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Regular Article

Large animal and primate models of spinal cord injury for the testing of novel therapies

Brian K. Kwon [a,*], Femke Streijger [a], Caitlin E. Hill [b], Aileen J. Anderson [c], Mark Bacon [d], Michael S. Beattie [e], Armin Blesch [f], Elizabeth J. Bradbury [g], Arthur Brown [h], Jacqueline C. Bresnahan [e], Casey C. Case [i], Raymond W. Colburn [j], Samuel David [k], James W. Fawcett [l], Adam R. Ferguson [m], Itzhak Fischer [n], Candace L. Floyd [o], John C. Gensel [p], John D. Houle [q], Lyn B. Jakeman [r], Nick D. Jeffery [s], Linda Ann Truett Jones [t], Naomi Kleitman [t], Jeffery Kocsis [u], Paul Lu [v], David S.K. Magnuson [w], Martin Marsala [x], Simon W. Moore [y], Andrea J. Mothe [z], Martin Oudega [aa], Giles W. Plant [ab], Alexander Sasha Rabchevsky [ac], Jan M. Schwab [ad], Jerry Silver [ae], Oswald Steward [af], Xiao-Ming Xu [ag], James D. Guest [ah], Wolfram Tetzlaff [a]

[a] University of British Columbia, ICORD, Room 6196, Blusson Spinal Cord Centre, 818 West 10th Avenue, Vancouver, BC V5Z 1 M9, Canada
[b] Burke Medical Research Institute/Weill Cornell Medical College, 785 Mamaroneck Ave., White Plains, NY 10605, USA
[c] U. C. Irvine, 2030 Gross Hall Stem Cell Research Center, USA
[d] International Spinal Research Trust, International Spinal Research Trust, Bramley Business Centre, Station Road, Bramley, Guildford, Surrey GU5 0AZ, UK
[e] University of California at San Francisco, 1001 Potrero Ave., Bldg 1 Rm 101, San Francisco, CA 94110, USA
[f] Heidelberg University Hospital, Spinal Cord Injury Center, Germany
[g] King's College London, The Wolfson Centre for Age-Related Diseases, Wolfson Wing, Hodgkin Building, Guy's Campus, London Bridge, London SE1 1UL, UK
[h] University of Western Ontario, Robarts Research Institute, University of Western Ontario, Department of Anatomy and Cell Biology, 1151 Richmond Street, North, N6A 5B7, Canada
[i] Asterias Biotherapeutics, 230 Constitution Drive, Menlo Park, CA 94025, USA
[j] Acorda Therapeutics, Acorda Therapeutics, Inc., 420 Saw Mill River Road, Ardsley, NY 10502, USA
[k] Centre for Research in Neuroscience, Research Institute of the McGill University Health Centre, 1650 Cedar Ave., Montreal, Quebec H3G 1A4, Canada
[l] University of Cambridge, John van Geest Centre for Brain Repair, Robinson Way, Cambridge CB2 0PY, UK
[m] University of California, San Francisco (UCSF), Brain and Spinal Injury Center (BASIC), Department of Neurological Surgery, USA
[n] Drexel University College of Medicine, Dept. of Neurobiology and Anatomy, 2900 Queen Lane, Philadelphia, PA 19129, USA
[o] University of Alabama at Birmingham, 529C Spain Rehabilitation Center, 1717 6th Avenue South, Birmingham, AL 35249, USA
[p] University of Kentucky, Spinal Cord and Brain Injury Research Center, B463 Biomedical & Biological Sciences Research Building (BBSRB), 741 S. Limestone, Lexington, KY 40536, USA
[q] Drexel University College of Medicine, Spinal Cord Research Center, Philadelphia, PA 19129, USA
[r] National Institutes of Health/NINDS, 6001 Executive Blvd. North, Bethesda, MD 20852, USA
[s] Iowa State University, Lloyd Veterinary Medical Center, College of Veterinary Medicine, Iowa State University, Ames, IA 50011, USA
[t] Craig H. Neilsen Foundation, 16830 Ventura Blvd. Suite 352, Encino, CA 91436, USA
[u] Yale University and VA CT Healthcare System, Neuroscience Center (127A), VA CT Healthcare Center, 950 Campbell Ave., West Haven, CT 06516, USA
[v] VA-San Diego Healthcare System, University of California at San Diego, BMF2, Room 2126, 9500 Gilman Dr., La Jolla, CA 92093-0626, USA
[w] University of Louisville School of Medicine, 511 S. Floyd St., MDR Rm 616, USA
[x] University of California, San Diego, Department of Anesthesiology SCRM, Room 4009, 2880 Torrey Pines Scenic Dr., La Jolla, CA 92037, USA
[y] InVivo Therapeutics Corporation, One Kendall Square, Suite B14402, Cambridge, MA 02139, USA
[z] Toronto Western Research Institute, Krembil Discovery Tower, 60 Leonard Ave. , 7KD-406, Toronto ON M5T 2S8, Canada
[aa] University of Miami Miller School of Medicine, LPLC, 1095 NW 14 Terrace, Miami, FL 33136, USA
[ab] Stanford University, Lorry I. Lokey Stem Cell Research Building, Stanford University, 265 Campus Drive, Stanford, CA 94305, USA
[ac] University of Kentucky, B471, BBSRB, 741 South Limestone Street, Lexington, KY 40536-0509, USA
[ad] The Ohio State University, Neurology, USA
[ae] Case Western Reserve University, Dept. of Neurosciences, School of Medicine, 2109 Adelbert Rd., Cleveland, OH 44106, USA
[af] University of California Irvine, Reeve-Irvine Research Center, Department of Anatomy & Neurobiology, University of California Irvine School of Medicine, Irvine, CA 92697, USA
[ag] Indiana University School of Medicine, 320 W. 15th St., Indianapolis, IN 46202, USA
[ah] University of Miami, Neurological Surgery, USA

* Corresponding author at: Department of Orthopaedics, University of British Columbia, ICORD (International Collaboration on Repair Discoveries), 6th Floor, Blusson Spinal Cord Center, VGH, 818 West 10th Avenue, Vancouver, BC V5Z 1M9, Canada. Fax: +1 604 875 8223.
E-mail addresses: brian.kwon@ubc.ca (B.K. Kwon), femkestreijger@gmail.com (F. Streijger), cah2024@med.cornell.edu (C.E. Hill), aja@uci.edu (A.J. Anderson), mark@spinal-research.org (M. Bacon), Michael.beattie@ucsf.edu (M.S. Beattie), armin.blesch@med.uni-heidelberg.de (A. Blesch), elizabeth.bradbury@kcl.ac.uk (E.J. Bradbury), abrown@robarts.ca (A. Brown), Jacqueline.bresnahan@ucsf.edu (J.C. Bresnahan), ccase@asteriasbio.com (C.C. Case), rcolburn@acorda.com (R.W. Colburn), sam.david@mcgill.ca (S. David), jf108@cam.ac.uk (J.W. Fawcett), Adam.ferguson@ucsf.edu (A.R. Ferguson), Itzhak.Fischer@DrexelMed.edu (I. Fischer), clfloyd@uab.edu (C.L. Floyd), Gensel.1@uky.edu (J.C. Gensel), jhoule@drexelmed.edu (J.D. Houle), lyn.jakeman@nih.gov (L.B. Jakeman), njeffery@iastate.edu (N.D. Jeffery), linda@chnfoundation.org (L.A.T. Jones), naomi@chnfoundation.org (N. Kleitman), Jeffery.kocsis@yale.edu (J. Kocsis), plu@ucsd.edu (P. Lu), david.magnuson@louisville.edu (D.S.K. Magnuson), mmarsala@ucsd.edu (M. Marsala), smoore@invivotherapeutics.com (S.W. Moore), amothe@uhnres.utoronto.ca (A.J. Mothe), moudega@pitt.edu (M. Oudega), gplant@stanford.edu (G.W. Plant), agrab@uky.edu (A.S. Rabchevsky), jan.schwab@osumc.edu (J.M. Schwab), jxs10@case.edu (J. Silver), osteward@uci.edu (O. Steward), Xu26@iupui.edu (X.-M. Xu), jguest@med.miami.edu (J.D. Guest), tetzlaff@icord.org (W. Tetzlaff).

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ABSTRACT

Large animal and primate models of spinal cord injury (SCI) are being increasingly utilized for the testing of novel therapies. While these represent intermediary animal species between rodents and humans and offer the opportunity to pose unique research questions prior to clinical trials, the role that such large animal and primate models should play in the translational pipeline is unclear. In this initiative we engaged members of the SCI research community in a questionnaire and round-table focus group discussion around the use of such models. Forty-one SCI researchers from academia, industry, and granting agencies were asked to complete a questionnaire about their opinion regarding the use of large animal and primate models in the context of testing novel therapeutics. The questions centered around how large animal and primate models of SCI would be best utilized in the spectrum of preclinical testing, and how much testing in rodent models was warranted before employing these models. Further questions were posed at a focus group meeting attended by the respondents. The group generally felt that large animal and primate models of SCI serve a potentially useful role in the translational pipeline for novel therapies, and that the rational use of these models would depend on the type of therapy and specific research question being addressed. While testing within these models should not be mandatory, the detection of beneficial effects using these models lends additional support for translating a therapy to humans. These models provides an opportunity to evaluate and refine surgical procedures prior to use in humans, and safety and bio-distribution in a spinal cord more similar in size and anatomy to that of humans. Our results reveal that while many feel that these models are valuable in the testing of novel therapies, important questions remain unanswered about how they should be used and how data derived from them should be interpreted.

Introduction

Traumatic spinal cord injury (SCI) is a devastating condition for which therapies to improve neurologic function remain elusive. Scientific efforts to understand the nature of SCI and develop treatments for it have depended on animal models (Zhang et al., 2014). Although large animals, especially cats and dogs, were commonly used for spinal cord injury studies in the 1950s–1970s, rodent models have become the standard over the past 30 years. The routine use of rodent models of SCI has been facilitated by the development of standardized techniques and devices to reproducibly induce injury and standardized measures to evaluate post-injury outcome—both of which have become widely available to the scientific community (Kwon et al., 2002). Scientific initiatives that have relied heavily (albeit not exclusively) on such small animal models to evaluate the efficacy of potential treatments have led to the clinical testing of a number of experimental interventions, including methylprednisolone, GM1-ganglioside, nimodipine, gacyclidine, and activated autologous macrophages (Tator, 2006). To date, none of these have demonstrated convincing efficacy in human SCI. However, a growing list of treatments are currently entering clinical trials, including minocycline, riluzole, systemic hypothermia, the rho-antagonist BA-210 (Cethrin™), PEG-MgCl, bFGF, poly(lactide-co-glycolide)-poly-L-lysine (PLGA-PLL) scaffolds as well as a variety of cell types, such as Schwann cells, olfactory ensheathing cells, neural stem/progenitor cells, and mesenchymal stem cells (Ramer et al., 2014).

Alongside these efforts, there has been resurging interest in the use of large animal models and non-human primate models of SCI for the evaluation of potential therapies (Jeffery et al., 2011; Nout et al., 2012; Lee et al., 2013; Navarro et al., 2012; Iwanami et al., 2005; Kuluz et al., 2010; Cote et al., 2010; Pritchard et al., 2010). This has been motivated by uncertainties about how 'translatable' the promising results from rodent SCI models may actually be in human SCI, and an interest in demonstrating the clinical applicability and robustness of experimental therapies prior to committing to lengthy and expensive human clinical trials (Blesch and Tuszynski, 2009; Dietrich, 2003). Similar motivation exists in the stroke community, where many therapies have gone into clinical trial based on promising rodent data, only to prove ineffective (O'Collins et al., 2006). This has ultimately led to guidelines that advocate for multiple-species testing in the preclinical development of stroke therapies (Fisher et al., 2009). The use of such models is not new in the SCI field, and in fact Allen's century-old description of an experimental spinal cord contusion injury model employed a large animal (canine) species (Allen, 1911). Large animal systems have played an important role in the regulatory pathway for establishing safety and pharmacokinetics/dynamics for novel therapeutics for SCI (FDA, 2013). The growing number of large animal and primate models with well characterized biomechanical injury parameters and neurologic outcome measures provides investigators with increased opportunity to test the efficacy of such therapeutics en route to human translation.

As pointed out over a decade ago by Kleitman, the question of how much preclinical data are sufficient to justify proceeding with human testing is a difficult one to answer (Kleitman, 2004). In 2009, we (BK and WT) undertook a survey of the research community to garner opinions on this question of what demonstration of efficacy was required to justify the human translation of an experimental therapy for SCI (Kwon et al., 2010). This initiative was grounded in the notion that while the field desperately needs effective therapies, propelling treatments into clinical trials with limited preclinical evidence of efficacy could squander valuable time and resources. We also surveyed individuals living with SCI in order to characterize what their expectations were for the testing of therapies that they might be offered as potential subjects within a clinical trial (Kwon et al., 2012). These initiatives revealed strong sentiments both from the research community and from individuals living with SCI that demonstrating the efficacy of therapies in large animal and/or primate models was important before moving therapies into clinical trials.

These perspectives naturally lead to more specific questions about the use of large animal and primate models of SCI. *For example, if these models are available for the testing of drug or cell therapies, what specifically should they be used to demonstrate? Is it necessary to use both a large animal model and primate model? Furthermore, how should the demonstration of efficacy or lack thereof in such models be interpreted? Within the context of the preclinical development of a novel therapy, what data from rodent models are needed before it is rational to undertake the expense of testing in a large animal or primate model?*

The purpose of this present initiative was to address some of these questions by engaging members of the SCI research community in a questionnaire and a round-table discussion about the use of large animal and non-human primate models of SCI. We felt that stimulating a discussion regarding the use of such models in preclinical SCI research would provide the field with a range of perspectives and highlight important considerations for the preclinical development of novel therapies. In general, this initiative highlighted the diversity of opinions about the use of large animal and primate models in pre-clinical SCI research. Our results also reveal that while many (arguably most) feel that these models are valuable in the testing of novel therapies, important questions remain unanswered about how they should be used and how data derived from them should be interpreted.