JOURNAL OF NEUROTRAUMA XX:1–16 (Month XX, 2021)

DOI: 10.1089/neu.2020.7174

Original Article

Meeting Proceedings for SCI 2020: Launching a Decade of Disruption in Spinal Cord Injury Research

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Abstract

The spinal cord injury (SCI) research community has experienced great advances in discovery research, technology development, and promising clinical interventions in the past decade. To build upon these advances and maximize the benefit to persons with SCI, the National Institutes of Health (NIH) hosted a conference February 12–13, 2019 titled ''SCI 2020: Launching a Decade of Disruption in Spinal Cord Injury Research.'' The purpose of the conference was to bring together a broad range of stakeholders, including researchers, clinicians and healthcare professionals, persons with SCI, industry partners, regulators, and funding agency representatives to break down existing communication silos. Invited speakers were asked to summarize the state of the science, assess areas of technological and community readiness, and build collaborations that could change the trajectory of research and clinical options for people with SCI. In this report, we summarize the state of the science in each of five key domains and identify the gaps in the scientific literature that need to be addressed to move the field forward.

Keywords: assistive technology; neural plasticity; neural regeneration; neuromodulation; rehabilitation medicine; spinal cord injury

Introduction

A PANEL was convened by the National Institute of Neurological Disorders and Stroke leadership to develop and implement a conference with the following objectives: 1) to address and raise awareness of recent progress and current gaps in SCI research; 2) to provide opportunities for collaboration across research in the basic, translational, and clinical domains and consumer groups; and 3) to identify the top SCI research priorities for the coming 10–15 years, of and for the SCI research community, at the intersection of scientific, technological, and community readiness. This panel was composed of members from the National Institutes of Health (NIH) and a 12-member external steering committee. The external committee was comprised of SCI scientists ($n = 8$), persons with lived SCI experience ($n = 2$), and scientists from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)-funded Spinal Cord Injury Model Systems Knowledge Translation Committee ($n = 2$).

The participants identified the following five key scientific domains and one lived experience domain: 1) opportunities in the acute post-injury phase; 2) innovating repair, plasticity, and regeneration in the subacute and chronic periods; 3) with us, not for

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us: community activity and priorities; 4) neuromodulation to improve neurological function months and years after SCI; 5) health and secondary health effects of chronic SCI; and 6) technological facilitation, prosthetic and robotic interventions and therapies across the spectrum of mild/moderate/severe SCI. Six national experts were identified to serve as session chair for each of five key research domains and the lived experience domain. The session chairs identified key topics and goals for each session, nominated and advised on panelist selection, moderated and developed session organization, and advised on post-meeting outcomes. NIH facilitators participated in session planning, advised on panelist selection, and facilitated session presentations.

Panels were then asked to consider the following themes while preparing their sessions: 1) What are the research advances that should be highlighted to the broader community?; 2) What are the major obstacles to translating/achieving the next step for these research areas?; 3) Are there disagreements about interpretation of the research area in question?; 4) Is there a knowledge gap or resource gap that is preventing clinical application or U.S. Food and Drug Administration (FDA) approval?; 5) Why should this research area be a priority?; and 6) What are the limitations that prevent therapeutic potential of this research area and can they be overcome?

The conference occurred over 2 days and included a scientific keynote address, a lived experience keynote address, a presentation on scientific rigor in SCI research, and six primary sessions featuring brief presentations of recent scientific advances and critical research questions for the future. Facilitators and audience participation were encouraged to identify opportunities and areas for collaboration. The North American Spinal Cord Injury Consortium (NASCIC) and other public/consumer members provided personal context of persons living with SCI for defining future research priorities. Five final breakout sessions were held concurrently at the end of the second day focused on each of the five scientific domains. Stakeholders identified and discussed key scientific gaps and priorities for SCI research in the next decade. The conference culminated with a summary presentation of the top priorities identified in each of the five breakout groups.

Here, we provide an overview of the recent scientific advances, consumer perspectives, and scientific gaps that were identified in each of the primary sessions. The following sections summarize both the scientific content that was presented during the sessions as well as the discussions that occurred during the breakout sessions. This article does not address the resulting funding priorities because future communications or publications from funding agencies will address this information.

Session 1: Fire and Smoke—Opportunities in the Acute Post-Injury Phase

Session Chair: Linda Noble-Haeusslein, PhD
Panelists: William Whetstone, MD, Alexander Rabchevsky, PhD, and J. Marc Simard, MD, PhD
Discussion Facilitators: James Guest, MD, PhD, Dana McTigue, PhD

Identified scientific gaps

- Identify a clinically feasible intervention window that can be modeled in pre-clinical studies.
- Develop an optimized acute care approach to manage patients in the emergency department (ED).
- Create an infrastructure for acute spinal cord injury centers of excellence with specialty clinical expertise and patient/community education.

Brief review of the state of the science

Traumatic SCI initiates progressive secondary destruction of spinal cord tissue characterized by radial and axial lesion expansion.[1–4] Within the first 24 h after injury, the initiating mechanical insult triggers secondary events that drive subsequent pathogenesis. These include rapidly evolving hemorrhagic necrosis[5] coincident with a proinflammatory state.[6,7] The local environment is subjected to ischemia, glutamatergic excitotoxicity, mitochondrial dysfunction, dysregulated ionic homeostasis, autophagy, and generation of reactive oxygen and nitrogen species,[3,4,6,8,10] creating a noxious environment that is characterized by pronounced lipid peroxidation and cell death[6–8] and contributing to tissue loss and long-term neurological deficits.[9]

Historically, there has been an emphasis on vascular-directed pathogenesis in the acute phase after SCI,[1] including disruption of the blood–spinal cord barrier and post-traumatic hemorrhagic necrosis (PTHN). Disruption of the blood–spinal cord barrier within the first 24 h post-injury is evident in both animal models and humans. Whereas mechanisms underlying barrier disruption are multi-factoral,[10] loss of the barrier function exposes the cord to circulating proteins that promote vasogenic edema and neurotoxic factors, collectively degrading the extracellular matrix, which is essential for neuronal survival.[10]

PTHN, one of the most overt vascular consequences of SCI, is characterized by petechial hemorrhages in the central gray matter with expansion into the pericentral white matter and along segments rostral and caudal to the lesion.[1,11] With time, local edema and hemorrhage resolve and a classic fusiform cavity remains, extending along the axis of the cord. Although initially reported in animal models, these findings have been confirmed in human SCI by magnetic resonance imaging (MRI).[12,13]

Although mechanisms underlying PTHN had been debated,[14,15] there is now evidence linking PTHN to the sulfonylurea receptor 1–regulated channel.[5,16–18] Glyburide, a sulfonylurea used in the treatment of non-insulin-dependent diabetes mellitus,[19] reduces hemorrhagic expansion and lesion volumes and improves function in rodent models of SCI. This has led to a prospective single-armed, open-label, multi-center study to evaluate both safety and feasibility of oral glyburide.[19]

A central tenant of neuroprotection is to reduce early secondary pathogenesis. A critical question is whether the medical community can create a Code SCI similar to Code Stroke,[20] whereby a time-sensitive intervention is administered shortly after arrival at the trauma center. The Code Stroke model is based upon rapid assessment and treatment in the ED and includes prioritizing patients for computerized tomography (CT) and MRI scans as well as consent and administration of therapy while the patient is still in the CT scanner. The complexity of SCI poses unique challenges that compromise the timeline to therapeutic intervention, including whether the patient is transported to a Level I or II Trauma Center, polytrauma, need for biomarkers to gauge effectiveness of treatment, early control of blood pressure, and the standardization of early surgery.

Discussion

Toward early intervention. Participants commented on how management of stroke may serve as a model system for early intervention in SCI. Early intervention at the scene or on ED admission should be considered. There is currently no consensus candidate therapeutic, nor is there a standardized model for optimal care during transport or in the ED.

Moreover, the ability to recruit subjects for clinical trials is challenging given the low incidence of SCI. Further, unlike in the stroke model team, there is value in including physical medicine and rehabilitation specialists on the trauma team. Inadequate screening and physical evaluation are among the most common reasons for delayed diagnosis of SCI.[21] In addition to contributing to diagnosis, physical medicine and rehabilitation specialists have the expertise to provide early evaluation of all body systems that are potentially affected by SCI. Such care would allow advanced identification of secondary conditions and comorbidities, along with rapid intervention.

Expediting the pathway to clinical trials. Participants explored how various strategies could expedite the pathway from discovery to clinical trials. These include repurposing of FDA-approved drugs with a low risk profile, pursuing pathways related to early physiological management, and revisiting ''failed trials'' such as the ganglioside *GM-1*, which resulted in improvement in bladder function. Combinatorial therapies, associated with greater benefit in cancer-related trials, could likewise reveal beneficial synergism in SCI. There is also the opportunity to target other secondary consequences of SCI, including bone loss, that may be responsive to early intervention.

Optimizing acute care management. Beyond early pharmacological interventions, participants concurred that there is a need to optimize acute management, recognizing that ''time is cord.'' Steps toward optimization include extradural decompression and optimization of spinal cord perfusion pressure, blood pressure augmentation, and collection of physiological data that may determine prognosis. The path toward optimization poses challenges. Although there are encouraging data in support of decompression,[22] there has yet to be a randomized clinical trial to address surgical decompression. Additionally, the value of physiological data as biomarkers remains a nascent area of investigation, and time is needed to rigorously identify those indicators that best predict recovery. There are understudied variables, such as level of light that can affect circadian rhythms, feeding paradigms, genetic information, and imaging, that could contribute to more personalized care and impact recovery.

Acute care management would benefit from prospective studies that broaden our understanding of SCI. Robust data could be collected using electronic health records. A starting point could involve centers pooling data on augmentation of mean arterial pressure and related outcomes, cerebrospinal fluid biomarkers, and management of perfusion pressure. Large data sets would allow for natural history experiments.

There is a lack of measurement tools that would allow assessment of outcome trajectory very acutely and provide a beginning foundation for prognosis. The intent would be to develop simple tools related to physiological parameters that could be implemented in the ambulance, in parallel to biomarkers and electrophysiological assessments, that could be applied in the ED.

Learning from others. Participants described how other fields of acute care management offer strategies that could be applied to SCI. The NINDS has supported emergency care clinical trials networks, such as the Neurological Emergencies Trials Network, which is organized around the concept of a scalable and flexible network with a consortium of academic and community hospitals. No SCI trial has involved this type of network, and one limiting factor has been the lack of specialists to support this effort. An encouraging approach is Transforming Research and Clinical Knowledge (TRACK)-SCI, supported by the Craig H. Neilsen Foundation. This is a cross-disciplinary organization with eight study sites and the objective of collecting large data sets, including blood pressure, MRI, and time to surgery, as first steps toward addressing the optimal clinical pathway for patients.

Pre-clinical challenges. Pre-clinical studies have failed to produce a drug that has translated to a robust effect in acute SCI clinical trials, and the lack of effective, evidence-based treatment has been the major barrier to ultra-early intervention. Participants recognized that many inter-related issues likely contribute to this failure to translate, including lack of scientific rigor with standards to ensure that the research is robust and reproducible. Additionally, SCIs are heterogenous with differences in injury severity and segmental level, and humans with SCI often experience polytrauma with associated medical-surgical complications. There is the added uncertainty about whether the temporal pattern of pathogenesis is similar between pre-clinical models and humans, a limitation that influences decision making about the treatment window related to time to first treatment.

Strategies to improve translatability include increased attentiveness to rigorous experimental design, selecting a larger effect size, validating favorable findings from rodent studies in larger animal models, better defining temporal patterns of pathogenesis by mapping pre-clinical trajectories of bleeding onto clinical findings, and ''reverse'' translation whereby clinical biomarkers inform pre-clinical models. Last, we have yet to acquire national figures on transport time to a trauma center after an SCI, data that are essential for design of pre-clinical efficacy studies.

Feedback from consumers. Feedback was sought from people with SCI and family members who participated in the SCI 2020 meeting regarding their roles/contributions in acute trial design and planning. They serve as advocates for studies, are conduits for communication with potential study participants, assist families and those with acute SCI in navigating the complex terrain of the immediate post-injury period, and fund clinically impactful research through foundations. In the breakout discussion sessions, consumers supported several key ideas: developing a rich set of clinical data to optimize treatment, establishing a sensitive measure of neurological status that can serve as a reliable foundation for prognosis and treatment planning, improving hemodynamic management, and determining optimal timing for therapeutic intervention.

Community consultation. At the meeting, attendees expressed consensus that community consultation is a pathway to enable ultra-early, on-the-scene treatment of patients with SCI. People living with SCI should have an active voice in this process. Community consultation is a deliberative process that involves informing and seeking input from the wider community about a research study's procedures, risks, and benefits.[23,24] Although community consultation does not constitute community consent, the institutional review board of record considers feedback from this group in decision making.

Litigation. There were conflicting viewpoints regarding physicians' resistance to initiating treatments that lack definitive proof of efficacy (e.g., hypothermia, decompression, and methylprednisolone) given the high incidence of litigation in SCI. One viewpoint was that physicians are morally obligated to use approaches

where there appears to be obvious benefit, whereas others expressed safety concerns citing methylprednisolone and its related adverse events.[25,26]

The critical research needs identified included development of an optimized approach to acute management based on evidence that is not necessarily predicated on randomized clinical trials, identification of physiological processes that can be targeted in a clinically feasible time window (or, ideally, multiple windows), and defining an infrastructure that builds awareness of SCI that enables patients to be transported (or transferred) to centers of excellence in acute management of SCI.

Session 2: Innovating Repair, Plasticity and Regeneration in the Subacute and Chronic Periods

Session Chair: Michael Sofroniew, MD, PhD
Panelists: Zhigang He, PhD, James Guest, MD, PhD, and Jennifer Dulin, PhD
Discussion Facilitators: Veronica Tom, PhD, Sam Pfaff, PhD

Identified scientific gaps

- Identify what is needed to achieve repair of the injured spinal cord.
- Better understand the specificity requirements for repair and recovery.
- Develop technologies that transform the way we study SCI and repair in humans and animals and facilitate data sharing.

Brief review of the state of the science

For many years, it was felt that function could only be restored after SCI by regrowth to the original target across the lesion. The discovery that the adult nervous system was capable of undergoing use-dependent plasticity has transformed our views about intervention after spinal cord injury.[27] Although it is now clear that while there are multiple mechanisms limiting neural regeneration after neurotrauma, there are also multiple ways in which function can be restored. Here, we examine the current state of the science supporting the current thinking that functional recovery can be achieved in multiple ways after SCI that can bypass or bridge injury sites. We review current literature regarding the cellular physiology of an injury lesion as well as mechanisms both limiting neural regeneration and promoting functional recovery.

SCI lesions have three distinct cellular compartments: a central non-neural lesion core, an astroglial scar border, and spared reactive neural tissue above and below the injury.[28,29] The spared reactive tissue compartments above and below the injury contain all the elements of healthy tissue and can reorganize. Different cellular interactions and molecular mechanisms regulate different forms of axon regeneration in the distinct lesion compartments. Spared neural tissue contains cues that support and attract repair, plasticity, and reorganization. There is also good evidence that axon sprouting and synapse remodeling and longer distance regrowth occur in spared neural tissue.[27] In contrast, axons are not able to regrow and reconnect across non-neural lesions cores, and when such lesions span the width of the spinal cord they result in anatomically complete lesions. Fortunately, many lesions originally diagnosed as ''functionally'' complete are emerging as anatomically incomplete[30] and may therefore benefit from a wider range of potential repair interventions that target the reorganization of spared neural tissue.

In the case of incomplete SCI with spared neural tissue, augmenting plasticity and circuit reorganization are emerging as increasingly important therapeutic approaches. Two major forms of plasticity are recognized: 1) structural, relating to axonal sprouting and synaptic reorganization, and 2) functional, relating to axonal conduction and receptiveness of injured spinal cord to spared connections.[27] Various mechanisms can limit or prevent spontaneous functional recovery in spared tissue after SCI, including injury-induced homeostatic alterations and maladaptive reorganization. For instance, spinal shock and the subsequent recovery period are characterized by excitability changes within the injured cord. Injury also leads to inflammation, demyelination, and downregulation of key homeostatic regulators. KCC2 is a neuron-specific chloride potassium symporter that regulates neuronal excitability by reducing intracellular chloride concentration. SCI downregulates KCC2, making neurons less likely to be inhibited by gamma aminobutyric acid/glycine leading to neuropathic pain, spasticity, and impaired relay function mediated by propriospinal pathways.[31,32] KCC2 activators improve functional recovery, possibly reducing pain and spasticity. The capacity for axonal sprouting in spared tissue varies by subpopulation, with serotonergic axons capable of good spontaneous sprouting. In contrast, corticospinal axons have limited spontaneous sprouting. Active research is ongoing focused on promoting sprouting.[33] Axonal growth in spared tissue is influenced by both intrinsic (injury signals, growth competence, and axonal transport) and extrinsic factors (perineuronal nets). When considering incomplete SCI, future pharmacological approaches may be developed to boost neuron intrinsic growth, augment plasticity, modulate the perineuronal net, and activate dormant pathways.

Although different forms of regeneration can restore function after incomplete SCI, this does not happen spontaneously after complete SCI. Inhibitors dominated research in this area for decades and include both astroglial scars and inhibitory molecules such as chondroitin sulfate proteoglycans and myelin-related factors.[34] However, recent studies have shown that preventing or ablating chronic astrocyte scars does not lead to axon regrowth and growth can be stimulated despite the presence of scars, demonstrating that astrocyte scars are not the cause for regrowth failure.[1] The role of growth facilitators in axon regeneration was long neglected, but is now re-emerging in importance. Increasing evidence implicates inadequate neuron-intrinsic growth, inadequate matrix support, and inadequate chemoattraction as the key mechanisms underlying the failure of axon regrowth across complete SCI lesions.[28,35,36] In addition, remyelination is emerging as a key determinant of axonal conduction and excitability control and functional restoration in regenerating and repairing circuits.

Discussion

Meeting participants remarked that effective repair strategies for SCI will depend on an understanding of how to differentiate lesions of different severities and how to target compartment-related mechanisms. Approaches will need to vary based on the whether the injury is anatomically complete or anatomically incomplete with sparing of neural tissue. For example, persons with anatomically incomplete SCI may benefit from non-invasive strategies that promote axon sprouting, synaptic strengthening, and circuit reorganization. Whereas persons with anatomically complete SCI may require invasive strategies that provide facilitators of growth to bridge non-neural lesion cores. One approach to bridge anatomically complete lesions is cell grafting to replace endogenous neurons and form functional neural circuits.[37] In all cases, repair approaches will need to be combined with rehabilitation to

maximize functional recovery.[38] Rehabilitation will play a key role by promoting use-dependent plasticity, neuroprosthetic training, electrophysiological stimulation, and more routine combination of rehabilitation training with repair strategies and in animal models.

Many questions remain unanswered regarding repair after SCI. It is unknown which populations of host axons should be targeted to promote regrowth in which SCI contexts. It is not known how many regrown axons will be sufficient for functional recovery. More work is needed to determine the impact of inaccurate connections on functional recovery. Further research is also needed to determine the most effective strategies for manipulating excitability, such as epidural stimulation, targeting KCC2, rehabilitation-based strategies, or a combination of one or more of these approaches. It is also unknown what other excitability-relevant molecular substrates are altered by SCI or how to control maladaptive plasticity that manifests clinically as pain, spasticity, or autonomic dysregulation. At present, there is no objective measure of plasticity in human studies and there is no consensus on functionally relevant plasticity in animal models. In terms of cell-grafting therapeutic approaches, it is unknown what types of graft and host circuits best promote functional recovery and which phenotypes of grafted neurons can best support such circuits. More work is needed to determine the capacity for host/graft neural relays to form functionally appropriate circuits that can support recovery.[39] The potential for maladaptive outcomes after cell grafting, such as new or worsening pain or spasticity, is poorly characterized. Combinatorial strategies with various rehabilitation approaches, including electrical stimulation, use-dependent neuroplasticity, and bioengineering techniques, may also increase cell-grafting efficacy and have been understudied to date.

In all cases, effective strategies must be developed to translate the knowledge gained from basic science studies to the clinical setting. Human studies are critical to advance the field because it is unknown whether pre-clinical studies in animal models accurately predict human benefit. Additionally, there are opportunities for reverse translational approaches and advanced imaging techniques in the clinical setting that may add scientific value. Before clinical translation of findings, the benefit/harm ratio must be carefully weighed, clinical feasibility of the project must be established, access to the appropriate study population confirmed, outcome measures must be optimized to demonstrate benefit if present, and appropriate infrastructure and resources (both financial and intellectual) must be in place to support a clinical trial.

It is strongly felt that the field needs to set priorities and a strategic agenda for the next 10 years that aligns with the research priorities of consumers, including asking bolder questions with more conservative interpretations (not the other way around). Funding mechanisms are needed to support and incentivize cross-disciplinary and high-risk, high-reward approaches. The pooling of data across the field will accelerate progress, but standardization of methodology and outcomes is required for this to occur. Big data and artificial-intelligence–based analytical approaches may hold potential in the future.

Session 3: With Us, Not for Us: Community Activity and Priorities

Session Co-Chairs: Matthew Rodreick, Robert Wudlick
Panelists: Kimberly Anderson-Erisman, PhD, Alexander Rabchevsky, PhD, Barry Munro, John Chernesky, and Jennifer French, MBA

Identified scientific gaps

- Align research activities with the priorities of the SCI community.
- Incentivize meaningful consumer engagement in all phases of the research process.
- Develop a common language for effective communication among the many SCI research stakeholders (funders, regulators, researchers, clinicians, and persons living with SCI).
- Support promising therapies to move quickly along the translational spectrum.
- Increase investment in translational research from both the private sector and federal funding agencies.
- It is unrealistic to expect consumers to be aligned in their perspectives if the scientific community is not.
- It is essential to create a sense of greater urgency in the research community.
- Identify the ''simple solutions'' that we can quickly bring to the SCI community.
- Combine the resources of both the scientific and SCI communities to yield impactful outcomes.

A review of feedback from the spinal cord injury community

The NASCIC is composed of consumer-based organizations, persons living with SCI or directly representing a person living with SCI (such as a caregiver or family member), and organizations or persons with an interest or activities related to people living with SCI (http://nasciconsortium.org/charter/). In preparation for the session, NASCIC conducted an online survey of its membership to understand the key issues from the SCI community (those living with SCI, their families, and care-partners).[40] The results from this survey reflect a market survey, not research results. The results are presented in supplemental tables (see Supplementary Material Survey Results). A total of 1825 participants responded; 28% of respondents had injury levels (high cervical or lumbosacral) that are often excluded from clinical trials, and 34% of respondents were >20 years post-injury and are therefore ''aging'' with SCI.

Survey results suggest that the SCI community wants to be involved in the setting of research priorities and the designing of projects. The majority feel they are left out of the research process until researchers need clinical trial participants. They also need to understand more about research, but there are currently few opportunities to obtain this information. This is compounded by the lack of a common language shared by various stakeholders that limits the exchange of ideas. In the conduct of research, there are multiple competing incentives and biases that influence funding decisions, the peer-review process, and reporting of scientific results. This leads to a system that encourages scientists to be risk averse. The community living with SCI, however, has no effective way to influence or address any of these barriers. There is precedence for including people with lived experience of health conditions as research partners and there are multiple funding organizations that require this, including the Patient-Centered Outcomes Research Institute (PCORI), Department of Defense Spinal Cord Injury Research Program (DoD SCIRP), and the Canadian Institutes of Health Research (CIHR). These funders encourage or require the engagement of people in governance, priority setting, as expert reviewers, and increasingly require them to be partners on research projects. Integrated knowledge translation is the meaningful engagement of the right research users at the right time throughout the SCI research process. It is important to not just include people with SCI when trying to secure funding, when research participants are needed,

or for assistance with dissemination. Those affected by a decision have a right to be a part of the decision-making process.

Almost 60% of survey respondents felt that researchers, clinicians, funders, industry, insurers, regulatory agencies, and people living with SCI are not currently working together to successfully translate research findings to clinical care. There is also a lack of consensus on what ''ready for translation'' means. Perceptions vary regarding levels of acceptable risk associated with translation of novel findings. Half of the respondents felt that confirming safety was more important than prematurely implementing treatments that might be effective, but not safe. Nearly all respondents endorsed interest in a variety of treatment options, including medication, cells, devices, and/or rehabilitation.

There are existing funding mechanisms to translate science into clinical practice, such as the NINDS CREATE and the National Science Foundation Innovation Corp programs. However, there is a strong perception in the SCI community that public funds disproportionately support pre-clinical work leaving the private industry sector to invest in translational work. Translation is a process, not a single step. No one in the SCI community is an expert on the entire process. There is also a need to avoid overstating results when reporting them to the general public. The SCI community is overwhelmingly tired of media hype about research results that have not yet been translated to treatments and that are not clinically available.[41]

Over half of the respondents felt that research focuses too much on acute SCI while chronic injuries are understudied. Despite funding more chronic than acute studies, the total amount spent by the NIH on acute research exceeds that spent on chronic research. By way of comparison, incidence and prevalence of SCI and human immunodeficiency virus (HIV) are quite comparable. Yet, the NIH funds HIV research at 10 times the level of SCI research.[42] A recent publication of a 10-year study of HIV^+ persons with HIV^- partners found zero transmission of the virus when antiretroviral drugs were used, thus rendering HIV non-transmissible when available treatments are used.[43] That is to say, HIV is ''cured,'' yet it still receives 10 times the funding of SCI.

Ninety percent of the respondents agreed that funders should do more to support research on the development of treatments that reflect the needs of people living with SCI and their families. All injuries will become chronic within 12 months. Over the last 40 years, significant time and money have been invested in neuroprotection, both in terms of clinical trials and basic research, with no approved products resulting from this investment. The SCI community indicated that while waiting for new treatments to be discovered and then translated to clinical care, it is important to improve access to existing care and equipment, reduce the cost of living with SCI, and increase life expectancy. The SCI community feels that there are simple solutions that could improve care in the acute setting, such as blood pressure control and nutrition. Funding needs to align with the priorities of the people living with SCI. NASCIC and other SCI organizations are actively developing educational strategies to grow the capacity of the community living with SCI to become more engaged in the research process.

The reality is that those living with SCI are in a broken system. Research is driven so much by innovation that studies needed for translation are considered not innovative and rarely get funded. Many may believe that this system is working, and in the research, clinical, and business realms, that may be true. But this system is broken in the eyes of those living with SCI because nothing is delivered widely to the people living with SCI. The community feels that they are treading water just to survive every single day, and one can only tread water for so long before one drowns.

Those living with SCI do, in fact, want all functions back. But they understand that combination of treatments will likely be required to accomplish that. In the meantime, treatments leading to small improvements in daily life are now highly desirable. Ninety-eight percent of respondents agreed that restoring bladder, bowel, and sexual function are still important. This relays a clear message to the scientific community that there is an obligation to address these issues despite being scientifically complex.

The overwhelming message from those living with SCI is this: ''The *status quo* is not acceptable.'' People living with SCI need to be engaged at all points in the system. Funded research portfolios need to reflect the needs of people living with SCI. Investments in research have to yield tangible impacts in the lives of people living with SCI. The SCI community can be a strong, viable partner that can only enrich and bring great resources to the scientific community going forward. People with lived experience should be partners in all aspects of research, in one form or another. There is a sense of urgency while we work toward these advances. According to life-expectancy estimates for people living with SCI, those who have been injured for more than 30 years might not be alive for the next decade's NIH conference. Today, people are dying from common secondary complications of SCI, and this has not changed in 40 years. We need to continue to stress this urgency to accomplish a true disruption in the way we as a society fund and conduct SCI research. The next steps for SCI research should have guidance from the SCI community as we collectively define what a decade of disruption will actually be.

Session 4: No Plateau! Neuromodulation to Improve Neurological Function Months and Years after SCI

Session Chair: Edelle Field-Fote, PT, PhD
Panelists: D. Michele Basso, EdD, PT, Mary Jane (MJ) Mulcahey, PhD, OTR/L and Chet Moritz, PhD
Discussion Facilitators: Kimberly Anderson-Erisman, PhD, Grégoire Courtine, PhD

Identified scientific gaps

- Encourage longitudinal studies that are informed by outcomes important to people with SCI.
- Characterize the dynamic nature of chronic SCI and variables that indicate responsiveness of neuromodulation interventions.
- Harness the power of big data to mine outcomes of clinical care and cost-effectiveness of interventions that target use-dependent plasticity.

Brief review of the state of the science

The past quarter century has seen a transformation in our thinking about the capacity of the nervous system to change in response to experiences. Before this time, the accepted dogma was that the adult nervous system was made up of immutable networks that were impervious to change. Over the past few decades, it has become clear that not only is the adult nervous system plastic and responsive to experiences, but also that this potential for plasticity is present even in the nervous system that has been affected by SCI.[27]

Numerous studies have demonstrated that the potential to improve function through use-dependent plasticity exists even in the chronic stage of injury. Practice and training are powerful neuromodulators; in fact, many experimental pharmacological, biological, and stimulation neurotechnology intervention approaches target the very neural mechanisms that underlie training-related

neuroplasticity.[44] Experimental pharmacological, biological, and stimulation neurotechnology intervention approaches can be combined with practice and training to compound the neuroplastic effects of each. In pre-clinical studies of animals with SCI, the administration of a biological agent to promote neuroplasticity was found to be of value only when combined with training.[45–48]

Even in the presence of chronic human SCI, the high-priority goals of improved hand and walking function can be achieved through use-dependent plasticity.[49] Evidence from a systematic review of experimental interventions for improving physical functioning in persons with acute or chronic SCI indicated that experimental interventions of all types, including biological, pharmacological, and technological, are most effective when combined with training/rehabilitation.[50] Yet, key questions remain to be answered related to the required ''dose'' of training, in terms of numbers of repetitions and duration of training/practice. Unlike pharmaceutical trials, where participant engagement may be minimal and funds are available from an industry sponsor, rehabilitation studies are time-consuming for both the participants and study personnel, and funding can be elusive. This situation often results in underpowered studies with inconclusive results.[51] The rehabilitation field would benefit from applying the NIH Stage Model wherein trials are staged in a manner similar to pharmaceutical studies, and refinement of variables such as intervention dose are addressed before undertaking the next study phase.[26]

Cortical and spinal stimulation to drive plasticity through neuromodulation of brain and spinal cord circuits represent neurotechnologies with early evidence of promise for restoration of upper and lower extremity function in persons with chronic SCI,[52–54] as well as management of spasticity.[55,56] Some approaches use transcutaneous stimulation to activate cortical[52] or spinal circuits,[53] making these approaches clinically accessible. For stimulation intended to promote plasticity of spinal circuits, the evidence indicates that both transcutaneous and surgically implanted epidural stimulation have their primary effect through activation of the spinal roots.[57] Whereas the transcutaneous approach to spinal stimulation has the advantage of being non-invasive, this form of stimulation may activate peripheral nerve fibers across fiber types, and the activation of spinal extensor muscles and nociceptive fibers can occur with higher intensities. Epidural stimulation, despite the need for surgical implantation, has the advantage of having a sustained electrode placement. In addition, there are neurotechnologies that allow steering of the epidural stimulation current to the spinal levels appropriate to the phase of an ongoing movement.[54] Stimulation neurotechnologies have the potential to be potent drivers of use-dependent plasticity; however, evidence indicates that these approaches are most effective when used in combination with practice and training that activates the target circuits.[44,58]

Although the value of neuromodulation to drive plasticity for improved physical functioning seems evident, there are numerous internal and external factors that influence outcomes. In pre-clinical models, when the internal spinal cord microenvironment was manipulated to block the effects of inflammatory cytokines and chemokines, motor relearning was more robust than in the presence of inflammation.[59] Likewise, the external physical environment in which practice and training occur can influence the size of the neuromodulatory effects of training. For example, early evidence suggests that downslope treadmill training, which requires the nervous system to exert control over an eccentrically contracting muscle, appears to promote greater recovery of control than does walking on a level treadmill.[60]

For people living with SCI, motivation and goals for motor recovery and function vary and change over time. Neuromodulation therapies must deliver outcomes that enable everyday living and preserve health and well-being for the future. Consideration should be given to health in terms of the respiratory, urinary, musculoskeletal, and cardiovascular systems. The beneficial applications of neuromodulation extend beyond volitional motor activities to involuntary autonomic functions, including bladder control, and respiratory function. Technologies are available to modulate the activity of the neurogenic bladder using stimulation to activate neural control mechanisms in a way that mimics functioning of the intact nervous system.[61] In persons with high cervical SCI who might otherwise be dependent on mechanical ventilation for respiratory function, stimulation to control the phrenic nerve or pace the diaphragm can be used to control diaphragmatic activation. These approaches have successfully been used to free many persons with chronic high tetraplegia from ventilator dependence, even after many years of ventilator use.[62] There is some evidence to suggest that early use of these approaches is associated with recovery of independent respiration.[63]

In sum, we live in a hopeful time for persons with chronic SCI. The evidence that the potential for use-dependent plasticity extends for a lifetime makes functional gains possible for many persons with SCI. The availability of accessible approaches to neuromodulation in the form of practice/training/rehabilitation and clinically available stimulation means that interventions to capitalize on neuroplasticity have the potential to be within reach. Improved understanding of the dose of training/rehabilitation needed to have a clinically meaningful effect and the stimulation parameters that lead to optimal outcomes from neuromodulation therapies are essential for guiding practice.

Discussion

The participants acknowledged that inclusion of persons with *chronic* SCI in studies of neuromodulation and other experimental approaches offers many advantages. Given that the potential for neuroplasticity is present even in the chronic stage of SCI, people with chronic SCI may experience benefit from their participation in research. Given that the population of persons with chronic SCI is orders of magnitude larger than the population of persons with acute and subacute SCI, a greater focus on inclusion of persons with chronic SCI would facilitate the ability to meet study enrollment goals. Given that persons with chronic SCI have lived experience with their injuries, they have valuable insights about what intervention approaches are practical, and what outcomes are most meaningful to them. The priorities of persons with SCI may change over time, given that they live with their injuries, learn to adjust their lives and functioning, and gain knowledge about their injuries. This knowledge can be highly beneficial to informing the development and execution of clinical trials.

Much remains to be learned about the injury characteristics that indicate greatest likelihood of beneficial outcomes. The same neuromodulation intervention applied in persons with similar clinical presentation of SCI may result in different outcomes. Given the many possible interventions, understanding the factors associated with responsiveness to a specific intervention is essential for identifying which intervention, and at what dose, is best suited for which person.

Many neuromodulation approaches are accessible to persons with SCI, including practice/training and some stimulation neurotechnologies, with some approaches even being amenable for home

use. Despite the demonstrated safety and effectiveness of neuromodulation approaches for improving or restoring both volitional and autonomic function, there are challenges related to sustainability and accessibility. Effects of these interventions often require long time periods to become apparent, necessitating the use of longitudinal studies. In addition, given the relatively small size of the SCI population, neurotechnologies that are supported by grant funding in the early development stages may face hurdles in the commercial marketplace.

Understanding the longer-term value of neuromodulation interventions through longitudinal studies with extended follow-up periods is key to assessing the full value of these approaches. Likewise, capturing a broad range of outcome measures that access functioning at the level of body structure/function, activities, and participation is necessary to understand the full impact and value of these interventions and their cost-effectiveness. Outcomes such as decreased hospitalization, decreased need for caregiver support, and increased social/community participation can only be obtained through longitudinal studies.

The acquisition of large data sets necessitates the use of robust approaches to analyze and mine these data. Health services research based on data captured over the years after injury can quantify the value of interventions that target use-dependent plasticity and identify which approaches are most effective for specific injury characteristics. Such data can inform clinicians and also lay the groundwork for implementation science research that ascertains best approaches for advancing practice so that all people with SCI have the potential for optimal outcomes.

Session 5: SCI in Context: Health and Secondary Health Effects of Chronic SCI

Session Chair: Richard Shields, PT, PhD
Panelists: Phillip Popovich, PhD, Melissa Morrow, PhD, Michael Kennelly, MD
Discussion Facilitators: James Krause, PhD, Joetta Khan, PhD, MPH, RD

Identified scientific gaps

- Focus on multi-site and multi-disciplinary studies with common data elements to identify factors that influence health and development of secondary health conditions.
- Understand the impact of lifestyle and environmental factors on morbidity and mortality across the life span (health/obesity).
- Promote safe and efficient bowel, bladder, and sexual function and skin care and understand how it may influence infection and systemic inflammation in persons with SCI.
- Understand the impact of SCI on systemic and organ health with specific emphasis on stressors that affect immune function and the role of sensory and autonomic regulation (including mental health outcomes).

Brief review of the state of the science

Complications of SCI are a significant threat to health. Advances in early post-injury care have allowed many people who sustain SCI to survive their initial injuries, with the risk of death decreasing dramatically between the 1970s and 1980s.[64] However, recent data indicate an alarming increase in the odds of mortality since the 1980s.[64] Preventable secondary complications feature prominently among the factors associated with causes of death. Stage 3 or 4 pressure injuries, septicemia, and pneumonia are among the most significant contributors to mortality.[65–67] These findings demonstrate an urgent need to improve the prevention and management of complications that impede recovery, threaten health, and decrease quality of life.

Muscle activity is a key driver of health. Both in the general population and among those with SCI, activity is recognized as a key factor in promoting and maintaining health.[68–70] A growing body of work demonstrates the epigenetic role of activity—how activity alters gene expression in ways that may influence health.[71,72] Muscle activity activates a variety of molecular pathways that affect the functioning of the heart, bones, liver, brain, pancreas, and overall metabolic state.[71,72] Skeletal muscle is now recognized as a major endocrine organ that releases small molecules into the bloodstream that can regulate genes and tissues throughout the body.[73–76] The development of osteoporosis,[77–82] cardiorespiratory impairment,[6,9,83] and diabetes[84,85] is pervasive among persons with SCI. Reduced muscle activity, as a result of paralysis, likely creates an environment that impairs systemic health and promotes tissue deterioration.

Exercise guidelines have been developed to help healthcare practitioners and people with SCI set goals for physical activity.[86] Although these guidelines have emphasized the role of voluntary muscle activity, data suggest that electrically induced exercise also has the potential to produce changes in gene expression or biochemistry that improve neurological functioning.[76,87,88] Thus, electrically induced exercise may provide a tool to mitigate loss of voluntary muscle function in those with limited exercise capacity.

Systemic effects of SCI are gaining recognition. SCI creates a new physiological state, with implications for health and secondary complications. Disruptions in autonomic nervous system function post-SCI affect many organs, including heart, lungs, intestines, liver, and spleen.[89] Studies of both animals and humans with SCI demonstrate development of gut dysbiosis over time—a state in which the balance between beneficial and pathogenic microbes shifts in favor of those that create deleterious effects.[90–93] Animal models also suggest that gut dysbiosis may act upon pathways that relate to glial scarring, intraspinal inflammation, and immunity,[94] with implications for neurological damage and recovery. Gut dysbiosis may also affect signal transduction in ways that lead to increased muscle wasting and sarcopenia.[95] Animal studies have associated SCI with liver pathology.[96] Together, these observations demonstrate the need to consider how changes in organ system functioning after SCI may affect recovery and health.

Bladder dysfunction remains a major challenge. SCI produces several bladder function problems, including loss of voluntary control, bladder hyper-reflexia (neurogenic detrusor overactivity), urinary retention (poor voiding efficiency), and bladder-sphincter dyssynergia.[97] These primary problems create a cascade of secondary pathological changes and dysfunctions. Chief among these is incontinence, which increases risk for skin breakdown and can be a barrier to successful reintegration in community life. Urinary tract infections are also extremely common and a major driver of healthcare utilization.[98–100] Sepsis (for which urinary tract infection can be an initial cause) is among the most common causes of death for people with SCI.[48,66] There is a great need to improve long-term bladder management to avoid further disability, reduce healthcare costs, and prevent life-threatening complications.

Pharmacological agents are currently the primary treatment for lower urinary tract dysfunction. These agents may have various goals, including: 1) improve urine storage by suppressing neurogenic detrusor overactivity and reducing baseline intravesical pressure, 2) improve voiding efficiency by enhancing the amplitude and/or durations of bladder contractions, or 3) improve voiding efficiency by suppressing detrusor-sphincter dyssynergia and enhancing detrusor-sphincter coordination.[101] A number of medicines are currently in development, targeting both afferent and efferent approaches to regulation of bladder function.[101] Non-pharmacological treatment approaches that involve electrical nerve stimulation are showing promise.[102] Studies of sacral modulation show improvements in continence, urinary retention, and spontaneous voiding.[103,104] Further research is needed to ensure the best match between the person with SCI and the treatment.

Upper extremities are key to both function and health. Healthy upper extremities are key to achieving functional independence, but are also relied upon for exercise, a key factor in promoting health. The considerable demands placed on the upper extremities come at a cost. There is a high prevalence (40–70%) of upper extremity pain in people with SCI, and the pain is often chronic in nature and worsens over time.[105–111] Rotator cuff tears are reported in 40–60% of persons, with SCI with higher rates among older persons who have had more years of wheelchair use.[112–115] These musculoskeletal issues limit function and interfere with efforts to increase activity to maximize fitness.

Given the valuable and limited resource that upper extremities are for people with SCI, guidelines to preserve upper extremity function have been developed.[116] These include recommendations for maintaining strength and range of motion, providing appropriate equipment, stress-reducing techniques for performing daily life activities, as well as environmental modifications. Determining how best to implement these recommendations while also considering recent exercise guidelines[86] remains a key challenge.

Discussion

General needs to support advancement of state of the science in health and spinal cord injury. Discussion participants identified a need to build infrastructure and capacity for large-scale, population studies (an ''All of Us''[117] for SCI). Biomarkers, including real-world data capture of level of physical activity, were considered important in order to understand individualized risk for health issues. Participants suggested that restructuring electronic health records would allow important indicators of complications to be captured and would facilitate population-based research. Participants acknowledged a need to give greater consideration to psychosocial factors, including mental health and social support, that contribute to health and the prevention of secondary complications. Participants supported the need to examine SCI from a systemic standpoint, considering the roles of the microbiome, immune function, and gene expression when studying development or prevention of health issues.

Activity guidelines implementation. Discussion participants acknowledged a tension between current guidelines for exercise and upper extremity preservation and uncertainty about the best way to implement these guidelines in individual persons with SCI. Additionally, further study into the role of electrically induced muscle activation is critical to expand the range of exercise options available to those with high-level injuries and reduce burden on the upper extremities.

As with all guidelines, user engagement is key to translating these guidelines into real-world practice.[118,119] Key stakeholders include people with SCI, clinicians, researchers, and others in the community that provide support on a day-to-day basis to persons with SCI, such as family and personal care assistants. Effective application of guidelines will require individualization, successful dissemination and implementation efforts, discovery and utilization of regenerative medicine interventions, and evidence to support policy change.

Meeting participants discussed anticipated challenges in guideline implementation among those with limited resources. Lack of transportation and insurance coverage limitations pose challenges to traditional in-person, hospital-based intervention programs. Options for managing these challenges include telerehabilitation or Web-based interventions. Partnering with community-based organizations (fitness centers, recreation programs, private businesses, etc.) may offer opportunities to make fitness interventions more accessible to persons with SCI without the constraints of relying on traditional healthcare channels. Cost-effectiveness was considered a critical element to be examined in future research. Rehabilitation researchers may benefit from partnerships with economists and members of other disciplines accustomed to evaluating cost-benefit ratios and assessing value of interventions. As part of the individualization of guidelines, participants expressed a need for more information on how age (at time of injury) and aging (changes over time post-injury) may affect implementation of guidelines.

As for many rehabilitation interventions that involve activity, optimal dosing for physical activity has not yet been determined. To what extent do levels of daily activity influence the required dose of exercise? Are there lesser levels of activity that still provide benefits, even if they do not meet the standard set forth in the recommendations?

Bladder interventions. With respect to bladder function, participants identified a need for more research into non-pharmacological approaches to the treatment of bladder dysfunction. Larger-scale studies of promising neuromodulatory approaches were encouraged, as were studies to assess whether using devices to provide sensory input on bladder urine volume can help people with SCI better manage bladder emptying in a manner that prevents negative consequences and achieves functional goals.

Session 6: Technological Facilitation, Prosthetic and Robotic Interventions and Therapies Across the Spectrum of Mild/Moderate/Severe SCI

Session Chair: Jose Contreras-Vidal, PhD
Panelists: Ann M. Spungen, EdD, Jennifer Collinger, PhD, and Grégoire Courtine, PhD
Discussion Facilitators: Vivek Pinto, PhD, Jennifer French, MBA

Identified scientific gaps

- Demonstrate how assistive devices can be used to promote independence and improve recovery.
- Incorporate user input, comparative effectiveness research, and data-sharing strategies to establish robust evidence for adoption of technologies.
- Improve the reliability and stability of devices and tissue interfaces to lower barriers to adoption and improve embodiment.
- Develop approaches for devices to adapt to changes in physical and developmental needs, abilities, and priorities of the user over the life span.

Brief review of the state of the science

A spectrum of devices designed to replace lost function have been developed and tested in various phases of clinical research, including different forms of brain-computer interfaces (BCIs),[120–124] and other technologies that create the potential for context-aware detection of user intent, as well as power transfer between persons with SCI and machines in changing environments.[125]

Among the few devices that have been approved for use outside of research are locomotor exoskeletons, which enable or assist walking-impaired persons in clinical settings with others approved for use in the community.[126] A variety of clinical/functional benefits have been reported in the literature, including reduced body fat mass and increased lean mass,[127] improved seated stability,[128] positive energy expenditure effects,[129–131] positive neuromuscular activation, and postural control.[132,133] Moreover, user feedback and observations of trainers suggest that exoskeletons serve as a new form of exercise, but slow walking speeds and the need for a companion limit their value as mobility devices at this time. Several factors limit the pool of potential users, including user interest and eligibility, need for extensive training, and availability of a companion when walking in the community.

Substantial research has been done to assess safety and feasibility of nonsurgical[106] and implantable BCI devices, which remain in research use only. Potential applications of these devices include computer access, communication, and restoration of limb function. As of February 2020, ~20 persons with amyotrophic lateral sclerosis or SCI have participated in safety-focused studies under FDA Investigational Device Exemptions, with duration of implantation ranging from 1 to 5 years.[134] BCI devices combined with functional electrical stimulation systems are capable of enabling grasp of objects and completion of functional tasks such as self-feeding.[121,135] BCIs tap into a natural motor command that is preserved after chronic SCI and requires little user effort. However, the motor command is highly context-dependent, creating challenges for the transition of BCI technology from the laboratory to real-world use.[136]

Electrical stimulation technologies seek to activate or modulate circuits that influence motor activity. Potential applications include locomotion, upper limb functional activity, blood pressure regulation, bladder management, and others. It has become evident that the circuitry of the spinal cord is a ''smart'' information-processing interface that requires a certain level of excitability to process information.[137] External electrical stimulation of spinal cord circuitry enables spinal circuits to process sensory information and residual signals from the brain.[138–140] Findings demonstrate an association between training and the specificity of stimulation provided, such that highly targeted stimulation is needed to provide facilitation of function without training.[54,141,142] Brain-controlled neuromodulation therapies increase use-dependent plasticity, but pose significant technological, practical, and ethical issues given the inherent risks of electrode implantation in the brain.[135,143,144]

Discussion

Discussion participants identified the key challenge of the coming decade as being to bridge the gap between innovations in research and making effective, affordable technologies accessible to persons with SCI in the ''real world.'' Several factors slow the pace of commercialization of innovative technologies. Most devices have specific user requirements, necessitating extensive screening and limiting the pool of potential users. Other challenges include risk, poor performance reliability, high cost, need for interoperability, and a business environment that tends to discourage data sharing, as well as small market size for many of these technologies slowing the process of development and regulatory approval.

Meeting participants encouraged technology developers to consider questions of marketability, cost, and reimbursement at the beginning of the development process rather than the end. They encouraged designers to consider how a given technology could be useful to populations beyond SCI to increase the size of the future market for the product, and to attract commercial partners. Participants also encouraged device developers to partner with the FDA early in device development. However, FDA approval should not be seen as the end goal—ongoing outcome assessment is needed to determine the value of a technology for health and function. Other recommendations were to promote and incentivize industry-university partnerships, device interoperability, standards, and the training of clinicians to prescribe new technologies.

Personalization of technology was considered critical for both effectiveness and adoption of technology. Meeting participants emphasized the need for technology to align well with the needs and priorities of end users. Devices and technologies need to be adaptable to be useful in real-word contexts, considering such factors as ease of donning/doffing, space requirements, and battery life. User training is critical for safe and effective use. When evaluating the cost-effectiveness of a technology, both training-related costs and device costs should be considered. Key questions include:

- Who are the best candidates for which device(s)?
- Who are responders and non-responders?
- Can the device be engineered to broaden their target population?
- How much training is needed to become proficient?
- What tests should be used to define proficiency?

Meeting participants identified areas in need of technological development. Upper extremities are critical for function, but are underaddressed in current technological interventions, which often focus on mobility. Few technologies have been developed for children, a population that may see considerable benefits of technology for both functional and social development.[145] Technologies capable of addressing secondary complications (not just mobility) were also encouraged.

Considerable discussion centered on the extent to which underlying mechanisms of neuromodulatory technologies must be understood before clinical or community application. A tension exists between the time and effort required to characterize underlying mechanisms and accelerating the movement of technologies into real-world application. Remaining questions include:

- Can early use of technologies be detrimental to the natural course of recovery?
- What dosing level is required to achieve and maintain benefits for health- or medical-related outcomes?
- Will/can these devices be used in the home/community as a form of exercise?
- Can these devices be used safely and effectively during inpatient rehabilitation and continued after discharge to prevent/mitigate secondary adverse changes?
- What is the optimal timing of use in the post-injury recovery period?

Meeting participants also discussed how some devices and technologies have the potential to be used for multiple purposes. For example, exoskeletons have the potential to be used as assistive technology to replace lost function, as diagnostic tools to assess the

state of the user, to promote motor recovery, and/or address secondary complications associated with a lack of weightbearing or upright movement. Work remains to be done to develop design approaches, training paradigms, and use protocols to accommodate multiple uses. Similarly, if different/multiple devices are required, what is the best way to address the potential challenge of lack of interoperability across devices?

Meeting participants identified research gaps pertaining to exoskeletons. More data are needed to understand the effect of exoskeleton-assisted walking on the activity of neural circuitry, muscle activation, movement patterns, and the role of sensory feedback in enhancing function. Training protocols need to be optimized to maximize efficiency of time and staff use. Enhanced portability and battery life would also aid community use. Meeting participants also expressed a need for improved mobility characteristics, including ability to stop quickly, walk faster, walk at variable speeds, and traverse non-level surfaces (stairs and ramps), preferably without the need for a companion. The ability to perform other activities while wearing exoskeletons (such as toileting) and improved aesthetics are other important considerations. Exoskeleton use imposes the risk of falls. Current exoskeleton systems use different strategies to mitigate the fall risk.[146] Importantly, this risk and others (e.g., user's errors) prevent users from becoming functionally independent because of the need for a trained companion during exoskeleton use. Research should address how to endow exoskeletons with dynamic stability and fall prevention features.

With respect to brain-computer interfaces, additional work is needed to determine the optimal end effector. Whereas current systems are typically used to control a robotic arm, users would prefer to use BCIs to restore function to their own arms and hands. It is not known whether BCI devices could both restore limb function and serve as assistive technology to replace lost functions. Additional work is needed to determine how best to combine BCI with other devices, and how that should that be done to enable FDA approval. Moreover, implantable BCI devices should remain operational and serviceable throughout the user's life. Stable recording technologies and robust decoding approaches are needed to deliver reliable and functional technology to potential users.

Several gaps in understanding were identified for electrical stimulation neurotechnologies. Engineering strategies must take advantage of spared circuits after SCI to improve neurological recovery while considering the user's current condition, capabilities, age, and level of risk acceptance. More data are needed to determine how to safely and effectively combine biological repair and engineering strategies to achieve desired results. The extent to which neurotechnologies can translate from clinical tools to assistive devices to support activities of daily living remains to be determined.

Additional Considerations

Although the scope of topics discussed in the SCI 2020 meeting was broad, it is important to note that there are other relevant research areas that may be considered critical to SCI that fell outside the scope of this conference. Social determinants of health, skin health, pain, respiratory function, spasticity, tendon and nerve transfers, bone density, psychological well-being, aging, children's needs, and the influence of healthcare coverage policies are among the many areas that deserve additional consideration. Problems related to any of these areas have negative consequences for physical functioning, quality of life, and participation, and therefore research related to these issues are also deserving of emphasis.

In addition, there are many issues that affect the pace of scientific discovery and the translation and clinical implementation of research findings that were not specifically addressed by the SCI 2020 meeting. These issues must be addressed to achieve improvements in the lives of SCI survivors and warrant discussion in future meetings and articles. Social determinants of health, including access to social support, insurance coverage, accessible housing, and other resources, affect the ability of people with SCI and other disabilities to access and utilize effective interventions. Although these represent policy concern, they also impact research, limiting the translational potential of findings from pre-clinical and clinical studies. In addition, personal biology drives heterogeneity in treatment response and is often not captured in pre-clinical studies, limiting generalizability of findings and complicating efforts to appropriately match persons and treatments. A myriad of secondary conditions (both those discussed in the meeting and many more) interact to affect function and quality of life.

Beyond the barriers that limit translation of pre-clinical and clinical SCI studies to the real-world healthcare of persons with SCI, the limited representation of persons with disability in studies of general healthcare has negative implications for persons with SCI. Several barriers to research participation for persons with disabilities exist, such as lack of knowledge about research opportunities, attitudes and concerns about research, geographical proximity to research centers, and access to transportation. These barriers limit the populations that contribute to, and benefit from, research studies and their findings. All these factors are part of the larger landscape to be navigated to enable formidable progress at all levels of discovery, translation, and implementation science to enhance function and quality of life for people with SCI.

Summary

In these proceedings of the SCI 2020 conference, we summarized the state of the science in each of six key domains based on input from thought leaders in each of these areas. Preservation and restoration of physical functioning, health, and wellness were the dominant themes of the conference, given that these represent priorities of persons with SCI and affect community participation. Scientific gaps were identified that are considered critical to advancing science in these domains. We have also identified a number of other important considerations that have implications for the conduct and translation of research, and that require consideration as part of forming and implementing a future research agenda.

The SCI 2020 conference was a valuable forum for interaction among clinicians, consumers, researchers, industry associates, and funding agency representatives. The discussions identified specific gaps in current knowledge and practice providing an opportunity for focused effort. Early specialized care, biomarkers that guide intervention, pooling of clinical data to answer key questions, technologies to augment impaired function or replace lost function, and emphasis on health and function across the life span are all salient targets for intensive research efforts that will be of tremendous value for people living with SCI.

Acknowledgments

The contributors to this article gratefully acknowledge Lyn Jakeman, PhD, for her vision and leadership in promoting SCI research. The NIDILRR is a center within the Administration for Community Living (ACL), Department of Health and Human

Services (HHS). The contents of this article do not necessarily represent the policy of NIDILRR, ACL, or HHS, and you should not assume endorsement by the federal government.

Funding Information

This article was developed with funding support from the NIDILRR (grant nos.: 90SI5014 [M.B., J.C.], 90SI5015 [J.C., L.R.M.]., 90SI5016 [E.F.F., C.R.K.], 90SI5018 [S.J.M.], 90SI5019 [Y.C., C.Y.-F.], 90SI5021 [C.S., R.Z.], 90SI5026 [J.Z.], 90SI5024 [M.J.M., M.S.-R.], and the Department of Neurology Dell Medical School, University of Texas at Austin [L.N.-H.].

The SCI 2020 Meeting was supported, in part, by the American Spinal Injury Association, Craig H. Neilsen Foundation, Texas Institute for Rehabilitation and Research, Christopher & Dana Reeve Foundation, NASCIC, NIDILRR, Praxis Spinal Cord Institute, United Spinal Association, Wings4Life, Blusson Integrated Cures Partnership, and the International Collaboration on Repair Discoveries.

Author Disclosure Statement

Grégoire Courtine is founder and shareholder of ONWARD, a company involved in the development of treatment for SCI. Dr. Courtine also holds several patents in relation with some of the concepts presented in this article. Edelle Field-Fote serves on the medical advisory board of ONWARD, and as a consultant for Greenwich Biosciences. James Guest is a consultant to AbbVie and has an ownership interest in Aceso Therapeutics. Michael Kennelly has received grant support for research pertaining to neuromodulation from Axonics, FemPulse, and EBT Medical. J. Marc Simard holds a US patent (#7,872,048), ''Methods for treating spinal cord injury with a compound that inhibits a NC (Ca-ATP) channel.'' Dr. Simard is a member of the board of directors and holds shares in Remedy Pharmaceuticals and is a paid consultant for Biogen. Robert Wudlick receives income from AbiliTech Medical Inc., GUSU2Cure Paralysis, Mayo Clinic, and Adapt Design Works.

SCI 2020 Working Group

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Supplementary Material

Supplementary Material Survey Results

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