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Translational Research in Spinal Cord Injury: A Survey of Opinion from the SCI Community

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Abstract

Much like our colleagues studying neuroprotection for acute stroke, we in the spinal cord injury (SCI) community have witnessed the preclinical emergence of numerous promising neuroprotective and neuro-regenerative treatments that have then disappointingly failed to demonstrate convincing efficacy in clinical trials. In contrast to the stroke field, the SCI community lacks guidelines to steer the preclinical development of therapies and maximize their chance of success prior to translation into expensive and laborious clinical trials. We conducted a survey of the SCI research community to garner perspectives on the question of what preclinical evidence was required before translating an experimental treatment into clinical trials. The opinions of the 324 respondents about what constitutes necessary preclinical evidence before moving to human SCI trials revealed strong support for the demonstration of efficacy in large-animal models, cervical injury models, and for independent replication of promising results. Marked differences exist between the sentiments of the respondents and the translational experience of our field. A framework for guiding the preclinical development of novel therapies prior to human translation would be helpful for ensuring clinical success. Greater dialogue on this issue is necessary to improve our chances of successfully bringing effective treatments to patients with this devastating injury.

Key words: secondary insult; spinal cord injury; surgery

Introduction

The fewer the facts, the stronger the opinion.
Arnold H. Glasow

The suffering from lifelong paralysis following a severe spinal cord injury (SCI) has been recognized for centuries, and has sparked intense global research efforts over the past four decades to establish treatments for this catastrophic injury. While tremendous advances in the medical, surgical, and rehabilitative care have been made for an injury that was inescapably fatal just 100 years ago, a specific treatment that improves neurologic recovery after complete SCI has remained elusive. This is, of course, not for the lack of trying. Over the past three decades, a handful of promising therapies have emerged from the laboratory, and entered into prospective randomized clinical trials (reviewed by Tator, 2006). All were deemed to provide insufficient evidence of efficacy (and subsequently abandoned), with the lone exception of methylprednisolone (Bracken et al., 1990, 1997), which initially gained widespread acceptance as the "standard of care" for acute SCI in the 1990s, but more recently has been abandoned by many institutions due to skepticism about its efficacy and mounting concern about its side effects (Hurlbert and Hamilton, 2008). Even fampridine (4-aminopyridine), a drug that appeared promising in both preclinical and early clinical studies for incomplete SCI paralysis (Cardenas et al., 2007; Grijalva et al., 2003; Hayes, 2007), disappointingly failed to demonstrate convincing neurologic benefit in large-scale human SCI trials, although fampridine's efficacy in multiple sclerosis (Goodman et al., 2009) has the FDA currently assessing it for approval for this indication.

The justifiable despair over the barren landscape of therapeutic options available for SCI today is mitigated by the almost palpable hope from clinicians, scientists, and patients that effective treatments are "around the corner." This hope is fueled by the growing list of potential treatments for SCI that show promise in the laboratory setting, and incited further by media reports of therapeutic success stories in patients who have received as-yet unproven "treatments" (Dobkin et al., 2006; Layden, 2007; PBS, 2004). With a small handful of promising therapeutic candidates now embarking upon clinical trials, and many more vying to follow suit in the near

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future, optimism is not unwarranted. However, as a growing number of experimental therapies emerge "from the bench" and seek to be translated "to the bedside" in human clinical trials, the SCI community would be remiss not to heed the lessons of our close but much larger neighbors: the researchers in stroke

> *A common perception of neuroprotection research is that everything works in animals but nothing works in people.*
> O'Collins et al., 2006

This sentiment is the opening sentence of an exhaustive review of 1,026 promising experimental drug treatments for stroke, of which 114 went on to some form of human investigation, and none were found to be effective (with the sole exception of the thombolytic therapy, tissue plasminogen activator) (O'Collins et al., 2006). More than illustrating the collective frustration of the stroke community, the review highlights the inconsistent (and arguably occasionally inadequate) scope of preclinical experimentation and substantiation performed on potential treatments prior to their plunge into human trials. In response to the repeated failures of their clinical trials, the stroke community has developed recommendations regarding the evidentiary milestones that a potential therapy should meet prior to being translated into humans (Fisher et al., 2007, 2009). As O'Collins and associates (2006) point out, these Stroke Therapy Academic Industry Roundtable (STAIR) recommendations have not been uniformly adhered to, but the mere fact that they actually exist is noteworthy to the SCI community, within which such formal guidelines do not even exist. In this context, it could be argued that what operationally distinguishes the SCI and stroke communities is that the former needs only another decade (or two) of failed clinical trials and a few thousand more ineffectively treated patients before arriving at the latter's current level of frustration.

While such frustration is obviously undesirable, the reality is that a roadmap for the preclinical development and substantiation of experimental therapies in SCI is poorly defined. Because no experimental neuroprotective or neuro-regenerative SCI therapy has emerged on the other side of clinical evaluation with convincing efficacy, a clear example of the extent of preclinical evidence required to successfully translate a therapy into an effective treatment is lacking. In the absence of such "data" within the SCI field, we are forced to rely to some extent upon the opinion and perspectives of its members. We therefore undertook this survey in an attempt to garner the community's perspective on "the scientific evidence that should be demonstrated in preclinical studies prior to being translated into human trials." Additionally, acknowledging that scientific discovery is ultimately a human exercise, we sought to characterize what the community's perception of bias was, and this bias might influence the process of translation.

Methods

A 63-item questionnaire was developed to survey the opinion of clinical and scientific members of the SCI community on (1) the extent of preclinical evidence necessary to justify translating a potential therapy into a clinical trial, (2) the methodology and outcome measures widely utilized in animal-based research to generate such evidence, and (3) the biases that influence the interpretation of that evidence. The questions were worded so as to present an "unambiguous" statement, to which the respondents could provide their extent of agreement or disagreement as: 1, Strongly Disagree; 2, Mildly Disagree; 3, Neither Agree Nor Disagree; 4, Mildly Agree; 5, Strongly Agree; or 6, Do Not Know Enough to Offer an Opinion.

The three-page questionnaire was distributed at four neuroscience and clinical conferences in November/December 2008 (the Canadian SCI Solutions Network Annual Meeting and Toronto Rehab Network SCI Precourse Meeting in Toronto, Ontario; the Society for Neuroscience Annual Meeting in Washington, DC; and the Cervical Spine Research Society Meeting in Austin, TX). Additionally, the Microsoft Word version of the questionnaire was distributed via e-mail to spine surgeons, clinicians, scientists, regulatory officials, and industry representatives. The questionnaire and study design was reviewed and granted approval by our institutional Behavioral Research Ethics Board.

Results

A total of 324 responses were received between November 2008 and January 2009, representing just under 50% of approximately 700 questionnaires distributed. One hundred and five respondents classified themselves as "Scientific Principal Investigators" running a laboratory-based research program, 34 as "Clinician Scientists" (clinicians who additionally operate a laboratory-based research program), 76 as "Spinal Surgeons", 20 as "Clinicians" (nonsurgical), 69 as "Trainees" (graduate student, postdoctoral students, research associates), and 20 as "Others" (industry or research foundation representative, clinical research assistants, regulatory officials; Fig. 1). SCI patients were not asked to participate.

Out of those respondents who described themselves as actively conducting SCI research, 43.1% reported involvement in studies on acute neuroprotection (pharmacologic treatments given as early as possible to minimize secondary injury), 39.2% on transplantation-based therapies (cell/biomaterial strategies to be directly transplanted into the cord), 43.1% on axonal growth or sprouting-promoting therapies (e.g., anti-Nogo Ab or chondroitinase ABC to address inhibitory CNS), and 36.6% on physical rehabilitation strategies (e.g., locomotor training). A total of 30.2% reported conducting clinical research in acute SCI patients, 31.47% in subacute/chronic patients, and 21.12% reported doing "other" research (such as chronic/ neuropathic pain, gene therapy, neuroplasticity, SCI circuits, etc).

Demonstrating efficacy in animal models of spinal cord injury—how much is enough?

It is difficult to argue against the need for some demonstration of neurologic efficacy in an *in vivo* animal model of SCI, prior to testing a potential therapy on human patients. But how much is enough? Does the animal species utilized for such experiments matter? Does the method by which the SCI is experimentally induced matter? Does the timing of the therapy matter? Is the "burden of proof" different between a noninvasive therapy (such as a drug), or an invasive therapy (such as a cell transplant)? We began our questionnaire with an attempt to address these issues of preclinical efficacy.

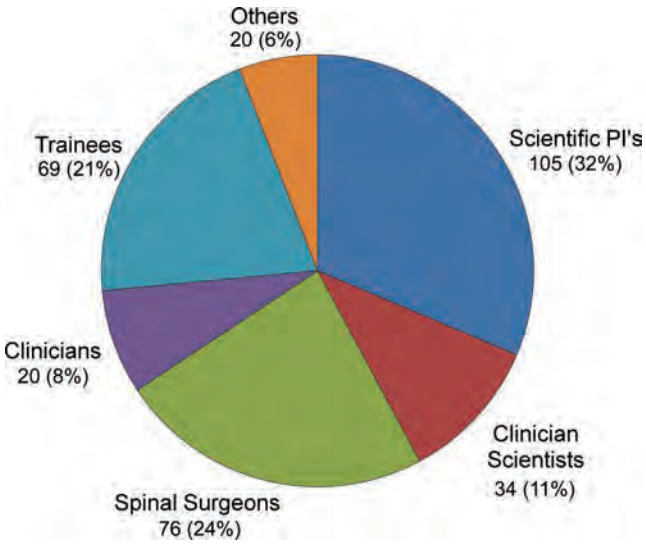

FIG. 1. Classification of survey respondents. Of 324 respondents, approximately one third were scientific principal investigators running research laboratories in SCI research, and a third were clinicians, clinician scientists, or spinal surgeons (orthopaedic and neurosurgical) who treat SCI patients. Trainees included graduate students and postdoctoral fellows in scientific laboratories, while representatives from industry, research foundations, and regulatory bodies made up the "others." Color image is available online at www.liebertonline.com/neu.

First, we asked about the animal species used to model SCI. Under the tacit assumption that SCIs in higher-order animals (e.g., primates) would be more representative of the human condition than lower animals (e.g., rodents), we asked the community whether a therapy's demonstration of efficacy in a rodent model was sufficient to proceed to clinical trials, or whether a large-animal or primate model was necessary. For a noninvasive pharmacologic therapy, the minority (41%) agreed that efficacy in a rodent model was adequate, while the majority (54%) did not agree that this was sufficient to proceed to a clinical trial. The majority (64%) felt that efficacy in a large-animal model (e.g., cat/dog/rabbit/sheep) was necessary, while only 46% felt that primate evidence was needed. The majority (64%) also felt that the demonstration of efficacy in an animal model of cervical-cord injury was needed if the therapy was to be applied in patients with cervical paralysis. In comparison, the SCI community appears to view the burden of proof slightly differently for an invasive cell-transplant therapy. Given the additional potential risk, only 20% felt that efficacy in a rodent model was adequate, while 75% disagreed that this was sufficient to proceed to clinical trial. A large majority agreed that evidence of efficacy in a large-animal and primate model was necessary (77% and 74% respectively), and confirmation in a cervical model was also needed (75%). Nearly 50% of the respondents for each of these three questions "strongly agreed" with the need for efficacy data in these cervical or higher-order animal models (Fig. 2).

The opinions regarding the need for efficacy data in these animal models paralleled the sentiments concerning the need for safety data prior to moving to clinical trials. For noninvasive drug therapies, 56% disagreed with the statement that the demonstration of safety in rodent models was sufficient (36% agreed), while 70% and 57% felt that large-animal and primate models were necessary respectively. For invasive cell-transplant therapies, 73% disagreed that safety in rodent models was sufficient (23% agreed), while 80% and 76% felt that large-animal and primate models were necessary (Fig. 3).

Next, we inquired about the types of injury models utilized in experimental SCI research to establish the efficacy of new treatments. It is widely acknowledged that human SCIs occur with substantial variability, and as such differ a great deal from the controlled experimental conditions of the laboratory. Given that a potential SCI therapy would need to work for the 26-year-old intoxicated Caucasian male who drives his car off a 25-m cliff as well as the 62-year-old diabetic Asian female who falls off her stepladder, one could reasonably conclude that a single, narrowly controlled experimental paradigm is unlikely to suffice as a valid testing ground. With respect to the method by which SCIs are experimentally induced, the majority of respondents (72%) felt that the contusion injury model was the most clinically relevant model of human SCI (as compared to models in which the spinal cord is squeezed/compressed, or sharply cut in part or in entirety). This reflects the awareness that most human SCIs are caused by very sudden yet blunt, nonpenetrating trauma, for which a number of "impactor" devices have been developed to impart such an injury to the rodent spinal cord (e.g., the Infinite Horizon, Ohio State University, New York University, or generic weight drop). Recognizing the variability of human injuries, however, the majority of respondents also felt that a therapy should demonstrate efficacy in different injury models (60%) and in different injury severities (61%) prior to entering clinical evaluation (Fig. 4).

Finally, one of the most puzzling issues facing both clinical and scientific investigators is that of extrapolating the time window of efficacy for a therapy in an animal model with the time window of efficacy in the human condition. This is particularly relevant for acute neuroprotective therapies, which aim to attenuate pathophysiologic processes that may only be relevant very soon after injury. For a therapy shown to be neuroprotective when given 1 h post injury to a rat, asking individuals to predict how long after a human injury such a treatment would remain effective would be highly speculative. Therefore, we framed the question in a more operational manner that reflected the reality of inclusion and exclusion criteria that are being applied to SCI patients in clinical trials. For a treatment that would be administered to human SCI patients up to 12 h after their injury, we asked what the community's evidentiary expectations were in terms of the treatment's time window of efficacy in animal studies (i.e., should the treatment's efficacy be demonstrated when administered with a delay of 1, 4, 8, 12, or 24 h after injury?). Interestingly, over half of the respondents (57%) felt that preclinical efficacy with an intervention delay of 12 h or more was necessary, and an additional 24% felt that efficacy after a delay of 6 to 8 h was necessary. For a treatment to be given to patients up to 5 days after injury, preclinical efficacy with a delay of 5 days or more was felt to be necessary by 59% of respondents, and a delay of 1–3 days by an additional 38%. For a treatment to be administered to chronic SCI patients 18 months post injury, preclincial efficacy with a delay of 6 weeks to 3 months was deemed necessary by 52% of respondents, and a delay of 12 months or more by 44% (Fig. 5)

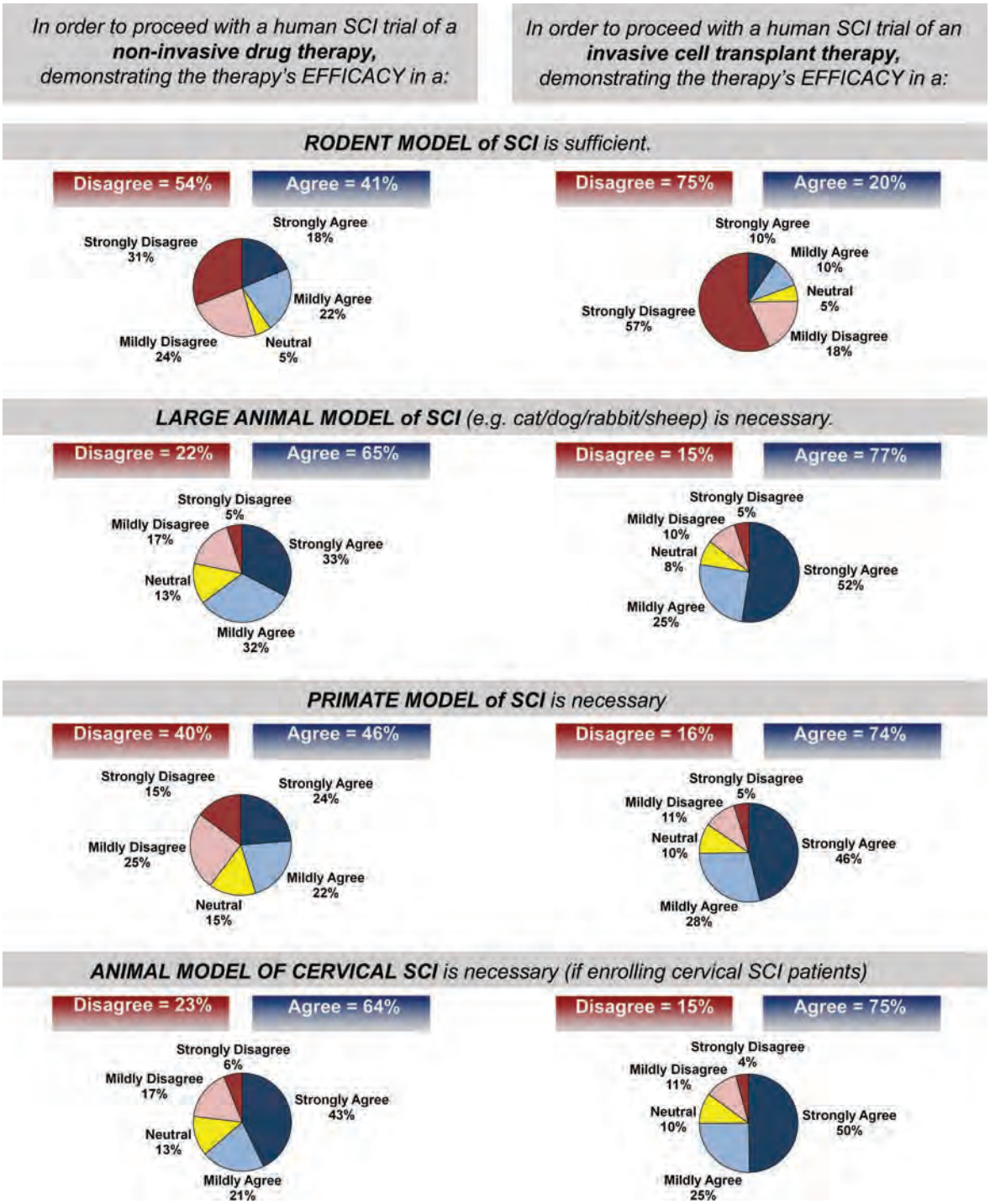

FIG. 2. Animal species used to demonstrate efficacy in experimental SCI research. In the context of a noninvasive drug therapy or an invasive cell-transplant therapy, respondents were asked to provide their opinions about the adequacy of preclinical efficacy in rodent models of SCI, and the necessity for demonstrating efficacy in large-animal, primate, or cervical SCI models. In general, for the more invasive cell-transplant therapy, there was stronger support for large-animal and primate data. Color image is available online at www.liebertonline.com/neu.

What actually constitutes "clinically meaningful efficacy" in animal models of spinal cord injury?

While much of our questionnaire addressed the settings in which the demonstration of efficacy was felt to be important prior to clinical trials, the definition of what actually constitutes "clinically meaningful efficacy" is still somewhat undefined. Animal research allows for the application of a myriad of histologic, biochemical, physiologic, and behavioral outcome measures, and in many instances an investigator will report on a number of these in a single paper. Given that human SCI is fundamentally defined by its *functional* deficits,

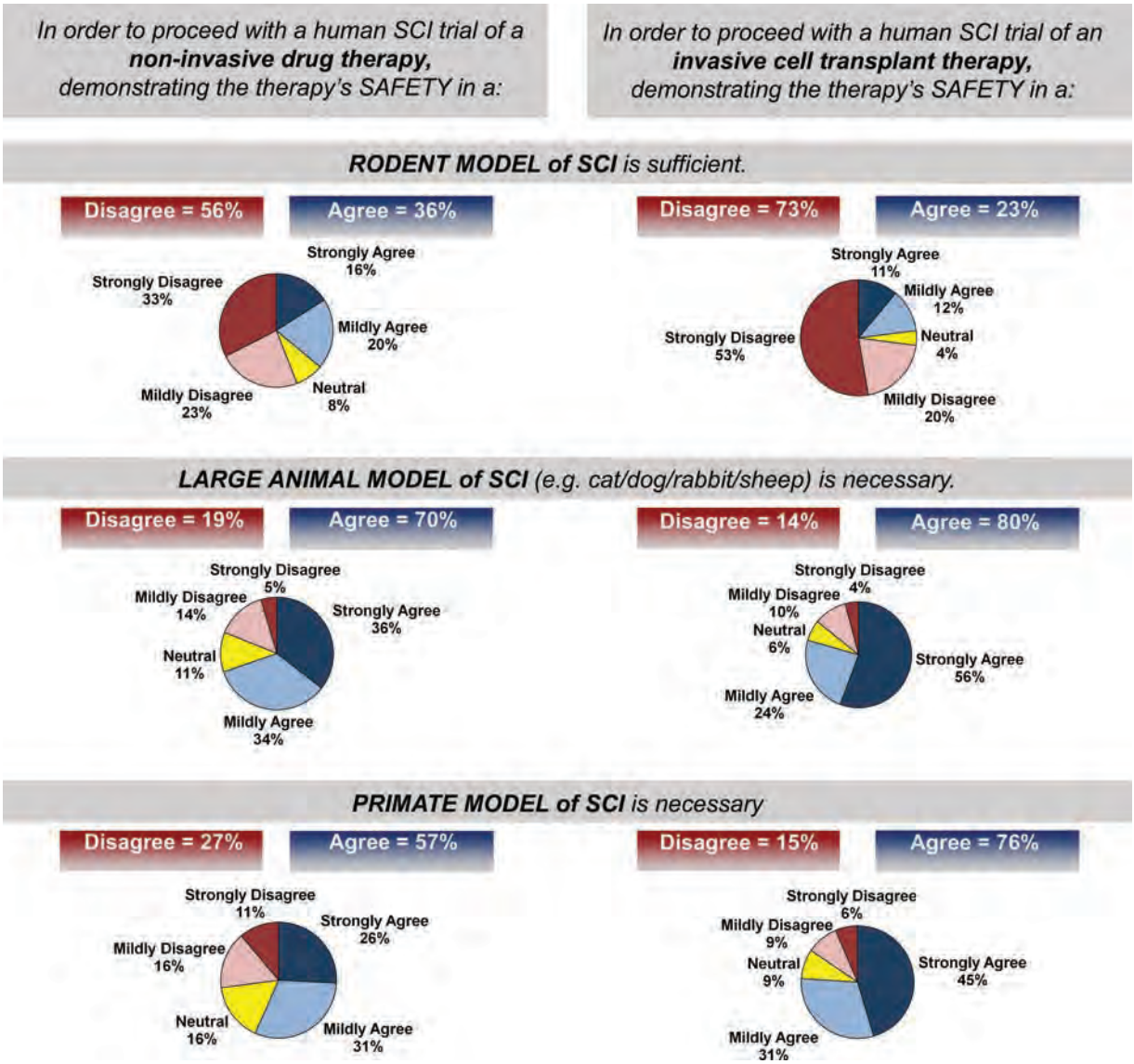

FIG. 3. Animal species used to demonstrate safety in experimental SCI research. In the context of a noninvasive drug therapy or an invasive cell-transplant therapy, respondents were asked to provide their opinions about the adequacy of preclinical safety data in rodent models of SCI, and the necessity for demonstrating safety in large-animal, primate, or cervical SCI models. Similar to the question of efficacy, there was stronger support for large-animal and primate data for invasive cell-transplant therapies. Color image is available online at www.liebertonline.com/neu.

substantial importance is typically placed on the impact that a therapy has on functional/behavioral outcomes in the animal models. In keeping with this, the majority of respondents (59%) were of the opinion that improvements in nonbehavioral outcomes (e.g., histologic/biochemical/physiologic paralogic parameters) without any behavioral recovery *did not* represent "promising, clinically meaningful efficacy." With respect to behavioral recovery in rodent models of SCI, a therapy's ability to promote plantar weight-supported stepping (while the control animals still drag their hindquaters), or its ability to promote coordination between the forelimbs and hindlimbs (while the control animals make only uncoordinated steps) were considered by most respondents (75% and 72%) to be a demonstration of clinically meaningful efficacy. Interestingly, while there is often a heavy emphasis placed on the restoration of hindlimb locomotor function (with the obvious hope that a therapy that facilitates walking in the animal might do the same in humans), the majority of respondents (66%) also felt that improvements in nonlocomotor outcomes, such as reductions in neuropathic pain and autonomic dysreflexia, would by themselves be indicators of clinically meaningful efficacy (Fig. 6).

Perceptions of bias within the spinal cord injury community

While rigorous peer review remains the cornerstone of scientific progress and dissemination, it would be naïve to think that bias does not play some role in how information about "promising new therapies" is brought forth by the scientific community. The final section of the questionnaire attempted to characterize some of this bias. Responses to these

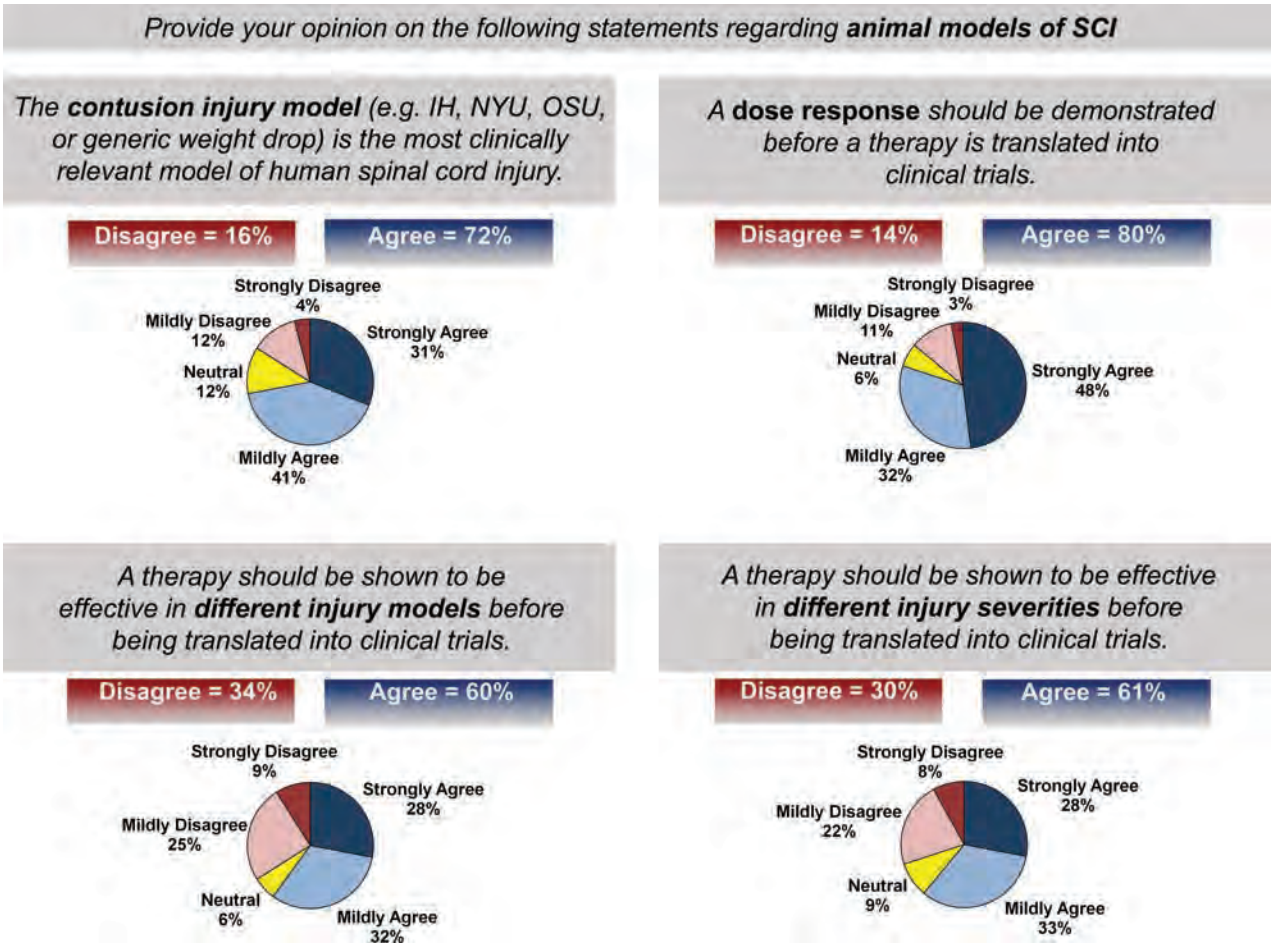

FIG. 4. Injury models utilized in experimental SCI research. Given the variable nature of human SCI, respondents were asked about the types of injury models they felt were most representative and to what extent efficacy should be demonstrated. There was agreement that contusion models were most clinically relevant, and that efficacy should be shown in different injury models, different injury severities, and that a dose response should be demonstrated. Color image is available online at www.liebertonline.com/neu.

inquiries were surprisingly revealing. For therapies whose efficacy had been demonstrated by a single laboratory, 94% of respondents agreed that replication of that efficacy by an independent laboratory was necessary before moving to clinical trial; 76% "strongly agreed," making this the most unanimously agreed-upon statement in the entire questionnaire. Such strong sentiments about the perceived need for independent replication infer a degree of skepticism about promising results that have been demonstrated by only a single laboratory.

The responses to other questions within this section shed some light on the basis of this perception. A total of 84% of respondents felt that scientists are reluctant to publish their own negative results on a therapy, a number that increased to 87% if the scientists had a "vested interest" in the specific therapy ("vested interest" meaning that they had commercialized the therapy or that it was a key focus of their research program for which they were known for). This reluctance to publish may be influenced to some extent by the fairly strong perception (81%) that high-impact journals tend to reject submitted papers that describe the negative results of a specific therapy.

Outside of the actual publication bias, the questionnaire revealed interesting sentiments about the community's perception of the fidelity of the published research, which undoubtedly contributes to the aforementioned skepticism around promising results. A total of 31% of respondents agreed with the statement that scientists commonly adjust their results to achieve statistical significance when such significance is not initially reached in the experiment (only 44% disagreed, and 25% remained neutral). A total of 43% of respondents agreed with the statement that such "negative" experiments are repeated until they reach statistical significance. Finally, the community was divided about the blinding of staff (trainees/technicians/associates) who were generating data for these scientific studies, with 41% disagreeing and 42% agreeing with the statement that these individuals were rigorously blinded (Fig. 7).

Discussion

In summary, the questionnaire provided an extensive array of opinions from the SCI community on the extent of preclinical evidence necessary before translating a potential

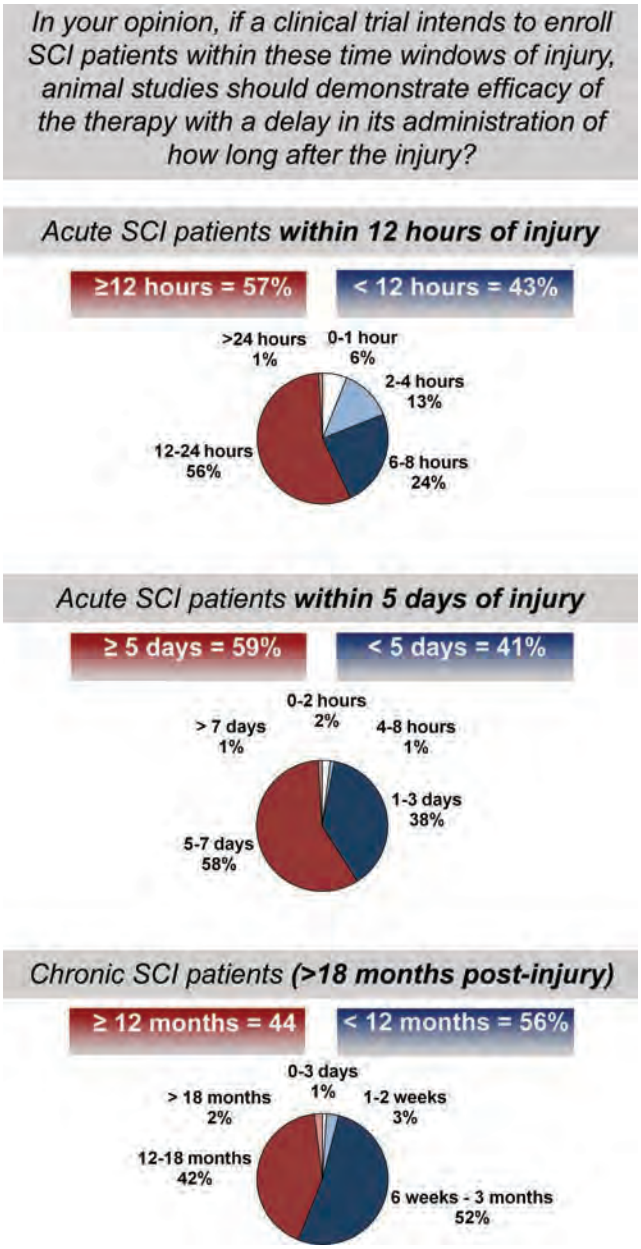

FIG. 5. Time window of intervention in experimental SCI research. The recruitment of SCI patients for clinical trials can occur at different times post injury, and experimental treatments can be administered to animals at different times post injury. Here, the respondents provided their opinion about the time window of efficacy that was necessary to demonstrate in preclinical experiments for a therapy that would be administered to humans at various times post injury (12 h, 5 days, or 18 months). Color image is available online at www.liebertonline.com/neu.

therapy from the laboratory into clinical evaluation. It was evident that a therapy's promotion of behavioral recovery (either in locomotor performance or other functional outcomes) was viewed as the most important representation of "clinically meaningful efficacy." Demonstrating such efficacy in rodent models alone was not felt to be sufficient to move a therapy to clinical trials, and much of the field opined that evidence in large-animal and/or primate models was necessary, particularly for invasive cell-transplantation treatments. Contusion injury models were considered to be the most clinically relevant injury models, and the demand for efficacy in models of cervical SCI was high if the therapy was to potentially be administered to patients with cervical SCI. There was a strong sentiment that a therapy's efficacy be demonstrable in different injury models and injury severities, in recognition of the variances in human injury. The majority felt that therapies being applied to humans within an acute or subacute time frame should be found to be efficacious within similar time windows post injury in animal models of SCI. Most importantly, the SCI community overwhelmingly supported the need for the independent replication of claims of promising efficacy prior to translating a therapy into a clinical trial.

With that being said, what is actually occurring in spinal cord injury research?

For those of us performing laboratory-based experimental research in SCI, the evidentiary landmarks that are seemingly required (as per the opinion of none other than ourselves) before translating a "promising" therapy into a clinical trial of human SCI appear markedly different from the current reality. For an outsider with little familiarity with the detailed technicalities of the scientific field (which, incidentally, may include some clinicians who actively treat SCI patients), the lack of resemblance between the opinion of what apparently "should" be demonstrated in preclinical models prior to clinical translation and what is actually published to support that translation may be a bit surprising.

Examples from the history of human SCI translation to demonstrate this point are not isolated, but for the sake of demonstration, let us look at a treatment that received quite a lot of scientific and media attention at its inception: the transplantation of activated autologous macrophages. This therapy emerged from the exciting, pioneering work of Professor Michal Schwartz on the immunologic response to SCI (Hauben et al., 2000a, 2000b; Schwartz, 2000; Schwartz and Yoles, 2006; Yoles et al., 2001), and consisted of the harvesting of blood-borne monocytes, their *ex-vivo* stimulation/activation to macrophages by exposure to autologous peripheral nerve, and their subsequent transplantation into the spinal cord. In July 1998, a widely heralded study was published by Dr. Schwartz and colleagues in *Nature Medicine*, describing the substantive locomotor, histologic, and electrophysiologic improvements in rodents transplanted with activated autologous macrophages after a complete thoracic transection model of SCI (Rapalino et al., 1998). No further preclinical efficacy data on this treatment was published before July of 2000, when the first of eight human patients with SCIs received this cell-transplant treatment in an FDA-sanctioned human Phase 1 clinical trial launched in Israel by Proneuron Biotechnologies Inc. (Weizmann Science Park, Ness-Ziona, Israel) (Knoller et al., 2005). This safety study (the results of which were published in September 2005) led to the initiation in 2003 of a subsequent Phase 2 clinical trial in Israel and five American institutions (the "Procord Clinical Trial"). After enrolling 50 patients, this trial was unfortunately suspended, reportedly due to financial reasons (*not* for efficacy or safety reasons).

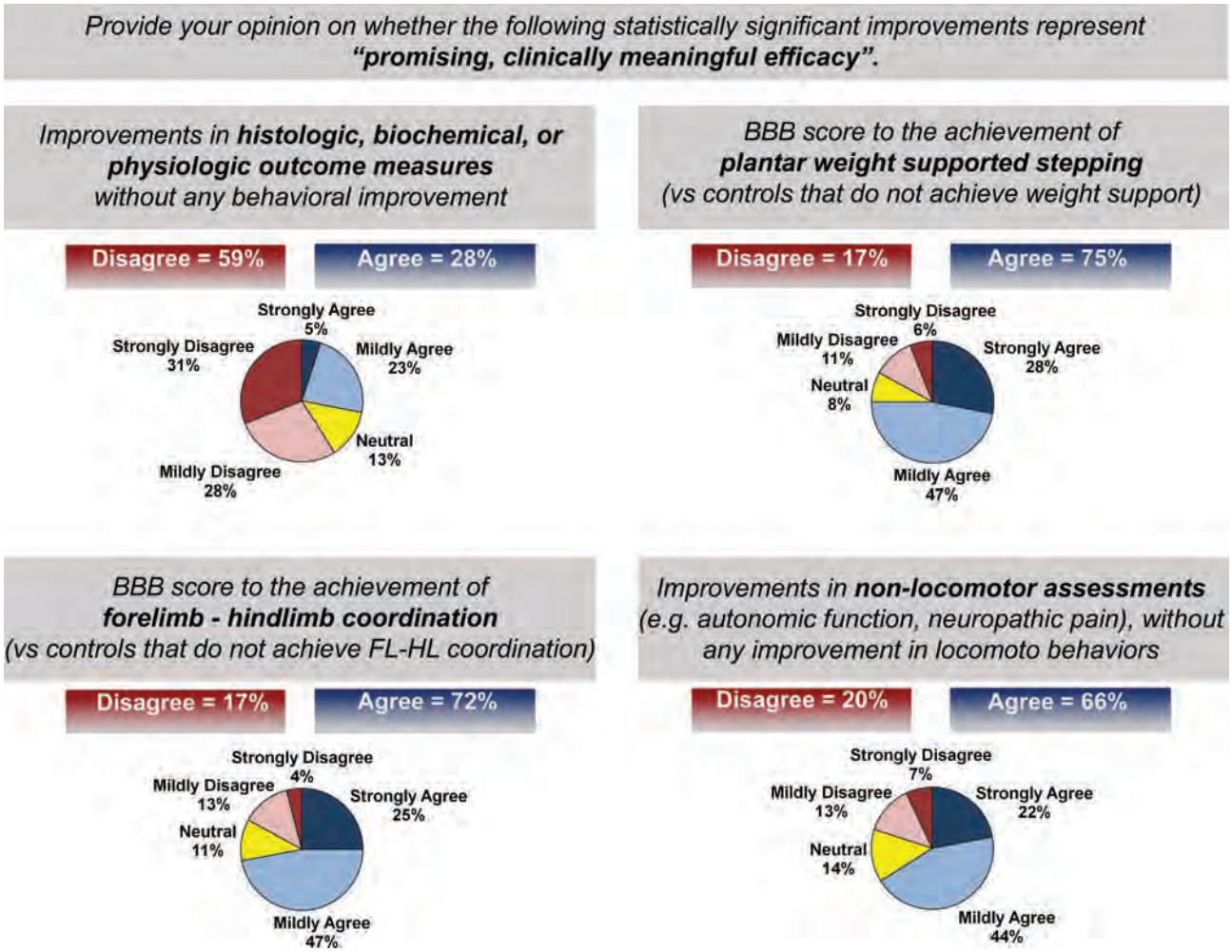

FIG. 6. Defining "promising clinically meaningful efficacy." A myriad of outcome measures are utilized in preclinical experiments of potential SCI therapies. Here, the respondents provided their opinion on what they believed to represent "promising, clinically meaningful efficacy." In general, improvements in behavioral outcomes were considered to be most important, and improvements both in locomotor function (as evidenced by specific changes in the BBB score) and in nonlocomotor function were considered to be relevant. Color image is available online at www.liebertonline.com/neu.

It would obviously be untrue to suggest that the preclinical development and refinement of this therapy ended after the 1998 publication of the promising results in a transection model of SCI. Proneuron investigators, in fact, published the positive results of their cell-transplantation intervention in a rat thoracic contusion SCI model in 2003 (Bomstein et al., 2003), and further time-window experiments were described in a review article published in 2006 (Schwartz and Yoles, 2006). While these emerged in the literature *after* the conclusion of enrolment in the Phase 1 clinical trial, we would speculate that the study sponsors actually had this data and quite a lot more supportive but unpublished "in-house" evidence when they translated this treatment into human patients. Nonetheless, it is apparent that the peer-reviewed efficacy evidence available at the time that this treatment traversed the translational gap from bench to human bedside consisted of the single study published in 1998 (Rapalino et al., 1998). Interestingly, in keeping with the opinions expressed in this questionnaire regarding animal models and independent replication, an extramurally funded large-animal (beagle) study of this macrophage transplantation paradigm was published in November 2008 (Assina et al., 2008). These investigators reported no histologic or locomotor benefits in the four macrophage-transplanted animals compared to the two control animals, although in fairness to Proneuron, it could be justifiably argued that the small group sizes and subtle differences in macrophage preparation from their proprietary technology may have contributed to this study's negative findings.

Given the results of the survey, it may be tempting to vilify the autologous macrophage treatment on the basis of the extent of published preclinical efficacy available prior to entering human evaluation. This would be unfair and unwarranted. First, it is hardly unique in this regard. Despite considerable progress in the SCI field since 1998, similar concerns regarding the extent to which preclinical evidence actually supports human translation were voiced as recently as January 30, 2009, in a *Science* news feature that covered the much-publicized FDA approval for Geron's clinical trial in oligodendrocyte progenitors derived from human embryonic stem cells (hESCs) (Couzin, 2009). The published behavioral efficacy data for this specific hESC-derived therapy consists of

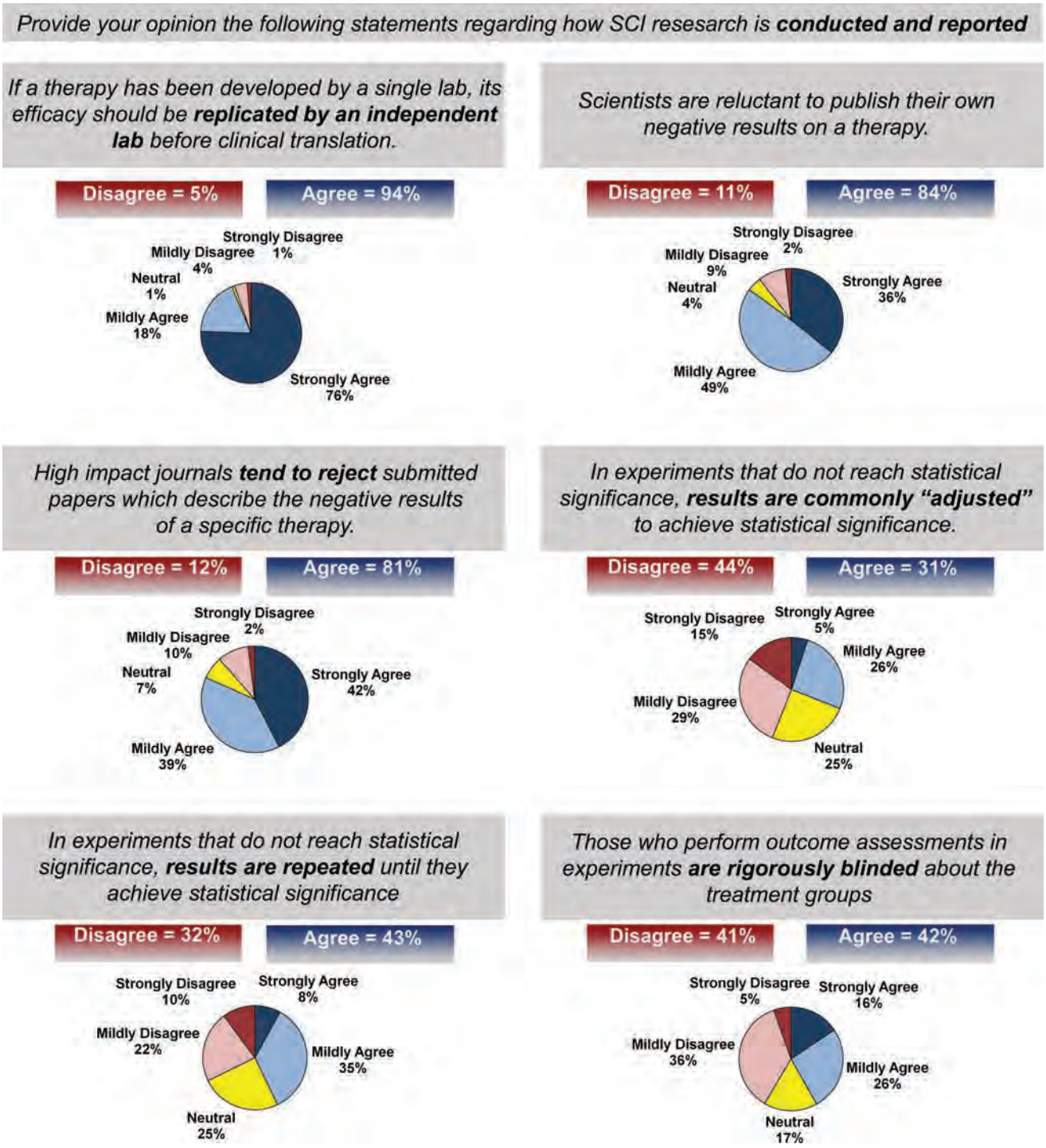

FIG. 7. The perception of bias. Here, respondents provided their opinion about the biases that influence the perception of "promise" in SCI research. There was very strong support for the independent replication of a potential therapy's efficacy, and a strong perception that negative results are not published – either by the reluctance of the investigators or rejection by high-impact journals. Respondents were divided about the veracity with which experimental data are generated and handled. Color image is available online at www.liebertonline.com/neu.

a single study, reported in 2005 (Keirstead et al., 2005), although other independent labs have supported the "proof of concept" behind the remyelination strategy that Geron is pursuing with their oligodendrocyte progenitors (Hofstetter et al., 2005; Karimi-Abdolrezaee et al., 2006). Again, we suspect that more extensive "in-house" safety and efficacy data exists for this technology that will hopefully be made available in the future (particularly given that their FDA submission was reported to be 21,000 pages in length). Such was also likely the case for Cethrin®, a proprietary Rho antagonist (currently licensed by Alseres Pharmaceuticals, Inc., Hopkinton, MA), which, in 2005, entered into what is now a

complete, 37-patient human Phase I/IIa trial after behavioral efficacy was reported in a single publication in 2002 (Dergham et al., 2002). This study reported that the application of C3 transferase (a Rho antagonist derived from *Clostridium botulinum*) to the spinal cord at the time of injury promoted improved locomotion and increased axonal regeneration in a mouse dorsal hemisection model of SCI. Further supportive behavioral efficacy data for the proprietary Cethrin treatment in a rat contusion injury model with time windows of efficacy was published last year by the authors of the original findings (Lord-Fontaine et al., 2008).

Second, it is hard to criticize well-meaning scientists and clinicians for not adhering to a "roadmap" of preclinical evidentiary milestones when such a roadmap does not actually exist in the SCI field, and additionally, when the means to achieving some of the proposed landmarks are not even well established. For example, the questionnaire reveals strong support for demonstrating a therapy's efficacy in large-animal models of SCI and even in primate models, particularly for cell-transplantation therapies that incur addditional risk. However, large-animal or primate SCI models with precisely defined biomechanical contusion injury characteristics and validated behavioral and histologic outcome measures are not readily available, although descriptions of such models exist (Iwanami et al., 2005), and primate studies in noncontusive SCI models (ie., partial transection injuries) have been previously published (Freund et al., 2006; Rosenzweig et al., 2009). Even if these models became widely available and accessible, the costs of doing such experiments would also undoubtedly be prohibitive for the vast majority of academic researchers – although, as succinctly pointed out by Edgerton and colleagues, such primate studies are still only a fraction of the costs of a human clinical trial (Courtine et al., 2007). Even the costs of replicating promising rodent studies may be beyond the capacity of many scientists, whose primary focus is in discovery-based mechanistic research. To address this need, the NIH has initiated a grant-contract program (the "Facilities of Research – Spinal Cord Injury") to fund the replication of certain SCI studies and independently confirm the promise of specific therapies (Pinzon et al., 2008; Steward et al., 2008). The results of this survey further substantiate the need for such programs, and we would implore the editorial review boards of prominent peer-reviewed journals to acknowledge the importance of the data that such replications generate – even when negative. Ultimately, the devastation of this injury and the desperate need for effective treatments has served (and will continue to serve) as strong motivation to move what appear to be promising therapies purposely from bench to bedside, and we would be wrong to discourage such an initiative.

Those who cannot remember the past are condemned to repeat it.
George Santayana

That being said, there are important considerations that are difficult to ignore. The first is the frustration that our more-seasoned stroke colleagues have suffered in their search for effective neuroprotective therapies (as painstakingly outlined by O'Collins et al., 2006). In an effort to limit the conducting of clinical trials to treatments that have a decent chance of being effective, the STAIR guidelines have been put forth to steer the preclinical validation of new therapies. The absence of such guidelines in the SCI field cannot be attributed to our success in translating experimental neuroprotective or neuroregenerative treatments into human therapies, as our experience in this regard is not so dissimilar to neuroprotection researchers in the stroke field. The need for analogous guidelines for preclinical validation was actually discussed at the International Clinical Trials Workshop on Spinal Cord Injury held in Vancouver in 2004, and comments on the need for study replication, evidence of functional benefit, and larger-animal models (particularly for more "potentially hazardous" treatments) were made in the report that emerged from this important workshop (Steeves et al., 2004). Important preclinical considerations to improve upon the chances of success in clinical trials were also voiced recently in an excellent review by Blesch and Tuszynski (2009), who pointed out the importance of contusive injury models, replicability, and large-animal studies. Our questionnaire attempts to characterize more specifically the preclinical elements that our SCI community feels are important to the translation of promising therapies, and will hopefully foster further dialogue on this issue.

The second is the harsh reality that conducting a clinical trial in SCI is an extremely difficult undertaking. While it is impossible to grade the difficulty of doing clinical trials of SCI in relation to stroke, at least in the latter, patients are of a more homogenous age distribution, they do not typically arrive at the hospital intoxicated and bleeding from their compound femur fractures, and their annual incidence is far greater (allowing for a faster enrolment of the many patients required in large randomized trials). It is not uncommon to hear the argument that "if it's safe in the animal models, we may as well try it in human SCI patients." While there may be some practical justification to that sentiment, it unfortunately overlooks the fact that such human evaluation is so challenging, time consuming, and expensive to do – a fact that served as the rationale behind four seminal reviews of the conducting of such clinical trials, published in 2007 by a panel of SCI experts from the International Campaign for Cures of Spinal Cord Injury Paralyis (ICCP) (Fawcett et al., 2007; Lammertse et al., 2007; Steeves et al., 2007; Tuszynski et al., 2007). The difficulty in doing human SCI trials is illustrated by Sygen (GM-1 ganglioside), the last acute SCI treatment to complete a large-scale human evaluation. Sygen crossed the "bench to bedside" divide when it was first administered to acute SCI patients in a small randomized clinical trial that began in 1986 (Geisler et al., 1990). Its human evaluation concluded *15 years later* with the publication of the negative results from a 760-patient randomized controlled clinical trial, the patient recruitment for which took 28 neurotrauma institutions 5 years to complete (Geisler et al., 2001). Clearly, the clinical evaluation of a promising therapy for SCI is no trivial endeavor, and one that should not be undertaken lightly.

The final consideration is that despite the relatively modest expectations that researchers may justifiably have when introducing new therapies into initial clinical trials (generally these are focused on safety and feasibility), there is a tacit expectation from our paralyzed patients that what is being translated from the laboratory might actually work for them. It seems absurd to expect that the patients themselves (particularly in the acute setting) will understand the complex biologic rationale and nuances of experimental methodology that serve as the preclinical foundation for the treatment whose clinical validation they are being asked to participate

in – they simply hope that whatever is being offered to them might make them even a slight degree better. It is hard to disregard this hope. If the patients invariably believe that treatments being offered to them in experimental clinical trials might be even slightly efficacious, then it would be up to us in the scientific community to ensure that we feel the same way. The opinions of the SCI community that emerged in this questionnaire suggest that the way in which we view preclinical evidence and subsequently formulate our views on the promise of new therapies may require a bit of recalibration. We intentionally did not seek the opinions of SCI patients themselves in this particular survey, but are currently engaged in an initiative to garner their important perspectives on this issue.

Conclusion

The pace of discovery in SCI has only accelerated in the past two decades, and this is undeniably good news for our patients. While we have witnessed the emergence and failure of numerous clinical trials during this period, each has taught us invaluable lessons that have been incorporated into subsequent clinical trials. The fact that researchers are anxious to push scientific innovations forward into the clinic is highly desirable and need not be discouraged, as the common goal of the research community is to effect some improvement in the lives of individuals who have suffered this very cruel injury. The purpose of this questionnaire was not to highlight the deficiencies of our field, or single out specific treatments as being more or less promising based on preclinical data (or lack thereof), or create unrealistic, insurmountable barriers to the future translation of new therapies. It was simply an attempt to identify what we ourselves consider to be necessary in order to rationalize the translation of promising new treatments, and to characterize some of the biases that might influence how we perceive their promising potential.

This dialogue now needs to continue, with the goal of lucidly establishing a realistic framework for guiding the preclinical validation of novel therapies. Advocating for preclinical standards that are impractical or impossible to reach would benefit no one, and would only serve to slow important translational progress (and enthusiasm) in the field. We would echo the sentiments of Blesch and Tuszynski (2009), in that a framework for preclinical translation is needed – and that it needs to balance carefully the many important considerations and interests of the stakeholders in this field: the scientists, clinicians, industry sponsors, regulatory officials, granting agencies, and, of course, the patients themselves. The scientist whose hard-fought, extramurally funded survival comes mainly from mechanistic, discovery-based science may have few resources to indulge in the opined "importance" of independently replicating experiments using different injury models of varying injury severities and mechanical properties. The vast majority of scientists would find large-animal or primate studies simply unattainable, even if the validated injury models were widely available to confirm efficacy in such species. Industry sponsors, essential for refining new therapies, providing safe passage through regulatory bodies (would any independent scientist be capable of submitting a 21,000-page application to the FDA?), and bankrolling expensive clinical trials have entirely valid intellectual-property issues that may clash with the scientific mantra of peer-reviewed dissemination. Full-time clinicians, eager to try anything that appears to be safe and possibly efficacious on their patients, may have little familiarity with the methodological details of the science (and may not even fully comprehend the enormity of the clinical evaluation process), but have little interest in waiting for what may appear to them as an endless stream of animal experiments. And finally, there are the SCI patients themselves, whose desperation for such treatments is hard to overestimate. Of course, for all this justifiable enthusiasm and anxiousness to move forward, there is the indisputably frustrating experience of our stroke colleagues that cannot be denied. Clearly, this is no simple issue. The goal, however, is obvious: we all wish to see the validation of effective treatments for individuals who suffer SCIs. Our hope is that this survey will help to facilitate the rational and collaborative establishment of a practical and realistic preclinical research framework that will maximize our chances of attaining that goal.

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