Brief Report

Spinal cord injury pharmacotherapy: Current research & development and competitive commercial landscape as of 2015

Jason R. Guercio¹, Jason E. Kralic², Eric J. Marrotte³, Michael L. James ^{3,4}

¹North American Partners in Anesthesiology, New Britain, Connecticut, USA, ²Innervate BD Solutions, LLC, Hillsborough, North Carolina, USA, ³Department of Neurology, Brain Injury Translational Research Center, Duke University, Durham, North Carolina, USA, ⁴Department of Anesthesiology, Brain Injury Translational Research Center, Duke University, Durham, North Carolina, USA

Context: Current treatment of spinal cord injury (SCI) focuses on cord stabilization to prevent further injury, rehabilitation, management of non-motor symptoms, and prevention of complications. Currently, no approved treatments are available, and limited treatment options exist for symptoms and complications associated with chronic SCI. This review describes the pharmacotherapy landscape in SCI from both commercial and research and development (R&D) standpoints through March 2015.

Methods: Information about specific compounds has been obtained through drug pipeline monographs in the Pharmaprojects® (Citeline, Inc., New York, New York, USA) drug database (current as of a search on May 30, 2014), websites of individual companies with compounds in development for SCI (current as of March 24, 2015), and a literature search of published R&D studies to validate the Pharmaprojects® source for selected compounds (current as of March 24, 2015).

Results: Types of studies conducted and outcomes measured in earlier phases of development are described for compounds in clinical development. Currently four primary mechanisms are under investigation and may yield promising therapeutic targets: 1) neuronal regeneration; 2) neuroprotection (including anti-inflammation); 3) axonal reconnection; and 4) neuromodulation and signal enhancement. Many other compounds are no longer under investigation for SCI are mentioned; however, in most cases, the reason for terminating their development is not clear.

Conclusion: There is urgent need to develop disease-modifying therapy for SCI, yet the commercial landscape remains small and highly fragmented with a paucity of novel late-stage compounds in R&D.

Key words: Spinal cord injury, Pharmacotherapy, Clinical trials

Introduction

In the United States, approximately 17,500 new spinal cord injuries (SCI) are reported each year with an estimated 285,000 Americans currently experiencing consequences of SCI (http://www.msctc.org/lib/docs/Data_Sheets/_SCIMS_Facts_and_Figures_2017_August_FINAL.pdf). Current treatment focuses on cord stabilization to prevent further injury, rehabilitation, management of non-motor symptoms, and prevention of complications. Urgent need to develop disease-modifying therapy for SCI exists.

Describing pharmacotherapy landscape in SCI from both commercial and research and development (R&D) standpoints, this review will focus on small-molecule and biologics. Studies and outcomes measured in early development and compounds no longer under investigation will be mentioned. While stem cell therapies account for considerable research investment, recent excellent reviews already exist, and detailed discussion is beyond the scope of this review.¹

Information about specific compounds has been obtained through drug pipeline monographs in the Pharmaprojects® (Citeline, Inc., New York, New York, USA) drug database (current as of a search on May

Correspondence to: Michael L. James, MD, Associate Professor, Brain Injury Translational Research Center, Duke University DUMC 3094, Durham, NC 27710, USA. Email: michael.james@duke.edu

30, 2014), websites of individual companies with compounds in development for SCI (current as of March 24, 2015), and a literature search of published R&D studies to validate the Pharmaprojects® source for selected compounds (current as of March 24, 2015). Information on current clinical trials in SCI is current as of October 2, 2014. The purpose of this report is to provide a frame of reference to understand the obstacles and successes related to SCI therapeutic development and as a historical perspective of the SCI landscape as of 2015.

Compounds in clinical development

No established commercial leader exists for SCI clinical development (see Table 1) with balanced funding mix from academic institutions, small start-up companies holding compound licenses, private foundation, federal (Department of Defense, National Institute on Disability and Rehabilitation Research, and Telemedicine and Advanced Technology Research Center), and license-holding company sources. Many funding agencies support preclinical programs with traditional models but are increasingly investing in experimental model organisms, such as non-human primates and miniature pigs.² Acorda Therapeutics, Inc., (Ardsley, New York, USA) was the only company with more than one program in clinical development for SCI. Notable lack of large pharmaceutical company activity existed.

Therapeutics under investigation

Repurposing of older therapeutics approved for other indications and/or symptomatic relief, including generics, was common. Few novel, target-specific compounds were being studied in acute cervical SCI, due to greater potential clinical response compared to thoracic injury.³ While work continues in neuroprotection (specifically anti-inflammation), increasing focus involves strategies promoting neuronal regeneration and repair.

Active clinical trials in SCI

Table 1 summarizes the 14 clinical trials testing 11 potential therapeutics in clinical development for SCI. The proposed mechanism of action and route of administration of compounds in clinical development are outlined in Table 2.

Phase of development, type, and location of injury

Dogma holds that acute intervention holds greater probability for improving motor recovery; thus, potential therapeutics for acute SCI address motor outcomes, while potential treatments for chronic SCI

predominantly focus on non-motor (e.g. bladder control) symptoms. Novel therapeutics under investigation (BA-210, SUN-13837, AC-105) target acute injury, while repurposed medications target the spectrum of SCI. Because cervical injuries a) are more common,⁴ b) result in greater disability,³ and c) may provide the lowest threshold for detecting efficacy, trials tend to favor acute cervical SCI. Severity of injury for study inclusion varies widely and is not correlated with acute or chronic status. Trials are in adults, i.e. ≥ 18 years, with one exception. No current trial information was available for 3 compounds in phase I development—MAP-4343, GM-603, and cyclosporine A.

Outcomes studied

Most primary outcomes incorporate the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) scores and the American Spinal Injury Association (ASIA) Impairment Scale (AIS) scores.⁵ ISNCSCI defines neurological level of injury as the most caudal segment of the spinal cord with normal sensory and antigravity motor function on both sides of the body. AIS grades injury completeness: complete injury indicates loss of sensory or motor function below the neurological level.

Compounds in active clinical trials with prior clinical development

Riluzole^{6,7} and SUN-13837 [unpublished data] are limited to safety and tolerability data; other compounds are noted below.

BA-210

The multi-dose phase I/IIa trial enrolled 48 patients with acute thoracic or cervical SCI (AIS A) to evaluate the efficacy of extradural doses during spine surgery performed within 5 days of injury.⁸ ISNCSCI motor scores at 12 months after injury were compared against baseline scores. The study found small changes in ISNCSCI motor scores across all dose groups in thoracic (1.8 ± 5.1) and cervical patients (18.6 ± 19.3). The largest change in motor score was observed in cervical patients treated with 3 mg of BA-210 (27.3 ± 13.3). Conversion from AIS A to AIS C or D occurred in 6% of thoracic patients, compared to 31% of cervical patients overall and 66% given 3 mg of BA-210. Notably, patients with cervical AIS Grade A injury are expected to improve by approximately 10 upper extremity motor score points during the first year after SCI.⁹

Minocycline

In phase II study,¹⁰ 52 acute SCI patients received IV minocycline. Enrolled patients had AIS A-D injury or

Table 1 Current SCI clinical trials for interventions to improve neurologic function adapted from Spinal Cord Outcomes Partnership Endeavor (SCOPE) available at www.scope-sci.org (last accessed December 29, 2014).

Number	Compound	Sponsor/NCT	Intervention	Inclusion / Exclusion Criteria	Treatment Timing & Follow-up	Enrollment	Phase of Study	Primary Outcome	Comments
1	Minocycline	Rick Hansen Institute U of Calgary Alberta Paraplegic Foundation NCT01828203	Twice Daily IV Minocycline vs. Placebo for over seven days All patients receive decompressive spine surgery and blood pressure management per protocol	≥ 16 yr Age SCI C0-C8 AIS A, B, C, D	Acute SCI SCI ≤ 12 hours F/U 12m	Began 6/ 2013 Canada 248 subjects	Phase 3 RCT	Efficacy/Safety ISNCSCI Motor Score recovery from baseline to examination between 3 m and 1 yr post injury; ISNCSCI Sensory Scores AIS; SCIM; QoL: SF-36	800 mg initial dose tapered 100 mg each dose to 400 mg then continued twice daily x 7 days
2	Minocycline	Hadassah Medical Org NCT01813240	Minocycline vs. Placebo; dose and route of administration not specified	18-65 yr Age SCI: AIS B, C, D Spinal Tumors causing cord compression	Not Specified: Treatment Initiation Treatment Duration F/U Duration	Not begun Israel 444 subjects	Phase2/3 RCT	Efficacy/Safety ASIA score (ISNCSCI) comparison from baseline to 6 months follow-up; SCIM, FIM	Prevention of Imminent Paralysis Following Spinal Cord Trauma or Ischemia by Minocycline
3	Human Growth Hormone	Hospital Nacional de Paraplejicos de Toledo (Spain) NCT01329757	Daily SQ Human Growth Hormone vs placebo dosing for 1 yr; 6 months of rehab	18-75 yr Age SCI C4-T12 AIS B,C	Chronic SCI > 18 m SCI 1 yr F/U	Began 4/ 2011 Spain 76 subjects	Phase 3 RCT Placebo Controlled	Efficacy/Safety ISNCSCI motor sensory examination; SCIM	Test of 1 yr of daily SQ Growth Hormone to improve neuro outcome in chronic incomplete
4	Riluzole	AOSpine N. Am Research Network NCT01597518	Riluzole 2 × 100 mg by mouth or feeding tube the first 24 hours followed by 2 × 50 mg for the following 13 days after injury vs. placebo in acute SCI	18-75 yr Age SCI C4-C8 AIS A, B, C	Acute SCI SCI ≤ 12 hours F/U 6m	Began 8/ 2013 N. America Multicenter 351 subjects	Phase 2/3 RCT Double- Blind	Efficacy/Safety Change in ISNCSCI total motor score from baseline to 6 months of F/U	Multicenter Phase2/ 3 trial of riluzole vs. placebo for improving motor recovery in
5	BA-210	Bioaxone Biosciences NCT02053883	3 mg or 6 mg of BA-210 (Cethrin™) vs. Placebo administered extradurally in a fibrin sealant during spinal decompression/ stabilization surgery	18-62 yr Age SCI C4-5 AIS A, B	Acute SCI SCI ≤ 5 days F/U 6m	Not yet recruiting US and Canada Enrollment target not specified	Phase 2 Placebo Controlled RCT	ISNCSCI UE Motor Score Other ISNCSCI parameters SCIM, GRASSP	acute SCI Phase 2 trial of Cethrin vs. Placebo administered during clinical spinal surgery in acute SCI

Continued

Table 1 Continued

Number	Compound	Sponsor/NCT	Intervention	Inclusion / Exclusion Criteria	Treatment Timing & Follow-up	Enrollment	Phase of Study	Primary Outcome	Comments
6	AC-105	Acorda Therapeutics NCT01750684	IV study med every 6 hrs x 6; AC-105 vs. Placebo; i.e. 6 doses over 30 hours	18-65 yr Age SCI C4-T11 AIS A, B, C	Acute SCI SCI $\leq$ 12hr F/U 6 m	Began 7/2013 Enrolling By Invitation Only N. America 40 Subjects	Phase 2 RCT	Safety / Tolerability: comparison of Adverse Event data between groups	Study to determine safety, tolerability and potential activity of AC105
7	Dalfampridine	Kessler Foundation; NIDRR; Acorda Therapeutics NCT01621113	Oral dalfampridine (Sustained release 4-aminopyridine) vs. placebo for 10 weeks in chronic motor incomplete SCI receiving locomotor therapy	18-70 yr Age SCI C4-T10 AIS C, D	Chronic SCI SCI $>$ 12m F/U 22wks	Began 6/2012 New Jersey 46 subjects	Phase 2 RCT Double-Blind	Change in 6 minute walk test at 10 weeks and 22 weeks F/U	Test of whether dalfampridine improves walking outcomes in chronic motor incomplete SCI
8	SUN-13837	Asubio Pharmaceuticals / Daiichi Sankyo NCT01502631	IV drug SUN-13837 daily for 28d. vs. placebo (ASCENT-ASCI (Asubio Spinal Cord Early Neuro-recovery Treatment for Acute Spinal Cord Injury))	18-80 yr Age C4-C7 AIS A 16-70 yr Age C3-C8 AIS B, C LEMS $\leq$ 5	Acute SCI, SCI $\leq$ 12hr, 26wk F/U	Began 1/2012 N. America / Europe 164 subjects	Phase 2 RCT Double Blind Placebo Controlled	Efficacy/Safety ISNCSCI examination AIS A: 2 motor level improvement AIS B, C: LEMS $\geq$ 40	Responder Definition: AIS A: 2 Motor Level Improvement AIS B, C: LEMS $\geq$ 40
9	Hepatocyte Growth Factor	Kringle Pharma, Inc. NCT02193334	IT injection of 0.6 mg Hepatocyte Growth Factor (HGF) vs. placebo starting at 72hr post injury, the weekly x5 weeks	20-75 yr Age SCI C4-C8 AIS A, B	Acute SCI SCI $\leq$ 72hr F/U 24wk	Began 6/2014 Japan 48 subjects	Phase 1/2 RCT Placebo Controlled	Safety/Efficacy Adverse Events ASIA Motor Score Change 24wk	Study of intrathecal HGF vs. placebo given within 72 h then daily for 5 days
10	Buspirone + Levodopa + Carbidopa	Nordic Life Science Pipeline Inc. NCT01484184	Oral dosing of buspirone + levodopa + cardidopa (Spinalon™); vs. placebo	18-65 yr Age SCI C3-T12 AIS A, B	Chronic SCI SCI $\geq$ 3m F/U 4hr post administration	Began 7/2013 Canada 51 subjects	Phase 1/2 RCT Double Blind Placebo Controlled	Safety / Tolerability Vital Signs Rhythmic Leg EMG	Multiple arms testing SPINALON vs. combination of drugs vs. placebo
11	Ibuprofen	Jan Schwab Elise Kroner Fresenius Foundation Charite University NCT02096913	Ibuprofen (Dolormin® Extra) 2400 mg daily (800 mg 3 times per day) for 4 wks (6 subjects) or 12 wks (6 subjects)	18-65 yr Age SCI C4-T4 AIS A, B	Acute SCI 4d $\leq$ SCI $\leq$ 21d F/U 6m	Began 6/2014 Germany 12 subjects	Phase 1 Open Label	Safety/Efficacy Severe Gastroduodenal Bleed Modified Ashworth Scale Neuropathic Pain Scale ISNCSCI	Safety study of oral ibuprofen for 1 or 3 months in acute SCI also measuring ISNCSCI, spasticity and pain outcomes

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Table 1 Continued

Number	Compound	Sponsor/NCT	Intervention	Inclusion / Exclusion Criteria	Treatment Timing & Follow-up	Enrollment	Phase of Study	Primary Outcome	Comments
12	Escitalopram	Rehab Inst Chicago (RIC) NCT01753882	Escitalopram (Lexapro®) 10 mg PO Daily x 4 weeks vs Placebo in patients enrolled in gait training regimen (3x per wk for 6 wks—2 wks prior to initiation of study med, then 4 wks combined gait training and study med)	18-75 yr Age SCI C1-T10 AIS C, D 1-9 m post SCI	Subacute/ Chronic 1m ≤ SCI ≤ 9m	Began 2/2012 Chicago 88 subjects	Phase 1 Randomized Double Blinded Crossover	Safety/Efficacy WISCI Peak Treadmill Velocity 6 Minute Walk LEMS	Studying the combined effects of gait training and escitalopram on motor function and ↑ in locomotor capability
13	Escitalopram	Rehab Inst Chicago (RIC) NCT01788969	Active (Serotonergic Modulation: escitalopram (Lexapro®) crossover with cyproheptadine) vs. placebo in patients enrolled in gait training regimen	18-65 yr Age SCI C5-T10 AIS C, D SCI < 6 mos or SCI > 1yr	Subacute (<6mos) or Chronic (> 1 yr) F/U 10-12wks	Began 6/2005 Chicago 120 subjects	Phase 1 Randomized Double Blinded Crossover	Safety/Efficacy WISCI Peak Treadmill Velocity 6 Minute Walk LEMS	Studying the effects of serotonergic modulation and gait training on motor function in subacute and chronic SCI
14	Escitalopram	Rehab Inst Chicago (RIC) NCT01538693	Escitalopram (Lexapro®) vs. cyproheptadine, vs. placebo in patients participating in a graded treadmill exercise regimen	18-75 yr Age SCI C1-T10 AIS C, D SCI > 1yr	Chronic SCI SCI > 12m F/U 7days	Began 12/2011 Chicago 30 subjects	Phase not specified Randomized Double Blinded Crossover	Change in blood serum concentration of neuroplastic proteins LEMS Locomotion parameters 6 Minute Walk Step activity monitor (7d) Modified Ashworth Scale	Studying the effects of graded exercise and serotonergic modulation on blood biomarkers of neural plasticity, LE strenght, locomotion

ASIA, American Spinal Injury Association; ISNCSCI, international standards for the neurological classification of spinal cord injury; SCIM, spinal cord injury measurement scale; FIM, functional independence measure; GRASSP, graded redefined assessment of strength, sensibility and prehension; WISCI, walking index for spinal cord injury; LEMS, lower extremity motor score.

Table 2 Current SCI therapeutic landscape (active clinical compounds).

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
1	Phase I glyburide, Remedy Pharmaceuticals glibenclamide, Remedy Pharmaceuticals RP-1127	Phase II	Remedy Pharmaceuticals	ATP-sensitive potassium channel antagonist	ATP-binding cassette, subfamily C (CFTR/ MRP), member 8	Injectable, intravenous	Neuroprotection
2	MAP-4343	Phase II	Mapreg	Microtubule stabilizer	microtubule-associated protein 2	Injectable, subcutaneous	Neuroregeneration (axonal plasticity)
3	GM-603	Phase I	Genervon	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection and Neuroregeneration
4	ciclosporin A, iv, NeuroVive CicloMulsion NeuroSTAT	Phase III	Sihuan Pharmaceutical; Maas BiolAB	Apoptosis inhibitor	peptidylprolyl isomerase A (cyclophilin A)	Injectable, intravenous	Neuroprotection
5	Escitalopram (Lexapro®)	Launched	Forest Laboratories	Antidepressant (selective serotonin reuptake inhibitor)	somatodendritic 5-HT1A and terminal autoreceptors	Oral	Signal Enhancement
6	Ibuprofen (Dolormin® Extra)	Launched	McNeil GmbH & Co. oHG (Johnson & Johnson)	Non-selective inhibition of cyclooxygenase	cyclooxygenase	Oral	Anti-inflammatory
7	Phase II BA-210 BA-210 + Tisseel Cethrin™	Phase I/IIa	BioAxone; Alseres Pharmaceuticals	Rho-associated kinase inhibitor	Rho-associated, coiled- coil containing protein kinase 2	Injectable, intraspinous	Neuroregeneration (axonal plasticity)
8	SUN-13837	Phase II	Asubio; Daiichi Sankyo	Fibroblast growth factor 2 agonist	fibroblast growth factor 2 (basic)	Injectable, intravenous	Neuroprotection, Neuroregeneration (axonal plasticity)
9	AC-105 magnesium, Medtronic magnesium, Acorda Therapeutics	Phase II	Acorda Therapeutics; Medtronic	Unidentified pharmacological activity	Unspecified	Injectable, intravenous	Neuroprotection
10	bupirone + carbidopa + levodopa Spinalon™	Phase II	Nordic Life Science Pipeline	5 Hydroxytryptamine 1A receptor agonist Dopamine receptor agonist DOPA decarboxylase inhibitor	5-hydroxytryptamine (serotonin) receptor 1A, G-protein-coupled dopa decarboxylase (aromatic L-amino acid decarboxylase)	Oral, swallowed	Neuroprotection
11	hepatocyte growth factor, Kringle ChronSeal KP-100 rhHGF, Kringle	Phase II	ChronTech Pharma; Kringle Pharma	Hepatocyte growth factor agonist	met proto-oncogene	Injectable, intrathecal Injectable, intravenous Topical, skin	Neuroprotection, Neuroregeneration (axonal plasticity)
	Phase III						

Continued

Table 2 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
12	dalfampridine 4-aminopyridine 4-AP Amaya Ampyra® Apriva BIIB-041 EL970 fampridine Fampyra Neurelan Riluzole	Launched	Acorda Therapeutics Biogen Idec UCB; Elan	Potassium channel antagonist	Unspecified	Oral, swallowed	Neuromodulation
13		Launched	Covis Pharmaceuticals	Blockade of continuous posttraumatic activation of neuronal voltage gated Na ⁺ channels	Neuronal voltage gated Na ⁺ channels	Oral	Neuroprotection
14	Minocycline	Launched		Tetracycline antibiotic	30S bacterial ribosomal subunit	Injectable, intravenous subcutaneous	Neuroprotection
15	Human Growth Hormone somatotropin	Launched		Multiple therapeutic effects			Neuroprotection, Anti-inflammatory, Signal Enhancement
16	Launched nabiximols cannabinoids, GW Pharmaceuticals GW-1000 GWP-42001 Sativex tetranabinex/nabidiolex THC:CBD	Launched	GW Pharmaceuticals; Bayer Almirall Novartis Otsuka Ipsen	Cannabinoid CB1 receptor agonist	cannabinoid receptor 1 (brain)	Oral, sublingual	Neuromodulation
17	baclofen intrathecal DL-404 Gabalon Intrathecal Lioresal Intrathecal Gablofen	Launched	Daiichi Sankyo CNS Therapeutics; Medtronic	GABA B receptor agonist	gamma-aminobutyric acid (GABA) B receptor, 1	Injectable, intraspinal Injectable, intrathecal	Neuromodulation

Sources: Pharmaprojects® Citeline, Inc. drug pipeline monographs (last accessed May 30, 2014), websites of individual companies holding license to listed compounds.

central cord injuries. Motor scores after cervical injury with treatment improved compared to placebo (33/100 vs 19/100 points). However, no improvement was seen after thoracic injury or in sensory scores in all groups.

Dalfampridine

In the 1990s, 4 small studies demonstrated mixed, but encouraging results that suggested potential improvement in neurologic outcomes in patients with chronic SCI.^{11–14} The subsequent phase II trial of dalfampridine used a double-blind, randomized, placebo-controlled, parallel-group design, enrolling 91 patients with chronic (> 18 months after injury) traumatic AIS C or D injury of the C4-T10 cord.¹⁵ While no differences were found based on the ASIA International Standards, Ashworth Scale, Tendon Reflex Score, Spasm Frequency Score, and CGI, the Ashworth Scale did trend toward improvement in subjects with more marked levels of spasticity at baseline. However, follow-up phase III study found no difference in reducing spasticity in 415 patients.¹⁶ After FDA approval for improving walking in multiple sclerosis, a second phase II study of dalfampridine in SCI began in June of 2012 (5 years after publishing the previous phase II trial) that includes gait training.

Compounds in active clinical trials with prior preclinical development

Preclinical models, type, and location of injury

Preclinical studies of SCI are sufficiently recent to be relevant to 8 of the 11 therapeutics in active clinical development. All 8 programs used rodent models of SCI (both rat and mouse models^{17–25} and mouse-only²⁶). Human HGF was also tested in non-human primates.²⁷ Most of these studies involved contusive cord lesions between T8 and T10, from impactor used on exposed dura after laminectomy. This replicates the most common type of SCI in humans and is generally considered to be most clinically relevant.²⁸

Outcomes studied

In most cases, the Basso, Beattie, Bresnahan (BBB) score was the primary behavioral outcome measure in preclinical modelling. However, the BBB score is considered to have poor sensitivity.²⁹ Small BBB score increases of 1.5–2 points may be viewed as therapeutic efficacy. Notably, spontaneous recovery of up to 6–15 points is common at 5 weeks after injury.³⁰ Thus, rodent SCI models prediction of therapeutic response in humans remains a topic of considerable debate.^{28,31} For example, most murine models do not exhibit cord cavitation at the site of injury; humans do. Further,

rodents have behavioral improvements after low thoracic spinal cord injury, whereas clinically significant improvement has not been demonstrated in patients.²⁸

Non-human primate model

One case of common marmosets used to study human HGF is published.²⁷ A novel behavioral rating scale with a maximum score of 20 was developed to evaluate motor function in the open field, including upper and lower limb weight-bearing, reach and grasp performance, somatosensory function, and trunk stability in a C5 contusive injury model. Force exerted during the animals' gripping reflex, and spontaneous motor activity were also measured and compared to pre-injury values. Across all 3 measures, improvement was greater at 12 weeks after SCI in animals treated with HGF vs placebo. In open-field testing, animals in both groups gradually recovered, reaching a plateau around 8 weeks after SCI. Animals given HGF vs. placebo saw increases of 15.9 ± 0.8 vs. 7.8 ± 1.8 of upper limb weight-bearing, $62.4\% \pm 2.6\%$ vs. $38.9\% \pm 4.3\%$ of their bar-grip strength, and $77.8\% \pm 12.7\%$ and $34.5\% \pm 10.9\%$ of their spontaneous motor activity, respectively. Importantly, rodent studies were completed before the work began in non-human primates for this compound.

Compounds in preclinical development

Similar to clinical development, preclinical testing in SCI was limited, fragmented, and dominated by small biopharmaceutical companies, most of which had 1 preclinical SCI asset (see Table 3). Support for preclinical programs was largely commercial and military. Large pharmaceutical company activity was notably lacking; however, some companies, such as Novartis (Basel, Switzerland) and Daiichi Sankyo (Parsippany, NJ, USA), appear to leverage their existing pipeline, capabilities, and neurology franchises to approach traumatic spinal cord and brain injury via line extensions or repurposing.

Mechanism of action, route of administration

All preclinical SCI compounds are novel molecules. Most are designed to promote neuroprotective, neuroregenerative, and anti-inflammatory responses, while only a few are under investigation for neuromodulation or signal enhancement (see Table 3).

Ongoing preclinical development of current preclinical compounds

Preclinical studies reporting outcomes were available for 10 compounds currently under preclinical investigation in SCI.

Table 3 Current SCI therapeutic landscape (active preclinical compounds).

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
1	Oxycyte	Phase II	Aurum Biosciences; Oxygen Biotherapeutics	Not applicable	Not applicable	Injectable, intravenous Topical	Neuroprotection
2	SLx-2119 KD 025 ROCK2 inhibitors, Nano Terra-1 ROCK2 inhibitors, Surface Logix-1 LPA-181	Phase II	Kadmon Pharmaceuticals; Nano Terra	Rho-associated kinase 2 inhibitor	Rho-associated, coiled-coil containing protein kinase 2	Oral, swallowed	Neuroprotection
3		Preclinical	Lipopharma	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
4	MDNA-11	Preclinical	Medicenna Therapeutics	Apoptosis stimulant	interleukin 4 receptor	Injectable	Neuroprotection
5	becaplermin + β -tricalcium phosphate, BioMimetic-3 Augment Injectable Bone Graft becaplermin + β -TCP, BioMimetic-3 becaplermin + β -TCP/ collagen matrix, becaplermin + β -tricalcium phosphate/collagen matrix, BioMimetic GEM-OS2 rhPDGF-BB + β -TCP, BioMimetic-3 rhPDGF-BB + β -TCP/ collagen matrix, BioMimetic rhPDGF-BB + β -tricalcium phosphate, BioMimetic-3 rhPDGF-BB + β -tricalcium phosphate/collagen matrix	Pre-registration	BioMimetic	Platelet-derived growth factor beta receptor agonist	platelet-derived growth factor receptor, beta polypeptide	Implant Injectable	Neuroprotection
6	chondroitinase, Acorda Therapeutics matrix modifiers, Acorda Therapeutics	Preclinical	Acorda Therapeutics	N Acetylgalactosamine 4 sulfatase stimulant	Unspecified	Unspecified	Neuroregeneration
7	anti-semaphorin 3A antibody, Chiome Bioscience	Preclinical	Chiome Bioscience	Semaphorin antagonist	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	Injectable	Anti-inflammatory, Neuroprotection
8	SC-0806 FGF1, BioArctic Neuroscience	Preclinical	BioArctic Neuroscience	Fibroblast growth factor 1 agonist	fibroblast growth factor receptor 1	Unspecified	Neuroregeneration
9	SY-300	Preclinical	Sygnis Pharma	Apoptosis inhibitor	Unspecified	Unspecified	Neuroregeneration

Continued

Table 3 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
10	NX-210	Preclinical	Neuronax	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
11	Nogo receptor, Axerion Therapeutics,	Preclinical	Axerion Therapeutics	Nogo receptor antagonist	reticulon 4	Unspecified	Neuroprotection
12	NgR(310)ecto-Fc rhIgM22 M1 MAbs, Acorda Therapeutics M22	Phase I	Acorda Therapeutics	Immunostimulant	Unspecified	Injectable, intravenous	Neuroregeneration (remyelination), Signal Enhancement
13	C-21, Vicore compound-21, Vicore	Preclinical	Vicore Pharma	Angiotensin II agonist	Unspecified	Unspecified	Neuroprotection, Anti- inflammatory, Neuroregeneration (axonal plasticity)
14	AP-325	Preclinical	Algiax Pharmaceuticals	Immunosuppressant DNA synthesis inhibitor	Unspecified	Unspecified	Anti-inflammatory
15	Neu-2000 Neu-2000KL Safaprotil	Phase I	JW Pharmaceutical; Simcere Pharmaceuticals; Global Neurotech (GNT) Pharma	Reducing agent NMDA antagonist	glutamate receptor, ionotropic, N-methyl D- aspartate 1	Injectable, intravenous	Neuroprotection
16	anticancer MAb, Lpath Lpathomab	Preclinical	Lpath	Angiogenesis inhibitor	Injectable	Not applicable	Neuroprotection
17	rolipram Adeo ME-3167 ZK-62711	No Development Reported	Meiji; Bayer/Miami Project	Phosphodiesterase 4 inhibitor Interleukin 1b antagonist	phosphodiesterase 4A, cAMP-specific phosphodiesterase 4B, cAMP-specific phosphodiesterase 4C, cAMP-specific phosphodiesterase 4D, cAMP-specific	Oral	Neuroprotection, Anti- inflammatory
18	LM11A-31 p75 ligands, Pharmatrophix		Elan	inhibits proNGF binding to p75 after spinal cord injury		Oral	Neuroprotection

Sources: Pharmaprojects® Citeline, Inc. drug pipeline monographs (last accessed May 30, 2014), websites of individual companies holding license to listed compounds.

Table 4 Current SCI therapeutic landscape (inactive compounds) - online supplement only.

Number	Compound / Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
1	ATI-355	No Development Reported	Novartis	Nogo receptor antagonist	reticulon 4	Injectable, intrathecal	Neuroprotection
2	monosialoganglioside GM-1, Amarin GM-1 ganglioside, Amarin Reflexan GM-1 Sygen	Launched	Amarin	Nerve growth factor agonist	Unspecified	Unspecified	Neuroprotection, Neuroregeneration (axonal plasticity)
3	arbaclofen placarbil baclofen, XenoPort-2 R-baclofen prodrug, XenoPort XP-19986	Discontinued	XenoPort	GABA B receptor agonist	gamma-aminobutyric acid (GABA) B receptor, 1	Oral, swallowed	Neuromodulation
4	SB-509 AdV-ZFP-VEGF ALS therapy, Sangamo diabetic neuropathy therapy, Sangamo VEGF activation, Sangamo-2 VEGF ZFP TF, Sangamo-2	Discontinued	Sangamo BioSciences	Vascular endothelial growth factor (VEGF) receptor agonist	vascular endothelial growth factor A	Injectable, intramuscular	Neuroregeneration
5	apadenoson ATL-146e ATL-193 BMS-068645 DPC-A78445-00 DPH-068645-01 DWH-146e Stedivaze	Discontinued	Forest Laboratories; Lantheus Medical Imaging	Adenosine A2a receptor agonist	adenosine A2a receptor	Injectable, intravenous	Anti-inflammatory
6	tolperisone, Sanochemia Agileo AV-650 Mydocalm SPH-3047 Viveo	Launched	Orion Pharma; MediciNova; Sanochemia Pharmazeutika	Voltage-gated sodium channel antagonist	Unspecified	Oral, swallowed	Neuromodulation
7	CPC-211 Ceresine sodium dichloroacetate	Discontinued	Questcor	Pyruvate dehydrogenase stimulant	Unspecified	Injectable, intravenous	Neuroprotection
8	CEP-075 CEP-075a CEP-075b trk agonists trk antagonists	Discontinued	Takeda; Teva	Tyrosine kinase inhibitor (TKI) Nerve growth factor agonist Tyrosine kinase stimulant	Unspecified	Unspecified	Neuroprotection

Continued

Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
9	bcl-2, Neuro-Genesis	No Development Reported	Neuro-Genesis	Bcl2 stimulant	B-cell CLL/lymphoma 2	Unspecified	Neuroregeneration
10	LINGO-1 fusion protein, Biogen LINGO-1-Fc antibody, Biogen	No Development Reported	Biogen Idec; Dyax	Nogo receptor antagonist	Nogo-66 receptor /p75 signalling complex	Unspecified	Neuroprotection
11	LINGO-1-Fc, Biogen Cordaneurin nerve injury therapy, Neuraxo	No Development Reported	SCT Spinal Cord Therapeutics	Proline hydroxylase inhibitor	prolyl 4-hydroxylase, alpha polypeptide I	Injectable	Neuroregeneration
12	BRX-220	No Development Reported	CytRx	Heat shock protein agonist	heat shock protein 90 kDa alpha (cytosolic), class A member 1	Oral, swallowed	Neuroprotection
13	spinal cord ther, Neuro Ther	No Development Reported	Neuro Therapeutics	Complement factor stimulant	Unspecified	Unspecified	Neuroregeneration
14	inosine, Alseres Axosine	No Development Reported	Alseres Pharmaceuticals	Protein kinase stimulant	Unspecified	Injectable, intracerebral	Neuroprotection, Neuroregeneration (axonal plasticity)
15	Pharmaprojects No. 6411	No Development Reported	Acorda Therapeutics; Athersys	Unidentified pharmacological activity	Unspecified	Unspecified	High-throughput screening platform development
16	IC-486051 PDE inhibitors, Lilly	No Development Reported	Eli Lilly	Phosphodiesterase 4 inhibitor	phosphodiesterase 4A, cAMP-specific phosphodiesterase 4B, cAMP-specific phosphodiesterase 4C, cAMP-specific phosphodiesterase 4D, cAMP-specific	Unspecified	Neuroprotection
17	RAR β 2 gene ther, Oxford Bio Cenurex Innurex neuropathy gene therapy, Oxford Renurex	No Development Reported	Oxford BioMedica	Retinoic acid beta receptor agonist	retinoic acid receptor, beta	Unspecified	Neuroregeneration
18	spinal cord gene therapy, AMT	No Development Reported	uniQure	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroregeneration
19	poloxamer 188, purified-2, CytRx CRL-1550	No Development Reported	CytRx	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection

Continued

Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
20	spinal cord injury vacc, Weizm	No Development Reported	Yeda	T cell stimulant	Unspecified	Unspecified	Neuroprotection
21	oligotropin HF-0420 (oral) oliogossaccharide C3	No Development Reported	Access Merrion Pharmaceuticals; Newron	Heparin stimulant	Unspecified	Injectable, subcutaneous Oral	Neuroprotection
22	Pharmaprojects No. 4664	No Development Reported	Non-industrial source	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
23	Pharmaprojects No. 5123	No Development Reported	Pfizer	Calpain inhibitor	calpain 1, (mu/I) large subunit calpain 2, (m/II) large subunit	Unspecified	Neuroprotection
24	gacyclidine GK-11	No Development Reported	Ipsen	NMDA antagonist	glutamate receptor, ionotropic, N-methyl D- aspartate 1	Unspecified	Neuroprotection
25	Pharmaprojects No. 3017	No Development Reported	Regeneron	Immunostimulant	Unspecified	Unspecified	Neuroregeneration
26	leteprinin potassium AIT-082 Neotrofin	No Development Reported	Spectrum Pharmaceuticals	Nerve growth factor agonist Neurotrophin-3 receptor agonist Oxygenase stimulant	Unspecified	Oral, swallowed	Neuroregeneration
27	SS-701	No Development Reported	Taisho	Nerve growth factor agonist	Unspecified	Unspecified	Neuroregeneration
28	SY-1200 neuroregenerative prog, Sygnis	No Development Reported	Sygnis Pharma	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroregeneration
29	COG-112 COG-68	No Development Reported	Cognosci	Apolipoprotein E stimulant	apolipoprotein E	Unspecified	Neuroprotection
30	FK-1706	No Development Reported	Astellas	Unidentified pharmacological activity	FK506 binding protein 4, 59kDa	Oral	Signal Enhancement
31	spinal cord therapy, Nanotope Parkinson's therapy, Nanotope stroke therapy, Nanotope	No Development Reported	Nanotope	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection, Neuroregeneration
32	anti-NogoR MAb, Teva	No Development Reported	Teva	Nogo receptor antagonist	reticulon 4	Unspecified	Neuroprotection

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Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
33	guanabenz, AcurePharma	No Development Reported	AcurePharma	Alpha 2 adrenoreceptor agonist	adrenoceptor alpha 2A adrenoceptor alpha 2B	Unspecified	Neuroprotection
34	AX-201	No Development Reported	Sygnis Pharma	Granulocyte colony stimulating factor agonist	colony stimulating factor 3 receptor (granulocyte)	Unspecified	Neuroprotection, Neuroregeneration
35	nerve regeneration therapy, Sangamo	No Development Reported	Sangamo BioSciences	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroregeneration
36	spinal cord injury therapy, Medipost spinal cord injury therapy, Genexine	No Development Reported	Medipost; Genexine	Nerve growth factor agonist	neurotrophic tyrosine kinase, receptor, type 2	Unspecified	Neuroprotection, Neuroregeneration
37	STP-805	No Development Reported	Sirnaomics	Gene expression inhibitor	Unspecified	Unspecified	Neuroprotection
38	PT-00114	No Development Reported	Protagenic	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
39	spinal cord injury therapy, ReveraGen Biopharma	No Development Reported	ReveraGen BioPharma	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
40	spinal cord injury therapy, Wintherix	No Development Reported	Samumed	Unidentified pharmacological activity	Unspecified	Injectable	Neuroprotection, Neuroregeneration
41	GTTI, Pharmaxon	No Development Reported	Pharmaxon	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
42	AIM-101	No Development Reported	AIM Therapeutics	Unidentified pharmacological activity	Unspecified	Injectable, intravenous Oral, swallowed	Anti-inflammatory
43	spinal cord injury ther, Thera	No Development Reported	Theralogics	Transcription factor NF-kappaB inhibitor	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Unspecified	Neuroprotection
44	NVA-011	No Development Reported	Neureva	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
45	spinal cord injury ther, Alnyl spinal cord injury ther, Merck	No Development Reported	Alnylam	Nogo receptor antagonist	Unspecified	Unspecified	Neuroprotection

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Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
46	PR-21, Pharmaxon cell mobility activator, Pharmaxon CMA, Pharmaxon PR-21C PR-21S	No Development Reported	Pharmaxon	Neural cell adhesion molecule agonist	neural cell adhesion molecule 1	Unspecified	Neuroregeneration
47	Cordaneurin nerve injury therapy, Neuraxo	No Development Reported	SCT Spinal Cord Therapeutics	Proline hydroxylase inhibitor	prolyl 4-hydroxylase, alpha polypeptide I	Injectable	Neuroregeneration
48	BIO-182	No Development Reported	Switch Pharma	Nerve growth factor agonist	Unspecified	Injectable, intravenous	Neuroregeneration
49	BIO-180	No Development Reported	Switch Pharma	Adenosine receptor agonist	Unspecified	Oral, swallowed	Neuroprotection
50	CanCorda	No Development Reported	SCT Spinal Cord Therapeutics	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
51	Corda-Chron	No Development Reported	SCT Spinal Cord Therapeutics	CXC chemokine receptor 4 agonist	chemokine (C-X-C motif) receptor 4	Implant	Neuroregeneration
52	antiangiogenics, Evotec antiangiogenics, Genentech	No Development Reported	Hoffmann-La Roche; Evotec	Angiogenesis inhibitor	Unspecified	Unspecified	Neuroprotection
53	AX-207 AX-201/AX-207	No Development Reported	Sygnis Pharma	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
54	AM-250 SCI therapy, AcurePharma SCI therapy, AnaMar	No Development Reported	AnaMar Medical; AcurePharma	Melanocortin receptor agonist	Unspecified	Unspecified	Neuroprotection
55	neuroprotective, Cambridge	No Development Reported	Cambridge Enterprise	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
56	gap junc modulators, Zealand-3 spinal cord injury ther, Zea	No Development Reported	Zealand Pharmaceuticals	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
57	L1, Acorda	No Development Reported	Acorda Therapeutics	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroregeneration
58	spinal cord injury ther,Cortex	No Development Reported	Cortex Pharmaceuticals	AMPA receptor agonist	glutamate receptor, ionotropic, AMPA 1	Unspecified	Neuroprotection
59	spinal cord injury ther, Parat	No Development Reported	Paratek	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection

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Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
60	PHA-55	No Development Reported	Pharma 21	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
61	ALE-0014439	No Development Reported	NPS Pharmaceuticals	Glycine transporter 2 inhibitor	solute carrier family 6 (neurotransmitter transporter), member 5 chemokine (C-X-C motif) ligand 10	Unspecified	Neuromodulation
62	neuroprotectives, Medarex	No Development Reported	Bristol-Myers Squibb	IP-10 antagonist	Unspecified	Injectable	Neuroprotection, Neuroregeneration
63	5HT1 receptor agonists, Dynog	No Development Reported	Dynogen	5 Hydroxytryptamine 1 receptor agonist	Unspecified	Unspecified	Neuroprotection
64	SRL NGF neurotrophic growth factor, SR	No Development Reported	Stratus Research Labs	Nerve growth factor agonist	Unspecified	Unspecified	Neuroregeneration
65	GCSF, Sygnis Pharma AX-200	No Development Reported	Sygnis Pharma	Granulocyte colony stimulating factor agonist	colony stimulating factor 3 receptor (granulocyte)	Injectable, intravenous	Neuroregeneration (neural plasticity)
66	CSF-G, Sygnis Pharma NWL-53	No Development Reported	New World Laboratories	Caspase 3 inhibitor	caspase 3, apoptosis-related cysteine peptidase	Unspecified	Neuroprotection
67	neurodegenerative therapy, Nerve Access	No Development Reported	Nerve Access	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection
68	RGS-2064	No Development Reported	Regenesance	Complement inhibitor	Unspecified	Unspecified	Anti-inflammatory
69	chondroitin sulfate modulators, Zacharon chondroitin sulfate modulators, Acorda Therapeutics	No Development Reported	Acorda Therapeutics; Zacharon	Chondroitin sulfate proteoglycan inhibitor	Unspecified	Unspecified	Neuroprotection
70	spinal cord injury therapy, TRB Chemedica	No Development Reported	TRB Chemedica	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroprotection, Neuroregeneration (axonal plasticity)
71	retinoic acid, NANOEGG Nanoegg	No Development Reported	NANOEGG	Retinoic acid receptor agonist	Unspecified	Transdermal	Neuroprotection
72	NM-101 TBOC	No Development Reported	NeuroMetrix	Potassium channel antagonist	Unspecified	Unspecified	Signal Enhancement
73	GSK-249320	Phase II	GlaxoSmithKline	Myelin associated glycoprotein antagonist	myelin associated glycoprotein	Injectable Injectable, intravenous	Neuroprotection

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Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
74	DF-2156A	Phase II	Dompe	CXC chemokine receptor 1 antagonist CXC chemokine receptor 2 antagonist	chemokine (C-X-C motif) receptor 1 chemokine (C-X-C motif) receptor 2	Oral, swallowed	Neuroprotection
75	glatiramer acetate 7-copaxone COP-1 Copaxone Copolymer-1	Launched	Teva Sanofi Takeda Proneuron Biotechnologies; Yeda	Myelin basic protein stimulant	myelin basic protein	Injectable, subcutaneous	Neuroprotection, Neuroregeneration
76	TRO-40303 TRO-040303 TRO-40X03	Phase II	Trophos	Apoptosis inhibitor	Unspecified	Injectable, intravenous	Neuroprotection
77	cyclosporin A, to-BBB 2B3-301 NVP-014 stroke therapy, NeuroVive stroke therapy, to-BBB	Preclinical	Maas BiolAB; to-BBB	Cyclophilin D inhibitor T cell inhibitor Immunosuppressant	peptidylprolyl isomerase D	Unspecified	Neuroprotection, Anti-inflammatory
78	AIM-102	Phase II	AIM Therapeutics	Unidentified pharmacological activity	Unspecified	Oral, swallowed	Anti-inflammatory
79	dexanabinol ETS-2101 HU-211 PRS-211092 PRS-211095 PRS-211220	Phase I	e-Therapeutics; Pharmos	NMDA antagonist Transcription factor NF-kappaB inhibitor Reducing agent Apoptosis stimulant	glutamate receptor, ionotropic, N-methyl D-aspartate 1 nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Injectable, intravenous Ophthalmological Oral, swallowed Topical	Neuromodulation
80	cutamesine dihydrochloride AGY-94806 Msc-1 SA-4503	No Development Reported	AGY Therapeutics; M's Science	Sigma 1 receptor agonist	sigma non-opioid intracellular receptor 1	Oral	Neuroregeneration
81	bcl-2, Neuro-Genesis	No Development Reported	Neuro-Genesis	Bcl2 stimulant	B-cell CLL/lymphoma 2	Unspecified	Neuroregeneration
82	F-spondin floor plate factor-5 FPF-5	No Development Reported	Paion	Nerve growth factor agonist	spondin 1, extracellular matrix protein	Unspecified	Neuroregeneration
83	FG-001	No Development Reported	F-Gene	Unidentified pharmacological activity	Unspecified	Unspecified	Neuroregeneration (axonal plasticity)
84	GRI-2 ALX-1393 ALX-1405 GlyT-2 inhibits, Allelix	No Development Reported	NPS Pharmaceuticals	Glycine transporter 2 inhibitor	solute carrier family 6 (neurotransmitter transporter), member 5	Injectable	Neuromodulation

Continued

Table 4 Continued

Number	Compound/Drug Name	Global Status (all indications)	Licensee/ Originator	Mechanism Of Action	Target Name	Delivery Route	Approach
85	axogenesis factor-1 AF-1, Alseres	No Development Reported Phase I	Alseres Pharmaceuticals	Nerve growth factor agonist	Unspecified	Unspecified	Neuroregeneration (axonal plasticity)
86	cimaglermin alfa GGF2, Acorda GGF2, Paion glial growth factor-2, Paion neuregulin-1 gene product, Paion rhGGF2		Acorda Therapeutics Bayer Paion	Growth factor receptor agonist	neuregulin 1	Injectable, intravenous	Neuroprotection, Neuroregeneration
87	DP-b99	Phase II	D-Pharm; Yungjin Wanbang Biopharmaceuticals	Hypocalcaemic agent Apoptosis inhibitor Chelating agent	Unspecified	Injectable, intravenous	Neuroprotection
88	TissueGene-N KLS-Nst TG-N	No Development Reported	Kolon Life Sciences; TissueGene	Bone morphogenetic protein stimulant Glial cell line-derived neurotrophic growth factor agonist	glial cell-derived neurotrophic factor	Injectable	Neuroprotection

Sources: PharmaProjects@Citeline, Inc. drug pipeline monographs (last accessed May 30, 2014), websites of individual companies holding license to listed compounds.

Preclinical models, type, and location of injury

Preclinical studies were performed in rat models exclusively for 5 compounds,^{32–36} in mouse models exclusively for 4 compounds,^{37–40} and in both rat and mouse models for 1 compound.⁴¹ Most injuries were contusive of low- to mid-thoracic cord, although cervical injury and cord hemi-section models were also used. Reported outcomes in rat studies were based primarily on the BBB score (with improvements of approximately 2-4.5/21 points), while the Basso Mouse Scale⁴² score (improvement of 2.5/9 points) and the modified BBB score (improvement of 4/14 points) were used primarily in mouse studies.

Compounds no longer in development

Although terminated programs might offer significant insight, information about compounds no longer in development was not readily available. In most cases, the reason for terminating is unclear but may include reevaluation of strategic focus or lack of funding. The vast majority of these compounds were novel therapeutics targeting neuroprotection. The remaining targeted neuroregeneration, or a combination of neuroprotection and neuroregeneration. Mechanisms of action varied widely with significant overlap with current programs.

Only 2 compounds have available information related to development termination (see Supplemental Table 4). Novartis halted research on ATI-355, a Nogo receptor antagonist. In 13 rhesus and cynomolgus monkeys subjected to cervical cord hemisection, manual dexterity improved after treatment with ATI-355.⁴³ However, results of the phase I trial (NCT00406016) were never published for unclear reasons. Christopher Reeve notably developed an anaphylactic reaction to monosialoganglioside GM-1 (Sygen), which failed to meet primary endpoints in a phase III trial.^{44–46} A 2009 Cochrane review of the phase II⁴⁷ and phase III^{44–46} trials found that poor study design and analyses precluded drawing meaningful conclusions about recovery.⁴⁸

Conclusion on the current R&D and commercial landscape

In providing systematic evaluation of recent R&D activity, this review is not an exhaustive analysis of every experiment or study conducted on all candidate molecules for SCI. Also, while it does not address which model or approach is most promising, this review identified trends and gaps that may influence future development and investment priorities. The pipeline has been hamstrung by significant heterogeneity of

modelling, study design, and outcome assessment. Most SCI programs continue to focus on motor improvement by targeting disease-modifying mechanisms, i.e. interfering injury potentiation or enhancing repair processes. However, non-motor symptoms remain significant challenges for patients.⁴⁹ As understanding of repair and regeneration mechanisms has increased, treatment window may expand beyond acute injury to weeks after SCI, requiring new study designs and offering options for combination therapies. In contrast to disorders, such as Alzheimer's disease, that focus on a limited number of targets, a wide array of mechanisms and approaches are being pursued for SCI. This is a reflection of the complex nature of SCI, relative disparity in research funding to identify key mediators of injury and recovery, and lack of universally accepted preclinical modelling. Finally changing demographics and aging of the US population will require further refinement of trial design and appropriate outcome selection. Studies to determine predictive reliability in other species, such as non-human primates and miniature pigs, and across the age spectrum would inform future trial design and decisions to enter clinical trials.^{2,50} Progress in the development of models, outcomes, and potential therapeutics rely on federal funding, patient advocacy groups, and scientific collaboration.⁵¹

Future outlook and directions

The direction of R&D for SCI treatments will continue to be driven by 1) patient need, 2) the opportunity to reduce cost of care and loss of productivity, and 3) emerging scientific and technological breakthroughs, such as nanomedicine, specific tissue targeting, cell therapies, and precision medicine. The complexity of SCI suggests that clinically meaningful improvements in outcomes will rely on selective, appropriately timed modulation of vascular, immune, growth, repair, and other signaling pathways;^{52–55} however, combination therapy will be challenging.^{56,57} Emerging drug formulation and delivery technologies will improve pharmacokinetics and -dynamics through blood-spinal cord barrier and scar tissue.^{58,59} Collective contributions of traditional R&D, increased transparency and data mining (e.g. Visualized Syndromic Information and Outcomes for Neurotrauma-SCI),⁶⁰ implementation of patient registries (e.g. Rick Hansen Spinal Cord Injury Registry),⁶¹ and development of data standards for clinical research (e.g. NINDS SCI Common Data Elements)⁶² will be essential. Advances in the prevention of injury, neurocritical care, rehabilitation, biomaterials, and devices will also play a key role in future pharmacotherapy.

However, until breakthrough in understanding the biology mediating SCI injury and recovery occurs, risk-averse companies will likely leverage repurposed molecules from non-SCI indications engaging SCI-relevant pathways.

Disclaimer statements

Conflicts of interest The authors have no conflicts of interest related to any of the compounds described in the manuscript.

ORCID

Michael L. James <http://orcid.org/0000-0002-8715-5210>

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