et al.; Shinozuka et al.)
Non-disease	3 (Braun et al.; Eve; Gonzalez-Rothi et al.)
Total	59

(NGF) and matrix metalloproteinases (MMP) (Cuello et al.; Iulita et al.) in DS, while a further two looked at the locus coeruleus and brain-derived growth factor (BDNF) (Granholm et al.) and chromosomal abnormalities (Granic and Potter) in DS, AD, and other disorders, and Blair et al. investigated the contribution of FK506-binding protein, 51 kDa, to AD. Additionally, Kelley et al. looked at how prenatal dietary supplementation with choline could be beneficial in DS. A further three attempted to enhance our understanding of TBI by examining CD36 and inflammation (Hernandez-Ontiveros et al.), the fractalkine receptor (Febinger et al.), and the brain histopathology (Pabon et al.) following TBI. Additional studies investigated cardiac effects following stroke (Vasconcellos et al.), the contribution of different synapses in drug-induced dyskinesias as a consequence of PD treatment (Zhang et al.), and Rab proteins in Huntington's disease (HD) (Smith GA et al.).

The use of drugs extracted from nature was reported, including spider venom in the treatment of stroke (de C. Lima et al.), an extract of a Chinese medicinal herb for the treatment of TBI (Chiang et al.), and an extract from club moss for the treatment of pain arising from SCI (Yu et al.). Smith AJ et al. reported on how the bioavailability of the potentially therapeutic polyphenol epigallocatechin-3-gallate (EGCG) was affected by crystallization, while the

ability of the bioflavonoid luteolin to potentially improve Fragile X syndrome was described by Portis et al. Drug cocktails of neurotrophic factors, such as cerebrolysin, were also reported for the treatment of SCI (Menon et al.) and heat stroke (Muresanu et al.), while stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) and their interaction with nuclear factor κ -light-chain-enhancer of activated B-cells (NF- κ B) were investigated for chronic stroke (Cui and Zhao; Duchamp et al.). The detrimental reduction in cerebral blood flow following methamphetamine was described by Kousik et al. as a possible risk factor for PD, while Paumier et al. demonstrated that the autophagy enhancer trehalose had no beneficial effect in one animal model of PD. Functional recovery from a long-term SCI was demonstrated in a rat model following intrathecal infusion of the small leucine-rich repeat protein decorin (Minor et al.), and Perez et al. identified new cannabinoid receptor agonists for the treatment of pain. One clinical trial reported on how albumin treatment improved the prognosis of TBI (Chao et al.).

Gene therapy studies included four clinical trials for adeno-associated viral (AAV) transduction of growth factors (Heiss; Kordower) or a catecholamine-synthesizing enzyme (Bankiewicz et al.) and lentiviral transduction of three genes critical for dopamine synthesis (Palfi et al.) for the treatment of PD. Additional gene therapy studies researched topics, such as lentiviral endomorphin-1 (Gordon et al.) and AAV-conotoxin (Priddy et al.), for the treatment of pain. Manfredsson et al. reported on gene therapy using recombinant (r)AAV2/5 for α -synuclein and demonstrated that decreased transgene expression in the nigrostriatal system was observed with aging.

The applicability of fetal ventral mesencephalon for the treatment of PD was highlighted in two studies (Bye et al.; Rumpel et al.), while Spruance et al. looked at fetal spinal cord tissue implantation for SCI, and Vorobyeva et al. transplanted embryonic leech tissue into rats to reduce cannabis addiction.

The presentation by Staples et al. provided support for the use of nonhuman primate as well as rodent animal models for stroke. Two studies analyzed the contribution of physical therapy (Schaar et al.) and socialization (Shinozuka et al.) in stroke, while Borlongan et al. examined exercise and hyperbaric oxygen exposure as a possible therapy for TBI, and Scott discussed currently available rehabilitation procedures for TBI. The use of antibodies to treat the overexpression of α -synuclein in an animal model of PD was also reported by Shahaduzzaman et al.

The Stem Cell Studies

Stem cells are a major focus of the ASNTR (see Table 3); the majority of the reports on which (more than 60%) were about their transplantation (see Table 4). The most popular stem cell group compared two or more different

Table 3. Stem Cell Studies at the 2013 ASNTR

Cell Type	No. (First Author)
Two or more stem cells	7 (Chou and Modo; Hsu et al.; Jendelova et al.; Kim SW et al.; Lee et al.; Porz et al.; Tamboli et al.)
Neural stem cells (NSCs)	6 (An et al.; Aurand et al.; Choi et al.; Dailey et al.; Rosetti et al.; Tajiri et al.)
Mesenchymal stem cells (MSCs)	4 (Andrzejewska et al.; Crane et al.; Kim DW et al.; Parsha et al.)
Induced pluripotent stem cells (iPSCs)	3 (Acharya et al.; Fink et al.; Leveque et al.)
Umbilical cord blood mononuclear cells (UCB-MNCs)	2 (Darlington et al.; Willing et al.)
Adipose-derived stem cells (ADSCs)	1 (Acosta et al.)
Amniotic fluid-derived stem cells (AFSCs)	1 (Antonucci)
Bone marrow mononuclear cells (BM-MNCs)	1 (Yang et al.)
Embryonic stem cells (ESCs)	1 (Denham et al.)
Total	26

stem cells, and all but one of these studies included neural stem cells (NSCs), the second most popular cell group, the exception comparing male-derived (Sertoli) and female-derived (menstrual) cells for stroke (Tamboli et al.). One combination study focused on how mesenchymal stem cells (MSCs) could be neuroprotective for NSCs by forming a glycoprotein complex (Kim SW et al.), while another explored how factors secreted by endothelial progenitor cells could affect endogenous NSCs (Porz et al.). Another study investigated how hydrogel scaffolds may effect NSC growth and differentiation (Aurand et al.). The MSC studies primarily used bone marrow (BM)-derived cells though one study also used umbilical cord blood-derived

mesenchymal cells (Crane et al.), while another only used Wharton jelly-derived cells (Kim DW et al.). Andrzejewska et al. explored different ways of labeling MSCs in vitro so that they could be tracked once transplanted and whether this affected their biological activity. Their results suggest that super paramagnetic iron oxide particles (SPIOs) may be the best label out of those they tested. Two of the three induced pluripotent stem cell (iPSC) studies involved predifferentiation to NSCs (Acharya et al.) or dopamine neurons (Leveque et al.). The embryonic stem cell (ESC) study also involved predifferentiation to neural progenitor cells (Denham et al.) and explored their ability to integrate into the CNS following neonatal transplantation. Fat (Acosta et al.) and amniotic fluid (Antonucci) were additional cell sources investigated this year. Clinical-grade NSCs from ReNeuron, Inc. (Guildford, UK) were studied with respect to optimal vehicle (Rosetti et al.) and neurovascular unit formation (Chou and Modo), while clinical-grade BM-derived MSCs were found to be more effective against stroke when cultured in platelet lysate (Parsha et al.). It is also worth pointing out that 20 of the 26 stem cell studies looked at human-derived cells, including the single ESC study, while the remaining six were evenly split between the mouse and the rat as sources.

Stem Cell Transplantation Studies

Examination of the donor and recipients for stem cells reveals that the primary donor source is human, while rat is the primary recipient (Table 4). No human-human cell transplants were reported this year, and there was only one definite autologous stem cell transplant study reported at this year's meeting, involving IV transplantation of BM-derived mononuclear cells (MNCs) for the interleukin (IL)-10-dependent treatment of a mouse model of stroke (Yang et al.). The Lee et al. study demonstrated that a modified inflammatory chemokine could still direct NSCs (derived from three different origins: fetal CNS, ESCs, and iPSCs) to home to the injury but not initiate an inflammatory response in a mouse model of the lysosomal storage disease, Sandhoff disease.

Table 4. Stem Cell Transplantation Studies at the 2013 ASNTR

Donor	Recipient				Total
	Human	Mouse	Rat	Unspecified	
Human		3 (Darlington et al.; Lee JP et al.; Willing et al.)	9 (Acharya et al.; Acosta et al.; An et al.; Choi et al.; Dailey et al.; Denham et al.; Jendelova et al.; Parsha et al.; Tajiri et al.)	1 (Antonucci)	13
Mouse		2 (Crane et al.; Yang et al.)			2
Rat			1 (Fink et al.)		1
Total	0	5	10	1	16

Two studies used human NSCs derived from epileptic patients to explore treatments for epilepsy (Dailey et al.) and the contribution of miRNAs to the disorder (Tajiri et al.). Three studies focused on intraspinal transplantation of three different types of human NSCs for the treatment of SCI with some degree of success (An et al.; Choi et al.; Jendelova et al.). The cells used by Choi et al. were engineered to express glial cell line-derived neurotrophic factor (GDNF) and were generally observed to differentiate into neuronal cells. Surprisingly, Crane et al. showed that intrastriatal transplantation of highly passaged mouse MSCs appeared to be more effective than that of lower passaged cells in the treatment of HD, while Fink et al. showed that rat iPSCs were more effective when given earlier rather than later (with respect to the HD lesion). The beneficial effect of multiple IV infusions of human umbilical cord blood cells was further explored in AD and Sanfilippo Type 3 B mice by Darlington et al. and Willing et al., respectively. Acharya et al. continued their studies to identify an optimal cell type (this time using iPSC-derived NSCs) for the treatment of radiation-induced cognitive dysfunction—a side effect of radiotherapy for cancer treatment.

These studies provide the groundwork for some potential translational therapies, but the limited information on the age and sex of the donors (and frequently also of the recipients) in many of these studies dampens enthusiasm, as it is unclear whether these factors have been considered.

Geographical Distribution of the Presentations

Twenty different countries from all of the major continents (except for Africa and Antarctica) were represented at the meeting with the lion's share coming from the US. Over 20% of the studies were in a collaborative fashion involving two or more countries with nearly 50% of these being stem cell studies. Thirteen percent of the total studies included the US collaborating with a total of 12 other countries, though one study involved six different countries. All Canadian, Korean, and UK studies involved more than one country, with Korea collaborating with Canada on two NSC studies, Canada collaborating with Korea, Japan, or the US, and the UK collaborating with the US (NSCs), France, and the Czech Republic (NSCs and iPSC-derived NSCs).

All but one of the iPSC studies had ties to the US (the exception being one of the multiple stem cell studies mentioned above) (Jendelova et al.) as well as three of the four MSC studies, four of the six NSC, and five of the seven multiple cell-type studies. The solo ESC study arose from Australia (Denham et al.), though both of the two combined stem cell studies that also included ESCs had ties with the US—one of them was using mouse-derived cells (Hsu et al.) and the other human (Lee et al.). Only 3 of the 13 human stem cell transplant studies did not have ties to the US, and two of these arose from single countries (Italy and Australia), while two of the US studies were collaborative with France and Japan. The two human umbilical cord blood mononuclear cell (UCB-MNC) transplant studies arose from the same US institution. A number of studies arose from single group collaborations between multiple countries. For instance, four non-stem cell articles arose from one Swedish/Romanian/Indian collaboration, while two NSC transplantation articles arose from a Korean/Canadian group.

This helps to demonstrate the collaborative nature of neural therapy studies, whereby multiple countries are working “together” to utilize stem cells as a regenerative therapy.

CONCLUSIONS

These studies highlight the rapidly developing field of regenerative therapy, with four studies highlighting gene therapy clinical trials for Parkinson's disease. TBI is emerging as an important field of study. Numerous studies also attempted to reveal more details about disease mechanisms and methods of possible treatments (e.g., stem cells, natural drugs, physical therapy, hydrogels, gene therapy, etc.).

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REFERENCES

The individual references are not included within this manuscript so as to eliminate the article's ability to influence bibliometrics. A version of the manuscript incorporating the reference list can be obtained from the corresponding author.