
Supported by:
The Stanford Institute for Neuro-Innovation and Translational Neurosciences (SINTN) and The Rick Hansen Institute (RHI)

Contributors:
Dr. Graham Creasey
Dr. Stephen McKenna
Lesley Soril
Cindy Samos
Greta Beekhuis
Introduction

The field of regenerative medicine, particularly stem cell research, offers a promising therapeutic avenue for many chronic neurological conditions, such as spinal cord injury (SCI). While translation of effective therapies from the bench to the clinic is still in its infancy, the excitement generated by the potential of having a long-lasting, biological therapy with regenerative, reparative and restorative capacities has stakeholders around the world engaged in efforts to support both the funding and infrastructure necessary to expedite translation. The California Institute for Regenerative Medicine (CIRM), for example, recently convened an expert group to establish a framework for a funding initiative to support clinical testing for the eventual delivery of cell therapies in California. In conjunction with this meeting, the Stanford Institute for Neuro-Innovation and Translational Neuroscience (SINTN) held an inaugural SCI 2012 Symposium at Stanford University, in Palo Alto, CA with the aim of developing a roadmap for the future of regenerative medicine in SCI.

The two-day symposium was held in November 2012, with additional support from the Stanford Center on Longevity and the Rick Hansen Institute (RHI), and brought together over 70 basic and clinical neuroscientists and clinicians, rehabilitation researchers, SCI research network affiliates and persons with SCI from across the US, Canada and Europe. Led by Drs. Graham Creasey, Stephen McKenna, Giles Plant and Corinna Darian-Smith with the support of Prof. Gary Steinberg, Chairman of Neurosurgery and Director of SINTN, the program reviewed the latest advances in neuroscience and clinical trials to initiate strategic discussions on the future of translational neuroscience, aiming towards effective cellular treatments for SCI.

Laying the foundation: Translating the basic science

Acknowledging its pivotal role in uncovering therapeutic targets and mechanisms, the first talks of the symposium focused on basic science and were described by moderator Dr. Naomi Kleitman (Craig H. Neilsen Foundation, RHI TRAC member) as falling within the five R’s: Rescue, Replace, Repair, Remyelinate and Rehabilitate. Studies presented in animal models examining the immune response following traumatic SCI (Dr. Phil Popovich, Ohio State) and the role of glial cells in central nervous system (CNS) development (Dr. Ben Barres, Stanford), highlight their significance for clinical translation given that proper immune system function and a permissive CNS environment are necessary for effective regenerative medicine approaches. Understanding the endogenous plastic behaviour of the CNS, demonstrated in studies presented by Drs. Corinna Darian-Smith (Stanford) and Jon Kaas (Vanderbilt) using nonhuman primates (NHP), also affords the opportunity for refining targets for repair and tailoring the regenerative and plastic response of the post-injury CNS.

Specific examples of current preclinical cell transplantation studies in California were also shown. Using human CNS stem cells (hCNS-SCs), Dr. Aileen Anderson (UC Irvine) presented initial preclinical evidence in a rodent model to support their translation to a clinical trial (Stem Cell Inc). Studies using human mesenchymal progenitor cells (hMPCs) are ongoing in the laboratory of Dr. Giles Plant (SINTN, Stanford) for sub-acute and chronic animal models of SCI in rodents. Research presented by Drs. Michael Beattie (UC San Francisco) and Jeff Kocsis (West Haven VAMC), members of the Veteran Affairs SCI Consortium, also illustrated the benefits of conducting studies in NHP models when examining specific modalities and outcomes, such as when developing appropriate outcomes measures, performing replication studies, and examining models of injury-induced plasticity.

Work presented from the field of engineering at the biomaterial (Dr. Sarah Heilshorn, Stanford) and biomechanical levels, lends practical tools that may augment the long-term efficacy of cellular
therapies. For example, studies presented on the use of functional electrical stimulation (FES) implants and neuroprostheses by Dr. Hunter Peckham (Case Western Reserve) demonstrated the benefits of combinatorial approaches for rehabilitation, as well as potential funding models to offset costs of such technologies.

**Mileposts along the way: Lessons learned from recent SCI clinical trials**

Collectively, the studies presented at the symposium contribute to a wealth of therapeutic opportunity for SCI. Many considerations, however, with regards to standardization, outcomes measures, models and efficacy must be defined before any promising treatment can be translated to the clinic. Results of a questionnaire administered to basic and clinical SCI researchers presented by Dr. Brian Kwon (University of British Columbia, ICORD), which surveyed topics such as animal and injury models, chronicity and clinically meaningful efficacy, echoed the need for clear benchmarks and expert consensus in each area. Similarly, Dr. Dan Lammertse (Craig Hospital) spoke of the ‘learning curve’ for conducting clinical trials in SCI that has driven the need for well defined *a priori* hypotheses, designing clinical trials with the natural recovery of SCI in mind, and remaining cognizant of the evolution of available outcome measures. Recognizing the challenges specifically encountered from previous clinical trials in cell treatments, Dr. Jane Lebkowski (formerly of Geron) remarked on the contentious aspects in cell therapy trial design, including knowing the efficacious mechanism of action, appropriate timing of intervention, the heterogeneity of the population, poorly defined end points, complications and costs associated with development and regulatory approval. The lessons learned from the currently active Stem Cell Inc trial, presented by Dr. Armin Curt (EMSCI), include consideration of inclusive protocols (i.e. not setting the bar too high for participant enrollment), which help to avoid the “leaky pipe model” for clinical trial participation by persons with SCI.

One particular highlight of the symposium was the Q&A session between symposium participants, past Geron clinical trial participant Katie Sharify and her physician Dr. Stephen McKenna on her experience during the Phase I trial and beyond. Ms. Sharify was quite candid about the consenting process she underwent and her level of readiness to participate in a cell transplantation trial based on the information available at the time—attributing her conversations with a past study participant as critical to her decision-making process. She hopes similarly to serve as counsel for others with SCI considering participating in clinical trials. Her advocacy efforts certainly shed light on the relative paucity and urgent need for accessible and reliable information for individuals who are newly injured or in the community. Dr. McKenna also highlighted that Katie’s experience as one of the first patients in the nation to receive stem cell therapies can serve as an example for all patients who are considering regenerative medicine therapies.

**Fuel for the journey: Communication and collaboration**

Collaboration and open communication between basic scientists and clinicians within the SCI research community were recognized at the symposium to be fundamental for accelerating the translation of cell therapies. Existing models of research consortia, international networks and funding initiatives were presented by various groups to serve as successful examples, either to learn from or to leverage for future preclinical and clinical trials in regenerative medicine. The VA SCI Consortium presented by Dr. Audrey Kusiak (VA) is composed of basic science, clinical and informatics teams working in concert as translational teams, facilitating the bidirectional flow of ideas, from bench to bedside and back. Many of the clinical networks such as the North American Clinical Trial Network

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(NACTN; presented by Dr. Robert Grossman), the European Multicenter Study about SCI (EMSCI; presented by Dr. Armin Curt), the RHI Clinical Research Network (presented by Mr. Bill Barrable) and those developed by the National Institute of Neurological Disorders and Stroke (NINDS) such as NeuroNEXT and NETT (presented by Dr. Naomi Kleitman) also spoke of the importance of standardization of language and datasets (e.g. common data elements), accepted outcome measures, large data registries and data platforms. Practices for overcoming administrative, ethical and regulatory barriers were also described by many of the speakers, with harmonization of protocols and institutional research ethics boards (IRB), centralized coordination (e.g. HUB and SPOKE models) and communication to the regulatory agencies for multi-center studies being among the most widely adopted by the networks represented at the symposium.

**Obstacles along the way: The future of clinical trials in SCI**

With open communication central to the symposium, Dr. John Steeves (ICORD) led an interactive session that stimulated discussion on issues likely to shape the future of clinical trials in SCI, including barriers in preclinical discovery and development, accurate assessment and classification of potential trial participants, determining appropriate measurement tools and clinical endpoints, and confounding factors that could impede accurate interpretation of trial results. Final breakout group sessions also enabled participants to discuss key areas of focus and strategies to move the field forward. Funding for the development and conduct of clinical trials, particularly for long-term cell transplantation studies, was noted as a major area of concern. As such, participants urged the need to adopt novel funding structures and to centralize coordination and fund raising efforts on behalf of a research consortium, in order to optimize funds raised from government, industry and philanthropic sources. A paradigm shift from publication-driven to collaborative translational science and service-directed research was also discussed, with studies in informatics and open data sharing being fundamental to successful clinical trial outcomes. Another worthwhile opportunity identified to ensure the success of future clinical trials was not related to the science directly, but rather to supporting information dissemination to potential participants and to creating a reliable and comprehensive knowledge portal assuring the safe and continued participation of persons with SCI in research.

**Action Items**

Principal action items established from the symposium include the formation of small, focused working groups composed of leading experts from the represented institutions. The working groups would be charged with developing collaborative strategies in areas such as bolstering participant enrolment for clinical trials, unifying outcome measures internationally, and aligning the financial drivers for regenerative medicine research. To capitalize on the momentum from the breakout group discussions, subsequent update presentations and meetings are also planned for upcoming national and international SCI conferences, such as the International Symposium on Neural Regeneration (ISNR).

**Conclusions**

The SCI 2012 Symposium was intended to pave the way for many future conferences of this kind. By establishing a co-ordinated series of international conferences, key stakeholders can develop a unified vision for the roadmap addressing the challenges in regenerative medicine. Publications resulting from this and future conferences will be geared towards developing strategic and focused policy statements to produce the roadmap for the future of regenerative medicine in SCI.

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