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NeuroPerspective formerly NeuroInvestment

Tracking next-generation neurotherapeutics

Spinal Cord Injury

NI Research

Commentary

No Free Lunch

In American politics these days, one of the fundamental debates has to do with the scale and reach of government, both in terms of what it takes in via taxation, and what it provides in terms of services/benefits. The uproar over taxation greatly exceeds the expressed willingness to cut services/benefits, and while this is a gross oversimplification, to some degree the conundrum comes down to this: People want their governmental services and benefits, but do not want to pay for them. The same can be said for the pharmaceutical industry, where there is no dearth of discourse over the decline of industry pipelines, and the need to replace revenues lost or soon-to-be-lost to generics. But there is a real disconnect between the cited need and the demonstrated willingness to invest in the next generation of drugs. As the abyss has yawned ever more near, the pharma and investment communities have in fact shrunken their level of fiscal engagement. In 2009, licensing upfront payments totaled $921 million, in 2008, $655 million. CNS partnering upfronts during 1H:11 (for drug development, not post hoc marketing or royalty agreements) have *totaled just $27.3 million*. Funding via stock offerings or VC rounds has totaled $257.1 million during the same period. This pace contrasts with the $821 million and $917 million provided during 2009 and 2010 respectively. While we expect activity to modestly improve in both categories over the second half of this year, the trend indicates a dramatic shortfall in both categories, at a time that the salience of pipeline deficits is increasing. This is almost bizarrely short-sighted and self-defeating.

News and Developments

Merck Serono Partners with Affectis

Affectis partnered its early-stage P2X7 program with Merck Serono, aimed at neurodegeneration. Affectis received $3.5 million upfront, and shares responsibility for discovery/preclinical research stage work, Merck Serono takes responsibility for development beyond that point (full preclinical development on).

Lundbeck/BioTie Complete Nalmefene Pivotals

Three trials of nalmefene in the treatment of alcohol abuse have now been completed, more than 2000 patients enrolled. Lundbeck and BioTie have reported that the pooled data shows that the number of heavy (more than 5 drinks per day for men, 4 drinks for women) drinking days per month is more than halved. However, more detailed information has not yet been released, which leaves some important questions unanswered. In particular, we would be interested in a less binary endpoint, since drinking is not an all or none phenomenon. For example, if male drinkers averaged five drinks per day, twenty days per month, and with nalmefene reduced their intake to four drinks average on ten days, our suspicion is that this would not be clinically meaningful. Abstinence on half those days likely would be, but the nalmefene premise has been that moderating the level of alcohol ingestion is a valid clinical goal, and that abstinence does not have to be the goal. Some undisclosed endpoints were apparently not reached, thus it will be necessary to await the formal presentation of data later this year before it will be clear whether this is a meaningful step or not.

Pfizer and Pain

It was a good news/bad news month for Pfizer and its inlicensed analgesia portfolio. **Pfizer/Acura** received FDA approval for their Oxecta, their version of a hopefully less-abusable hydrocodone. The prospects are questionable, since the companies had initially developed this program as Acurox, a combination of hydrocodone and niacin. The FDA had refused that on the grounds that the abuse-deterring effects of niacin might also deter appropriate analgesic use, thereby turning this into a redundant drug with no clear advantages. However, the Pfizer/**Pain Therapeutics** pain drug Remoxy, in theory another abuse-resistant, time-release opioid, was again rejected by the FDA, a manufacturing issue was cited. Pain Therapeutics said it could take a year or more to address this issue, one must wonder whether Pfizer's patience and interest may have been exhausted. Interestingly, Pfizer did note that it is looking at the possibility of acquiring **Icagen**, with whom it has a promising nonopioid analgesia R&D program.

Clinical, Regulatory, and Fiscal Notes

Alexza raised $16.1 million....**Targacept** raised $70.1 million (net) via a secondary stock offering....**Prexa Pharmaceuticals** raised $7 million...**Acadia Pharma** received a SBIR grant providing $2.4 million...**Seaside Therapeutics** has initiated a Phase III trial in Fragile X with STX209/arbaclofen...**Alkermes** is initiating a pilot study of ALKS-5461, which combines buprenorphine and an oral opioid modulator, for treatment-resistant depression. Targeting opioid receptors for TRD, given the ample competition, does not intuitively come across as a promising concept....**Titan Pharmaceuticals** will delay the unblinding of their Phase III study of probuphine in opioid dependence as the FDA, at the last minute, contemplates changing the statistical analyses to be done...**JNJ**'s NGF mAB fulranumab (licensed from **Amgen**) failed to hit its endpoints in a back pain trial interim analysis. Given that there is a clinical hold on non-cancer trials using NGF mAB, this may be all the data they will ever have from it....**Cortex Pharmaceuticals** sold an option on its rights to CX1632 to **Servier**, who has this Ampakine in Phase I. If Servier exercises the option, they will pay another $2 million, and Cortex will relinquish all rights. Cortex needed cash now, but parenthetically, if Servier does see enough promise in Phase I (and safety/tolerability has been the weak spot for this class) to exercise the option, that may stimulate more interest in Cortex's preclinical trophic Ampakines, which likely have some pharmacokinetic advantages....**GSK/Valeant**'s retigabine/ezogabine/Potiga was approved in both the US and EU, though the EU provided a lengthy list of alternative anti-epilepsy drugs which should be tried first....**Zogenix** obtained $30 million in a royalty deal with **Cowen**....

Rear View Mirror 1H:2011

Best News
'Nicotinics'

Worst News
The pace of partnering and funding deals lags far behind even last year's anemic performance

Could Have Been Better, Could Have Been Worse

Cephalon's sale to **Teva Pharmaceuticals**. It would have been better had Cephalon stayed independent and rekindled its fading investment in neuroscience. But better Teva than **Valeant Pharmaceuticals**. In Valeant's hands, Cephalon would have been stripped faster than a BMW parked overnight in East LA.

Realtor of the Century, thus far

"these condos are moving fast, you'd better put down a deposit, another couple saw it today, they loved the granite counters and the gazebo out back, I wouldn't be surprised if they come back with an offer tonight..."

Randall Kirk was able to convince **Forest Laboratories** that Viibryd was worth at least $928 million, with the slim possibility of contingent rights raising that as high as $1.2 billion.

Dumbest CEO: Interim Analysis

Avanir's launch of Nuedexta combines all the elements that Congress and the public like to hate about the pharma industry, in one easy-headline package. And CEO Keith Katkin baldly admits to off-label marketing. More on this on p.6

Making Grants That Matter

California Institute for Regenerative Medicine made a $25 million grant (technically a loan, to be repaid IF the cell therapy product is commerzialized) to **Geron** (more on p. 4)

Cutting-Edge, in Hiuman HOC/POC trials

Allon Therapeutics davunetide for PSP
NeuroNova sNN0029 for ALS, sNN0031 for PD
NeuralStem spinal stem cells in ALS
Ceregene CERE-120 for PD
NsGene NsGO202 for AD
Neurologix NLX-P101 for PD

Most Impressive VC Funding

NeuroPhage, raising $12.1 million for a very unorthodox neurodegeneration program

1H Highlights

1) 'Nicotinics:' In a drug development world where one might think that redundancy is the only alternative to failure, nicotinic alpha 7 modulation has become the novel mechanism of choice, at the head of the pack addressing cognitive dysfunction associated with schizophrenia. Two well-funded, quality-science companies (**Targacept** and **EnVivo**) are heading into pivotal testing with their own resources and control of the process. High-quality molecules using a novel mechanism to address a huge 'unmet need.' This is the way the industry is supposed to be run, but seldom has been.

2) MS and the Oral Therapeutic Generation: So far, **Novartis**' Gilenya has not run into a major obstacle in its quest to become the standard Plan B for patients not responding optimally to the ABC drugs, and for some patients, an option for first-line therapy. **Merck Serono**'s cladribine hit the regulatory wall in both the US and EU, and Merck Serono finally made the difficult but rational decision to drop cladribine, even in the countries where it had been approved.

For the time being, **Biogen-Idec**'s next-step oral MS drug, BG-12, holds the high ground vs. **Teva/Active Biotech**'s laquinimod. In Phase III, laquinimod reduced the annualized rate of relapse (ARR) by 23% compared to placebo. Biogen-Idec's relapse rate calculation for BG-12 was based on the proportion of patients relapsing over two years, where the drug group's proportion was 49% lower. But their secondary endpoint, effect on ARR, was much higher than laquinimod's, reducing it by 53%. The next two Phase III trials report during 2H:11, each comparing the oral drug to the competitor's mainstay injectible. With all due respect to the fact that these were not head-to-head trials, that is unlikely to fully explain the difference between 23% and 53% effects on ARR. The key for all of these programs will be Gilenya's safety profile over the next year or two.

Our guess is that by the end of the year, with the next two active-comparator trials having reported, that BG-12 will continue to have an edge in terms of efficacy. Laquinimod may have some potential utility, because of what looks like (comparing all of the clinical trial data obtained thus far) excellent tolerability. The fact that laquinimod is taken once-daily, BG-12 twice-daily, will not be a major consideration for a population that has long had to deal with subcutaneous and IV drug administration. Novartis has a more selective S1P1 drug in the clinic, **Receptos** is working in the same vein. **XenoPort**'s fumarate prodrug has just surfaced as a dark horse candidate; XP23829 showed better pk and efficacy results in an animal model than a traditional fumarate used in Europe.

The state of the therapeutic art in MS is where every other neurological indication hopes to be--by 2020.

3) Acorda and Ampyra: This has been a very successful launch, and the shift of sentiment by EU regulators should result in giving **Biogen-Idec** the opportunity to see what they can do in that challenging market(s).

4) Seaside Therapeutics and STX209: Fragile X and autism are receiving well-deserved attention, and privately held Seaside is at the forefront, having just launched a Phase III trial in Fragile X (a second is imminent) and a Phase IIb in autism. **Roche** and **Novartis** are also very active in this area.

5) Lilly and Medtronic Partner on PD/GDNF Project: It has been a long time since we have watched a major pharma company move ahead with a program that seeks to utilize a neurotrophic factor as a neuroprotectant, but Lilly is doing exactly that. Lilly has developed an altered form of GDNF that they believe will provide better access to key areas of the Parkinsonian brain, selectively targeted and delivered via a Medtronic infusion pump. This puts this very well-funded collaboration up against **MedGenesis** and their convection enhanced delivery method for GDNF, and against **Ceregene**'s gene vector delivery of neurturin.

6) Pre-Competitive Space: There is a nascent awareness that some elements of CNS R&D should be shifted into the 'pre-competitive space', where information-sharing rather than traditional black box secrecy can eliminate unacceptably expensive redundancy. Collaboration in the identification of relevant biomarkers and in identifying clinical trial 'noise' which make it even more difficult to achieve signal-detection (that a drug actually has a desired effect) has been a first step. One project under consideration by ISCDD is the pooling of clinical trial data to determine, amongst other things, if there are clinical trial sites with a consistent record of heightened placebo responses, which could reflect deficits in adherence to patient enrollment criteria.

7) Geron and a Grant that Matters: Last year's indiscriminate giveaway of $1 billion in federal money to companies that did not even have to be operating to qualify epitomized the worst of grant funding--providing enough (most companies received $792K) for a headline, not enough to actually make progress. In contrast, the **California Institute for Regenerative Medicine** made a $25 million grant (technically a loan, to be repaid if the cell therapy product is commercialized) to Geron, which allows Geron to run a clinical trial in Spinal Cord Injury.

1H:11 Funds Raised (US$ millions)

Company	raised (US$million)
Targacept	86.3
Corcept Therapeutics	41.9
BioTie	37.8
Alexza	16.1
Acadia Pharmaceuticals	15
NeuroPhage	12.4
NuPathe	10
StemCells	9.4
Sygnis	8.6
Prexa Phamaceuticals	7
Euthymics Bioscience	4
BrainStorm Therapeutics	3.6

This grant provides enough to make a difference, and the grantee repays the money if successful, allowing the funds to then go to another deserving program.

Mixed Bag

1) Somaxon's Silenor: We asked in January: "Can Somaxon, with a modest assist from **Procter & Gamble**, establish a beachhead for Silenor as a non-GABAergic insomnia alternative?" So far, no. But Somaxon did sell a package of Canadian and other ex-US rights to **Paladin**. A PR header read: *"Somaxon to Receive Up-front and Milestone Payments of Up to US$129 million."* That was a tacky evasion of the reality, which is that $500K was paid upfront, the other $128.5 million is predicated upon milestones. Paladin did buy $5 million worth of Somaxon stock.

Lowlights

1) Valeant Pharmaceuticals: Valeant acquired and quickly disemboweled **Biovail**, and had **Teva** not come along and outbid them, they might have done the same thing to **Cephalon**. All of this in the service of bloating themselves

1H:11 CNS Drug Development Partnerships/Licensings

Big Pharma	Indication	Small Company	Drug/Mechanism	Year	Phase	upfront	milestones
Merck Serono	neurodegeneration	**Affectis**	P2X7	2011	discovery	**3.5**	404.9
Elan Pharma	AD, PD, HD	**Proteostasis Therapeutics**	proteostasis modulators	2011	discovery	**20**	U
Takeda	Schizophrenia	**Intra-Cellular Therapies**	PDE1b	2011	preclinical	**U**	500
Merck Serono	Parkinson's	**Domain Therapeutics**	mGluR4 agonist	2011	discovery	**2.8**	178
Bristol-Myers Squibb	Stroke	**NeurOp**	NR2B	2011	preclinical	**1.5**	74

as quickly as possible, in the hope of then being taken out themselves. This kind of cynical, destructive strategy should be anathema in an industry whose survival in the long run will depend on extending, rather than contracting, timelines for growth.

2) Once again, Pfizer/Medivation's Dimebon lived down to our low expectations, failing in a 403pt Huntington's Phase IIb trial, and the HD program has been shelved. A pared-down Alzheimer's Phase III program limps on, primarily due to the rationale that, since it must be fully enrolled, they might as well see it through. The take home message? Even the biggest companies sometimes see what they want to see, not what is really there.

3) Avanir and Nuedextra for pseudobulbar affect. Some analysts project a half billion in peak annual sales, but we still have doubts about the salience of PBA in the context of MS and ALS. Avanir is now citing a US PBA population of 2 million, which must constitute the widest possible definition of the disorder. We would be surprised if the number of US patients whose PBA is clinically salient exceeds 20-25% of that.

Machiavelli's Bio Hall of Fame

Presuming that the Teva acquisition of Cephalon is eventually completed, after the FTC has made its usual inquiries in the service of looking like they are genuinely concerned about maintaining competition, it is worth noting the panoply of innovations and accomplishments that can be ascribed to Cephalon:

1) The Trojan Horse Orphan: Modafinil/Provigil was initially tested and approved for the treatment of narcolepsy, an orphan disorder comprising a patient population in the tens of thousands, with a market potential that likely would have topped out at couple hundred million dollars annually. This foot-in-the-door set the stage for additional innovations (see below) and an eventual billion-dollar plus annual sales pace.

2) 'Doctors Without Borders:' No, we are not referring to the commendable organization which provides medical services in some of the world's most desolate and devastated quarters; we refer to Aggressive Off-Label Marketing to physicians of all stripes. Cephalon promoted off-label uses for Provigil, Actiq, and Gabitril, boosting sales even as they carried out clinical trials to assess the validity of the claims. In 2008, they paid a $425 million penalty, a mere speeding ticket compared to the revenues gained.

3) Excessive Daytime Sleepiness: Who knew this was a disorder? Cephalon was the first neuro company that we know of that took a set of disparate symptom syndromes and successfully reframed them as an overarching disorder.

4) Pay-for-delay: Cephalon wrote the book on how to delay generic competition by cutting deals with generic companies, providing legal savings and certainty in exchange for another couple years of marketing exclusivity.

5) Minimally Differentiated Substitution: In the neuro sector, Cephalon was the first company to substitute a chemical relative with little or no clinical advantage (unlike Adderall's replacement by Adderall XR) in the hope of staving off a generic challenge to the forebear. Nuvigil, Provigil's enantiomer, offers no substantive advantage other than its patent life. But once approved, Cephalon jacked up the price of Provigil in order to steer patients to the newer option. We suspect that, once modafinil goes generic, this ploy will be revealed as a failure.

6) Confronting the FDA. When Myotrophin was stymied by the FDA, Cephalon loudly complained, and refused to run another trial. Instead, they rallied masses of patients, prescribers, and pundits to flood Washington D.C. and turn Congress against the FDA...OK, that did not work out so well. Myotrophin is still 'approvable.' But it did provide a teaching moment, where other companies learned that publicly 'dissing' the FDA was, and is, not a prudent tactical choice.

7) Hedging Against Risk: Cephalon created a separate business entity which held Myotrophin as an asset, and when Myotrophin demised, it was the holders of that entity that were burned far more badly than were Cephalon shareholders.

8) Inlicensing as a cheaper route to building a pipeline: Provigil, Actiq, and Gabitril were all inlicensed, indeed Cephalon never developed a neuro NCE other than enantiomer progeny one step removed from their parents.

One unfortunate dynamic is that Cephalon triggered what might be thought of as an allergic reaction at the FDA, sensitizing the Agency to future uses of the very tactics that served Cephalon so well. The FDA now sniffs out Trojan Horses, demanding that trials be run with a range of likely clinical populations, and off-label marketing has diminished, along with the lavish 'educational opportunities' (shrimp, skiing, scuba) that had greased the way. Pay-for-delay is under fire. Molecular tweaking is still attempted, but the pricing power now possessed by generics makes this look like a losing battle. The inlicensing model has become increasingly popular, as more companies eschew the costs and risks of CNS drug R&D. This is not a benign outcome.

All in all, Cephalon is a successful company which got there via clever maneuvers and opportunism rather than innovative science. And they essentially abandoned neuroscience, seeing easier paths in oncology and inflammation. Towards the end, there was a glimmer of a renewed taste for adventure (**Mesoblast**), but its viability has yet to be established. Ironically, when we first contemplated writing this piece, it was planned to be a congratulatory note of appreciation for a job well done. But it did not turn out that way. It is a sad statement that Cephalon is one of the best examples of a successful neuroscience company, in spite of the fact that its legacy is one that only a confirmed cynic could look at with unabashed pride. Provigil was, and is, a good drug which has provided benefit to millions. Other than that, Cephalon's lasting contributions to the CNS field are far outweighed by the tarnished history of its strategic maneuvers and opportunism.

That is just one of several problems that we see as tainting the Nuedextra story, and its prospects. Besides the magnitude of population inflation, which may be unprecedented, Avanir is openly discussing unlabeled uses for Nuedexta which to us, walks a risky tightrope indeed. During the most recent quarterly call, Avanir's CEO, Keith Katkin, was asked if the Avanir sales force was focused on MS and ALS PBA, which are the only two approved indications. In order to minimize regulatory scutiny, there is only one correct answer to this question: "Yes." Instead, Katkin bluntly replied "No", explaining that the Avanir sales force is not focusing primarily on ALS and MS at present, and in fact is devoting 40% of its time to non-neurologists. Given that ALS and MS are treated by neurologists, this blatant courting of prescribers for off-label indications is something that, if one is going to do it, one should be prepared to lie about it. Perhaps Katkin is hoping that this is too small a market to constitute an issue that the FDA will care about. However, Nuedexta is big enough to have attracted Congressional attention (see below), which means the FDA might also decide to make a show of force here, if only to show Congress that it can.

Finally, there is the pricing. Monthly costs for Nuedexta generally run in the $400-500 range, for a drug which combines two generically available subcomponents. It is red meat for Congressional critics who love to catch the pharmas 'in flagrante delicto,' and indeed, three members of Congress have already asked Avanir to explain the pricing model. The fact that Avanir spent considerable money searching for an indication, and then for a dosing regimen acceptable to the FDA, is unlikely to elicit great sympathy from anyone outside of Avanir, its bankers, and its shareholders. If one were seeking a new poster child for '*What is Wrong with the Drug Industry*', Avanir's audition is pretty compelling.

*4) **Corporate Self-Mutilation***: Virtually every BP with a CNS program worth mentioning has amputated thousands of staff members. They began with the armies of sales reps rendered irrelevant in a de facto price-controlled environment, but in many companies, huge swathes of R&D have been excised. Several companies deleted CNS from their roster of business units; others deleted inhouse research on psychiatry, or shelved entire indications, like **GSK**'s divestiture of depression and pain. The concept of shifting some R&D in order to utilize small company efficiency and focus, is something *NIR* has advocated for years. But this culling is ill-planned and transient. One high-profile CNS success--and there will be one--will trigger a 180 degree turn back to CNS.

*5) **Speaking of cynical strategies, Vanda Pharmaceuticals announced that they will develop tasimelteon for depression.*** Tasimelteon is the melatonin receptor agonist which was first directed to insomnia, where it failed, and then to the treatment of circadian rhythm disorders in the blind. Having seen TRD emerge as a hot area over the past year, Vanda is now jumping in, where the competition is far better equipped and prepared. The only likely outcome is that Vanda's still considerable cash position will be squandered more rapidly.

*6) **Jazz Pharmaceuticals:*** While they have done a better job marketing Xyrem for narcolepsy/cataplexy than we had expected, the pursuit of fibromyalgia was a fool's errand, given that there are three safer drugs already approved. Jazz overlooked that fact, but the FDA did not, and after several rounds of obfuscation, Jazz finally got the message that this label-extension was doomed. Having now tabled this program, we have little hope that Jazz's management will do anything more creative than licensing another me-too, has-been, or reformulated drug for their sales force to sell. They have the resources to do something more productive, but have yet to show the vision or energy.

*7) **NGF-blockers:*** This formerly promising novel analgesic class could be dead-before-arrival, unless the seemingly too-good-to-be-true premise that patients overdid activity because the drug was so effective pans out. Non-cancer pain trials remain on FDA hold, and JNJ recently reported that fulranumab missed all its endpoints in a back pain trial.

*8) **Captain Kirk's Enterprise: Randall Kirk plays on corporate fear more effectively than anyone else we know:*** He was undoubtedly able to play on **Forest**'s loss of patent protection on Lexapro next year, and their fear that someone else might get hold of vilazodone/Viibryd. Unfortunately, $928 million put into Viibryd is $928 million that is not going to be usefully invested.

Selected Quotations

"CNS is the New Oncology"

--**Roche** CFO, January 2011

That's it. The take-home quote for 1H:2011.

Selected Company Events

Acadia Pharmaceuticals raised money at a premium in order to fund the ongoing Phase III for pimavanserin in Parkinsonian psychosis. **Acorda Therapeutics** saw its prospects for Ampyra in EU improve greatly as an unexpected shift in regulatory sentiment came to light. The P2X7 program at **Affectis** took a surprising turn when **Merck Serono** partnered it for neurodegeneration. **Allon Therapeutics** is actively enrolling patients in their trial of davunetide in their Progressive Supranuclear Palsy trial. **CeNeRx** hopes to have results before year-end from their Phase IIb trial of TriRIMA in TRD. **Afraxis** encountered pharmacokinetic obstacles with their lead compound which has forced them to develop a backup, now hoping to enter the clinic in early 2012. **Alexza Pharmaceuticals** was able to raise money, now they must

wait for the FDA to announce their response to the NDA for AZ-004. **Alseres** is a corporate obituary waiting for space to open in the newspaper. **BrainCells** has entered a more quiescent period following the departure of their CEO, reformulating and vetting their combination drug (BCI-952) for TRD. **Cortex Pharmaceuticals** is again in the position of needing to partner or be acquired in order for its Ampakines to move ahead clinically.

Biogen-Idec's fumarate, BG-12, produced sufficiently impressive results in Phase III that it may be the competitor that **Novartis** must watch most closely. Biogen-Idec is also hoping that the drumbeat of escalating PML totals for Tysabri can be offset by their jcv test, which they hope can satisfactorily identify at-risk patients. **Catalyst Pharmaceuticals** entered a NIDA-financed Phase II for vigabatrin in cocaine abuse, while animal data showed their next-generation compound (CP-115) suppresses epileptiform spasms three times longer than does vigabatrin/Sabril. **Ceregene**, having revamped its dosing and tactics, has moved into another Phase II trial for CERE-120 in Parkinson's. **EnVivo Pharmaceuticals** produced strong data for EVP-6124, their nicotinic alpha7 agonist, in schizophrenia. Phase III is next, to be run inhouse. They have also initiated Phase I for their GSM Alzheimer's candidate. **Euthymics Bioscience** is running Phase IIb/III for their triple amine drug, EB-1010.

Intra-Cellular Therapies is preparing Phase IIb for their ITI-007 in schizophrenia, while partnering their earlier-stage PDE program with **Takeda**. **Lundbeck** (with **BioTie**) announced Phase III success with nalmefene in reducing the frequency of alcohol abuse. We continue to have some questions about the clinical meaningfulness of this modest decrease in severe drinking. So far, so good for **NeuralStem**'s cell therapy program in ALS, where no safety problems have emerged, and they are now able to raise the dose and treat patients with more potential for rescue. **Neuren** continues enrollment in their TBI Phase III. Trials in both ALS and Parkinson's, utilizing **NeuroNova**'s neurotrophic tactics, should report later this year. **NsGene**'s trophic approach to Alzheimer's has been safe thus far,and **ReNeuron** has begun enrollment in their cell therapy trial in stroke. **Naurex**'s Glyx-13 trial in depression is underway, reporting its results next year.

NeuroSearch, which divested/spun off research programs in order to focus on Huntexil, was informed by the FDA that they do have to run another Phase III. **Prana**'s plans to run the long-awaited Phase IIb trial for PBT-2 in Alzheimer's was scaled back to a small-scale biomarker study. **Neurocrine Biosciences** reported positive clinical results for its VMAT inhibitor, aimed at Tardive Dyskinesia, which would have been big news in 1985. **XenoPort** had an outstanding 1H:11, with the FDA's approval of Horizant (partnered with **GSK**) at the forefront. However, what is of equal interest is their announcement of a fumarate prodrug for MS, which might eventually be a competitor to **Biogen-Idec**'s BG-12. Tiny **Seaside Therapeutics** is launching two Phase III trials of arbaclofen/STX107 in Fragile X, and a Phase IIb in autism, a huge undertaking.

Targacept has set the stage for running its own pivotal trial program for TC-5619 in schizophrenia, raising $70 million in the wake of **AstraZeneca**'s unwise decision to not exercise their option. Proving that ending partnerships is not always a bad thing, this was the second such event, with **GSK** having exited their partnership earlier this year. These would have been potentially disastrous for a company lacking resources, but Targacept is well-equipped to proceed on their own, even though they have to pay for some of the Phase III costs for TC-5214, thosetrials being run by AstraZeneca.

Looking Ahead 2H:11

Questions

Invest or Divest: No Big Pharma company has yet devised a CNS pipeline that seems comprehensive and complete. Because failures reverberate loudly, it would be better for a company to simply withdraw, as **Amgen** did a few years ago, than to erect a Potemkin Village of half-hearted efforts. Watching for signs of genuine investment in CNS, and we are not talking about funding tenured faculty, will be a key for 2011 and beyond.

NeuroNova and neurotrophins: Will their trophic tactic work in Parkinson's and/or ALS?

Alexza's AZ-004: Will the FDA give hospitals a needed alternative to IM antipsychotics?

CeNeRx's TriRIMA: Is this going to be the safe MAO inhibitor option that American psychiatry has been lacking?

EnVivo and Alzheimer's: Will the Alzheimer's Phase IIb data this fall continue EnVivo's string of successes? **Targacept/AstraZeneca** did not score a success in AD, so if EnVivo does, that will put them in a select group of one. If so, one would think that a major pharma would try to make them an offer too good to refuse--but with **Fidelity** apparently willing to bankroll pivotal testing, EnVivo probably will.

Spinal Cord Injury

Spinal Cord Injury is one of those disorders whose prominence exceeds its prevalence: In the United States, 11,000 individuals suffer paralysis each year secondary to spinal cord trauma, with a total of more than 200,000 US patients living with SCI. Advances in acute care now produce a survival rate of 95%, 40% higher than ten years ago, thus the number of those facing a lifetime of disability has burgeoned. The functional loss takes on a kind of hideous irony for those who suffer spinal cord injuries as a result of sports activities, such as football, diving, or ice hockey. 80% of SCI victims in the US are male, consistent with the association between testosterone and risk-taking. Lives that were oriented to physical activity are suddenly shorn of this core capacity. 70% of those suffering spinal cord injuries in the US do so as a result of a motor vehicle accident or athletics, these young patients (60% are under age 30) face a lifetime of struggle without much realistic hope of regaining anything approaching full functionality. There is a cornucopia of other functional disabilities and consequences that are also destructive and demoralizing. Patients with SCI often suffer painful muscle spasms, neuropathic pain, bladder disorders and infections. What makes this fate particularly burdensome for these individuals is that they are cognitively intact, trapped within bodies that no longer respond to their commands and needs. Navigating even the most routine of days is a tremendous trial for the victims of spinal cord injury. It is reminiscent of ALS in this respect, but with one key difference; it is a transformation that takes place in a calamitous second, not years of slow exsanguination. And like TBI, it tends to impact people in young adulthood, as they approach the prime of life. As a result, they are vulnerable to psychiatric sequelae, particularly depression. Because of the intensity and duration of care required, SCI incurs care costs of more than $8 billion per year in the United States alone.

The Neurobiology

The spinal cord is a conglomerate of axons providing a conduit for communication between the brain and the body's periphery. The communication is two-way: Commands emanate from the brain to effector muscles, while proprioceptive, nociceptive, and kinesthetic signals return vital information regarding body position, condition, and sensation. The cord is protected within a bony canal, but that canal is vulnerable, and can become deformed or shatter in response to forces of dislocation. In SCI, the cord ends up compressed, or severed, partially or totally. Less than 5-10% of patients with spinal cord injuries suffer complete transections of their cord, and there is enormous variation in the type and degree of control retained by those whose cord contusions have left some fibers intact. Secondary assaults from glial scarring, apoptosis, ischemic damage, and excitotoxicity expand the extent of axon death. While less than 90% of patients have complete transections, about 60% have some detectable function remaining post-injury. Since afferent and efferent fibers connect to the spinal cord along its entire length, in rough correspondence to the areas of the body served; the higher up the cord that the injury occurs, the more devastating is the extent of functional loss, since all that is downstream of the break is at risk. A two syllable anagram denoting the location of the energy (e.g. C4, C5) communicates volumes to a neurosurgeon, neurologist, or physiatrist about a patient's prospects: an injury in the cervical area (which accounts for about half of all SCIs), means a 50% chance of quadriplegia. Individual cases do not always fall neatly into a category. Some patients have partial preservation of some limited function, others may differ from side to side. Others show some recovery, shifting from one category to another. Ultimately, functional outcome depends on where along the spinal cord the injury occurred; which fibers were damaged; how much demyelination occurred in the surviving tracts; and the degree of compensatory plasticity that can be obtained from neurorehabilitation. This heterogeneity complicates clinical trial design and execution. For some patients, there is limited retention of sensory or motor capacity, for others the experience is primarily of awkward and demoralizing spasticity. But for all, what was once automatic, becomes agonizingly slow and torturous, even with rehabilitation.

SCI is the spinal corollary to traumatic brain injury or stroke, involving a sequence of neuro-destructive processes. There is an immediate, primary locus of destruction, followed by a secondary process of cell death, via both necrosis and apoptosis. The immediate area of nerve 'crush' (most frequently) or laceration may be doomed, as is the primary infarct in ischemic stroke, but complete, immediate transections of the cord are rare. Instead, there is a potential battlefield involving nerve cells contiguous to the area of initial destruction, within which putative SCI therapies seek to operate. This battlefield encompasses areas affected by the acute sequelae of SCI, an unleashing of degenerative processes that include edema (further compressing nerve

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tissue), blood flow compromise, which causes ischemia, thus leading to excitotoxicity, and demyelination. Since the blood brain barrier also shields the spinal cord, and SCI generally means a breach of the BBB, this also allows the entry of T-cells. Some researchers believe that this T-cell activation causes degeneration, similar to the demyelination characteristic of multiple sclerosis.

Thus, there are circuits that can in theory be protected from secondary destructive processes, circuits that could remain functional, and perhaps even amenable to regeneration. Unfortunately, encouraging animal model data does not necessarily, or even often, translate into human benefit.

Acute SCI Treatment

There are a number of putative therapeutic strategies that address the direct functional/motoric consequences of spinal cord damage. The focus in this review is upon pharmacotherapy and cell therapy strategies addressing the biological damage of SCI, not the highly sophisticated neurorehabilitation and electrical stimulation programs that take physical therapy techniques to a whole new level, in the service of boosting inherent capacities for compensatory plasticity.

The acute treatment of SCI aims to reduce the scope of the damage that spreads from the initial locus of injury, due to inflammatory, necrotic, and apoptotic processes. In practice, this means neurosurgical stabilization and decompression. A 243 pt study showed that decompression of the cord less than 24 hours post-injury was associated with a quadrupling of the proportion of patients (from 5.3% to over 22%) who showed a two grade improvement on the ASIA scale. Once-routine steroid treatment has now been de-emphasized. The original premise was that steroids reduced inflammation and had antioxidant effects, but a 2004 paper in *Spinal Cord* showed that methylprednisolone's efficacy was an illusion. Indeed, steroids induced myopathy, and it was recovery from that iatrogenic myopathy that mimicked neuroprotection. Receiving increasing attention is the use of post-traumatic hypothermia, whose record is inconsistent in stroke and TBI, but may have a place with SCI.

Next Generation SCI Therapy

Neuroprotection

Given the evidence that post-injury cell death due to excitotoxicity is a key factor in SCI disability, neuroprotective tactics have been pursued for SCI, albeit pursued less extensively than in stroke or TBI. A PhII trial of the NMDA-antagonist Riluzole, which also has sodium-channel blocking effects, is scheduled to be completed in 2011. Given its poor efficacy in ALS, where it was approved due to the lack of any option, we are not optimistic about its likelihood of providing much benefit in SCI. **Pharmos** did nerve crush work with dexanabinol in the distant past, and reported neuroprotective results. **KeyNeurotek**, with a CB1/2 drug having shown preliminarily positive Phase IIa data in a 97pt TBI trial, could turn to SCI eventually. Germany's **Apogenix** received a US1.2 million governmental grant to study the preclinical use of a fusion protein combining part of the apoptosis C95 factor and a portion of IgG, to prevent apoptosis in SCI, but their focus now appears to be elsewhere.

There has been heightened interest in antioxidant and free radical scavenging strategies. Any antioxidant drug that proves effective in either stroke or TBI could be eventually considered for use in SCI. Other novel targets include the MAP kinases, which contribute to post-injury cell death; MAPK inhibitors have received attention from McGill and Harvard groups. The antiinflammatory cytokine interleukin-10 has shown preclinical promise in reducing impairment in a rodent model of SCI, so long as it is given soon after injury. Minocycline also can suppress caspases 1 and 3, thereby providing an antiinflammatory effect that should be neuroprotective, and a clinical trial is getting underway.

Sygnis/Axaron obtained preliminary positive findings with GCS-F in stroke, and eventually might consider expansion into SCI, but their prospects, indeed survival, hinge upon the stroke Phase IIb ending late this year. **Aeolus** had some preclinical data for its antioxidant AEOL1950 that shows protective benefit and functional improvement, but is focused elsewhere. **TetraLogic Pharmaceuticals** licensed a necrosis-inhibiting platform from Harvard, and cites SCI as one of the potential neuroprotective emphases.

A McGill group published animal work using fenritinide, a synthetic retinoid being studied in cancer. It is an anti-inflammatory that reduces the production of arachidonic acid and TNF-alpha. Improved function was reported from animal testing. An Italian group, which includes Daniele Piomeli, has reported that NAAA-inhibition can be neuroprotective in animal SCI models, reducing tissue damage via reduction of PPAR-alpha.

Regenesance is developing RGS2064, a complement inhibitor already in human use that Regenesance believes can be repurposed for use in acute contexts, such as Traumatic Brain Injury and/or Spinal Cord Injury.

Maprég is developing MAP4343, a neurosteroid derivative which is in clinical testing. It binds to pregnenalone's

receptor, MAP2. MAP2 (Microtubule assembly protein 2) is involved in microtubule assembly, and thus is expected to be neuroprotective and to generate neurite growth. MAP2 is reduced in SCI, MAP4343 restored MAP2 levels in spinal trauma models. Phase I was ongoing during 2010, and Phase II had been expected to begin before the end of the year. There has been no indication thus far of that occurring, and funding could be an obstacle.

Pharmaxon's PR-21S is a CAM modifier (a polysialic acid mimetic) which has shown the ability to reduce glial scarring post-injury in animal models and to thereby increase axonal growth and improve motor function. Preclinical tox testing was to be completed in late 2010. The basic premise is that NCAMs interfere with regenerative neuronal migration and/or growth, thus modifying them will enhance the effect of other growth-induction tactics.

Axonal Regeneration: Inhibiting the Inhibitors

One of the central themes of regeneration research has been identifying the factors that hinder the process of axonal extension and reconnection in the CNS, in contrast to the regeneration that occurs in the PNS. Even without augmentation, 5-20% (according to Martin Schwab) of affected fibers regenerate, though they have to do so working around scarring of the original issue, they cannot go through it. The scar is not just a physical barrier, it is also a neurochemical obstacle, activating growth inhibitors. While regenerating fibers appear to follow signaling molecules to find a meaningful 'hookup,' this is generally not enough to re-establish significant function, at least partly due to inhibitory factors which cause axonal growth cones to collapse and become nonfunctional. Finding a way to interrupt growth-inhibiting signals is the most heavily pursued strategy in SCI research. Many of these factors are components of myelin, and there is myelin 'debris' around the spinal injury site. Three of the inhibitory factors found in myelin: MAG (myelin-associated glycoprotein), OMGP (oligodendrocyte myelin glycoprotein), and the best known such factor, Nogo-A/Reticulon-4; all bind to different areas of the Nogo receptor. The Nogo receptor serves as part of a complex involving that receptor plus either p75 or the protein TROY (both related to the TNF family, and hence contributory to inflammatory processes), and/or the protein Lingo-1. When this receptor complex is activated via any or all of these binding sites, the next step along the pathway is Rho. When Rho is activated, the growth cones that guide axonal extension collapse, and growth stops. Additionally, inhibiting the inhibitors at this stage can also mean inhibiting apoptosis, since p75 is involved in apoptosis. Thus, classifying this pathway as purely regenerative is actually a misnomer for the sake of brevity: choosing the right target will not only allow regeneration to proceed, but will also protect surviving tracts from subsequent apoptotic cell death.

From a historical perspective, this crucial understanding of endogenous 'anti-growth' processes dates back to when Schwab first identified Nogo, in 1988. It has been recharacterized over time as a regulator of axonal sprouting, and multiple programs aimed at suppressing Nogo have been conceived since then. The first workaround licensed by Schwab to **Regeneron** involved the use of monoclonal antibodies (NI-35, NI-250), but those antibodies eventually proved nonviable. **Novartis** (with whom Schwab is now working) has produced another antibody, IN-1. In a primate model, where 90% of tracts were destroyed, full function was eventually restored. IN-1 blocks the Nogo protein itself, and was the basis for ATI-355, now in a Phase Ib that aims to enroll 51 patients. This drug requires a four week intrathecal infusion or repeated intrathecal bolus administration, beginning within 10-14 days of the injury. No adverse events, such as inappropriate growth-induced 'miswiring,' have been observed preclinically. Enrollment has been slow, they now project completion in mid-2012. **Biogen-Idec** had taken a slightly different tack, working with NEPI-40, a Nogo antagonist peptide, but this program has been dropped. **Sanofi** had a program pursuing the Nogo target, but sidelined it. **GSK** has continued with 1223249, their Nogo antibody, but is not addressing SCI, instead prioritizing ALS and MS. **Alnylam** had done work on RNAi for SCI, with Nogo as the target, but appears to have ended that program.

Some Nogo findings have not been replicable, and the primacy of Nogo in the inhibitor pantheon is not universally accepted; it plays a role, but it may not be the optimal target.

Yale's Martin Strittmatter is another seminal figure in the growth inhibitor arena. His most recent program is a fusion protein which is a decoy receptor, binding three anti-regenerative, myelin-based factors in combination: Nogo, MAG, and OMG. Strittmatter's work indicates that inhibiting all three nogo receptor ligands provided additive benefit, exceeding what could be achieved via a single factor. This program has become one of the core components of **Axerion Therapeutics**. Axerion believes that working with chronic SCI is easier, given that six months out, natural recovery has run its course, thus removing an element of placebo response, and permitting the use of smaller patient samples without the pressure of trying to enroll and treat

within a few days of the injury. They hope to raise enough money to continue work on this program inhouse.

Beyond their work with Nogo, Biogen-Idec had explored the use of the Lingo-1 component of this receptor complex as a target. They developed a fusion protein (Lingo 1-Fc) as a vehicle for axonal growth in MS, and it had entered Phase I, but has been dropped. **Lilly** has done some work with Lingo-1, and is devoting resources to identifying novel targets along this signaling pathway. A Harvard Medical School-affiliated group has discovery work going on addressing the OMGP pathway to Nogo modulation. A Johns Hopkins group has reported animal work wherein recombinant neuraminidase blocked MAG and enhanced motor function. A UCSD group including Mark Tuszynski has published *(J. Neuroscience)* data regarding yet another inhibitory factor, Netrin-1. Netrin-1 apparently functions as an oligodendrocyte-based repulsion factor that suppresses neurite growth. When Netrin-1's action is blocked, neurite growth and regeneration is enhanced, which could enhance axon regeneration. RNA interference is receiving much attention as a means of parsing out targets that are countertherapeutic in various disorders, and SCI is not an exception.

A Harvard-affiliated group has published work indicating that blocking PTEN, which is a tumor suppressor factor, may be another route to axonal regeneration. However, as was the case with **Curis**' hedgehog pathway activators, finding the fine line between permitting axonal growth and fostering tumor cell generation may be quite challenging. A University of Texas group has been working with GSK-3 as a inhibitory target,. **Neuréva** has an early stage technology employing glial cell grafts that they believe fosters axonal growth via inhibiting either one of the aforementioned inhibitory factors, or by ameliorating scar formation.

All Roads Lead to Rho-- or LILRB/PirB

There are a couple of candidates for the role of inhibitory mediator, through which growth-inhibiting signals from various sources must pass, which constitute particularly attractive targets for blocking these inhibitory processes. Rho is currently the most promising possibility. As noted above, activation of the two major Nogo complexes (combined with either p75 or TROY) eventually leads to Rho activation. Rho can also be activated by proteoglycans found in the scar tissue, the aforementioned neurochemical obstacle arising from the extracellular matrix components of scarring. Rho antagonism thus blocks not only the impact of Nogo, but also is involved in pathways triggered by other inhibitory factors, including proteoglycans and axonal repulsion factors. Rho proteins modulate signal transduction within the growth cone itself, controlling axon growth and cell proliferation. Blocking Rho promotes neuroprotection and axon growth, upstream of nogo, and both in vitro and in vivo studies have shown axonal growth after Rho antagonism. One theoretical downside to the Rho target is the fact that Rho proteins are ubiquitous throughout the body, although no safety/tolerability issues have arisen thus far. Rho's value comes from modulating the effects from a number of factors controlling growth. Rho has been the focus of two companies, **BioAxone** and **Migragen**. Both took a known Rho-antagonist with very poor absorption, the enzyme c3-transferase, and modified it. Migragen combined CT-3 with a component taken from botulinum toxin, which increased membrane permeability. But Migragen ran out of money and sold their IP to **Schering**, albeit only for screening.

In contrast, BioAxone has developed Cethrin, a recombinant version of c3-transferase that, in combination with a fibrin sealant, antagonizes Rho. It is neuroprotective (reducing apoptotic cell death 50% in one model), and reduces TNF-alpha, thus reducing inflammation and scar formation. They claim that it is effective in promoting growth, with at least a 24 hour post-crush window. No treatment related adverse events were seen from this locally-administered therapeutic. In a 48pt (mean time to treatment was 52 hrs post-injury) open-label PhI/II program using five doses of Cethrin, 43% of the patients showed functional gains of two ASIA grades or more, from a start point at ASIA A (complete loss of function below the level of injury). Some improved up to Level D, where at least half of the muscles innervated from below the injury have regained significant capacity. In the 12 patients with cervical injuries (thoracic injury patients tended to show little benefit, and were included primarily to assess safety), the mean improvement over twelve months was 27.3 points for the 3mg group, 21.3 points for the 1mg group, compared to 10 points for historical controls. Historical control data suggests about 10% of ASIA A patients show this level of ASIA-category improvement, and it usually occurs fairly early in the post-injury period. In contrast, the Cethrin patients continued to show improvement over the 12 months of the study, which suggests the gradual expression of regenerative effects, and argues against this being purely a placebo phenomenon. Motor function and sensory improvement were noted, and no adverse event or tolerability problems were reported.

Even though historical control comparisons must be viewed with some skepticism, these results are striking. BioAxone had originally partnered Cethrin with **Alseres**, but Alseres failed to carry out the promised PhIIb trial, and BioAxone

regained those rights. BioAxone has now reconstituted itself under its scientific founder, Lisa McKerracher, and has reassembled its clinical development team in the service of going into Phase IIb, when funding is obtained.

A **Genentech** group led by Marc Tessier-Lavigne published data in *Science* identifying leukocyte immunoglobin B2, or LILRB2 (in mice, known as PirB) as being bound by several inhibitory factors, including Nogo-A, OMG, and MAG. In mice, a PirB antibody significantly improved neurite growth, suggesting that LILRB2 antagonism in humans might be a 'one stop shopping' approach to restricting axonal growth inhibitors. Further animal testing is ongoing, and the investigators have suggested that LILRB2 may be relevant to other forms of neural plasticity, including learning/memory.

Axonal Regeneration: Promoting Regrowth

There are a number of proactive routes to the elusive goal of axonal regeneration in SCI. These include the providing or enhancing neurotrophic factors, the delivery of replacement cells, and the induction of endogenous progenitor cell proliferation. These not only are not mutually exclusive, but neurotrophin supplementation may be a necessary accompaniment to the other two approaches, providing the environmental context and cues for appropriate growth. Cell therapy has also been explored as a vehicle for neurotrophin delivery.

Neurogenesis

This has thus far elicited the least study from that group. Progenitor cells exist in the spinal cord, and their number increases markedly in response to injury. Whether they exist in sufficient number or malleability to make a functional difference is not known: Certainly in the natural context, they do not. The main cell-proliferation programs under development are in the hands of **BrainCells**, **StemCell Therapeutics**, **Neuronascent**, and **NeuroNova**. None of them have cited SCI as a priority. BrainCells pursued depression as a first target, and had positive data from a pilot trial with BCI-952, complex but intriguing data in depression/anxiety for BCI-540. **StemCell Therapeutics** had negative results for its stroke trial. NeuroNova has Phase I/II trials in both Parkinson's and ALS going, data expected mid:2011. Another option is the use of neurotrophic factors that might offer a neuroprotective effect, and could also promote the extension of neurites across the chasm of lost connections. A number of neurotrophic factors have been heralded as key to axonal regeneration, including NGF, BDNF, NT-3, and GDNF. **NsGene** has not emphasized SCI, but **Biogen-Idec** did license some of the rights to NsGene's proprietary neurotrophic factor neublastin, and continues that work--in neuropathic pain-- for the time being. NsGene itself has turned back to GDNF as its priority payload. A group from Japan's Riken Institute suggested that GDNF's trophic effect in adults may be restricted to certain neuronal subgroups, which could limit its overall utility.

Sangamo Biosciences used an AAV viral vector to deliver a transcription factor, thereby upregulating VEGF and spurring angiogenesis. They reported a 30% functional improvement in animals following a six-week trial, but this is not a priority for them. The use of an adenoviral vector delivering NGF, injected into the spinal cord, has been reported by academic researchers to produce axonal regeneration. Delivering these proteins into the spinal cord intrathecally is easier than getting them into the brain via a diffusion pump, but in terms of providing a longterm, consistent supply where needed, the use of cells engineered to produce desired neurotrophic factors is of interest.

A paper in the *Journal of Pharmacogenomics* identified Rit GTPase as a 'convergence point' for multiple signaling factors, which helps govern axonal growth vs. dendritic growth, Rit GTPase activation presenting a possible target for accentuating axonal growth, which is more critical to SCI repair. A University of Utah study used RNAi screening to identify a novel gene target, dlk-1, as a potential target for upregulating neuro-regeneration. In nematodes, upregulating this gene accelerated nerve repair significantly. **BrainStorm Cell Therapeutics** claims that neurotrophin producing cells derived from adult bone marrow stem cells improve recovery in a rat model of SCI. They state that the cells themselves do not survive more than a couple of weeks, thus it would be their neurotrophin production that would be presumed to induce the growth-enhancing effects. **Q Therapeutics** is working with progenitors of multiple cell types, but they do not cite SCI as an indication-of-interest.

A Harvard group has identified an enzyme, Mst3b, as controlling a signaling pathway that modulates axon growth. In a rat model, regeneration required the presence of Mst3b. They reported that several other pathway components (BDNF, NGF, inosine) work via Mst3b. Those other factors require Mst3b to achieve regeneration.

Neurotrophins

Given the delivery problems endemic to neurotrophic proteins, small molecule neurotrophin mimetics/stimulants were for a while, one of the most competitive areas in neuropharmaceutical research. In rats, the precursor for **Guilford**'s neuroimmunophilins, the immunosuppressant

FK506, was reported to increase axon number, diameter, and elongation. The first-generation neuroimmunophilin, GPI-1046, was shown to increase axon diameter and myelination in animal models, though elongation was not reported. SCI was one of the original possible targets, but the neuroimmunophilins failed in their primary indications, and the neuroimmunophilin IP ended up in the hands of **Gliamed, b**ut it is not being developed for CNS indications at present. 'Mitogard', the cyclosporin reformulation being developed by **Maas Biolab/NeuroVive**, is related, but they have not discussed any interest in SCI; TBI and ALS are their main indications.

Sweden's **BioArctic Neuroscience** has a biodegradable device made from alpha-calcium sulphate hemihydrate to deliver the trophic factor FGF-1 in SCI. It is expected to reach the clinic late in 2011. **Asubio** (formerly **Daiichi-Sankyo**) has developed a nonproliferative mimetic of bFGF, SUN13837, which is in Phase II, intended for both neuroprotection and axonal growth stimulation.

Inosine appears to stimulate a protein kinase that then turns on the transcription of factors that spur axonal growth. Inosine, in a rodent model, caused axons to extend around areas of damage. This claim of axonal elongation in response to a small molecule is very alluring. However, inosine's original formulation had no BBB penetrance, and has an extremely short halflife. **Alseres** developed a high-concentration formulation given IV, and claimed that some BBB penetration occurs, boosting brain levels of inosine fivefold during a two-hour infusion. This program was delayed for years due to lingering concerns that inosine might cause haphazard axonal elongation and interconnection, with particular worry about growth in nociceptive tracts. Alseres initially projected that the Phase I/II for inosine would begin 2Q:01. Ten years later, no human trial ever began. Alseres has surrendered these programs back to their originators, and is slowly exsanguinating itself via the doomed Altropane program.

Oxford BioMedica has an unusual neurotrophic angle in SCI, using their lentiviral vector system to deliver the gene encoding the retinoic acid-beta2 receptor. 'Innurex' produced nerve repair across the lesion and improved function in a rat SCI model. They are not working in SCI at present. Duke University researchers have shown that some glucocorticoids serve as agonists of the 'Smoothened' hedgehog pathway promote neuron precursor proliferation, and could be applicable to SCI--albeit with the tumorigenicity concerns that have dogged hedgehog agonists. In an unexpected twist, Max Planck Institute researchers found that low doses of the chemotherapy agent paclitaxel improved axonal regeneration and reduced scarring in an animal model of SCI. A Johns Hopkins group has in vitro evidence of axonal enhancement using MYH10 (myosin, heavy chain) inhibitors.

Immunotherapy

Michal Schwartz of the Weizmann Institute has been the champion of immunotherapy in the treatment of SCI. Her premise is that crosstalk between T-cells and endogenous stem cells improve neurogenesis, while T-cells also recognize antigens and protect new cells from damage, partly by generating neurotrophic factors, including BDNF and IGF-1. Overdriving the immune system in this case could lead to inflammation, but her belief is that there is site-specificity involved, with neurotrophic factors being primarily released in contiguity to the scar, around the periphery of the damaged area. Furthermore, she believes that T-cells release MMP-9, which in a second phase of activity, begins to break down the glial scar.

The ProCord Paradox: Having licensed Schwartz's work, Israel's **ProNeuron** moved aggressively into human trials based on this putative role of T-cells in the release of neurotrophic factors. 'ProCord' uses T-cells taken from the patient's blood plasma, processed via a proprietary technique, then reinjected into the site of the spinal cord injury. The treatment had a window of two weeks after injury, but it was said to take 6-12 months for any resultant improvement to manifest. A pivotal US Phase II/III, aimed at enrolling 60 pts began in the US, but after accruing more than half of that number, enrollment was suspended, and never restarted. Proneuron stated that this was because of patient nonavailability, related to the difficulty and expense of bringing a recent SCI patient to one of Proneuron's centers, of which there were six worldwide, and the requirement of two spinal surgeries. From the limited open-label data acquired, ProNeuron announced that 5 of 16 patients showed significant improvement, two moving up one ASIA scale category, three moving up two categories. Two others reportedly had limited recovery of bladder control. Proneuron announced that they would try to revamp their system, but no anecdotal 'buzz' ever developed about ProCord, which casts strong doubt on any hope for benefit. Proneuron is now primarily focused on their legal struggles with **Teva**.

Cell Replacement

Beyond neurotrophic upramping (albeit potentially complementary to it) is the strategy of providing neurons that can fill the role of those lost during and post-injury. Such utilization does beg the questions of cell-source,

cell-handling, and cell-adaptability that have yet to be resolved in the field. The variety of cell choices consists of the 'usual suspects': fetal, embryonic, porcine, adult stem cells (the provision of oligodendrocytes or Schwann cells for remyelination is discussed separately, below). The neurosurgical procedures are more straightforward, but one factor salient in SCI is the blockage produced by proteoglycans, which can narrow or eliminate the window of access for new fibers to interconnect. No single cell therapy strategy has stood out: while some axonal extension has been observed in several studies, fibers have often not appeared to be receiving sufficient local 'input' to orient and direct themselves correctly. Growth has been enhanced via factors such as BDNF and/or NT-3, co-administered with the implant.

Two cell therapy programs have moved into human trials. Using the 'shiverer' mouse model, where myelin is knocked out, **Geron**'s oligodendrocytes derived from human ES cells produced remyelination when injected into rat spinal cord. They reported that cells must be implanted early after injury: In their work, cells implanted seven days post-crush produce functional improvement, those implanted ten months later do not (obviously, there is a large window between those extremes). It may be that astrogliosis over time creates a barrier to later intervention, and it is not clear when the window of opportunity closes. Their GRNOPC1 ES cells, directed towards an oligodendrocyte fate, appeared to survive and promote remyelination for nine months after a single injection--in rats. Geron reports that no allodynia was found in this animal study. Additionally, the lack of immunoreactivity is cited as indicated that short-term immunosuppression may be sufficient, and that autologous-source cells are not necessary. However, the discovery of nonproliferative cysts contiguous to the implant sites in rats initially led to a clinical hold, and the requirement of further animal testing. Those results were apparently clean, and **Geron** (last October) announced the initiation of a SCI trial implanting GRNOPC1 cells. They will enroll only the most severely impacted patients, thoracic-level injuries with ASIA A scores, meaning complete loss of function. These patients must be enrolled within fourteen days of injury. The trial duration is one year, full data is expected in late 2012. For now, the good news is that the first two implanted patients have shown no adverse events, including no immunoreactivity (immunosuppression is used initially, then stopped).

StemCells initiated (in March 2011) a 12 pt Phase I/II trial in Switzerland, implanting human neural stem cells in patients with thoracic-level SCI, showing complete or incomplete loss of function, beginning the former (ASIA A). If these most severely impacted patients show no ill effects, they will gradually move to less severely impaired SCI cases, up to ASIA C at the time of implantation. Temporary immunosuppression will be used, and the duration of the trial is twelve months, followed by another four years of extended followup.

NeuralStem has reported that, in an animal model of SCI, their injected cells multiplied 3-4 fold over six months, and differentiated into neurons. However, no report was made regarding functional benefit, and they are focused on ALS for now. **StemCyte** is working with Rutgers University on a program combining umbilical cord stem cells with lithium (here functioning as a neurogenic compound) in SCI models.

New World Laboratories (formerly **Novagenesis**, previously **Total Re-Cord**): New World is developing cells they consider to be 'neural stem-like' because they are derived from a non-CNS cell source (undisclosed, other than they are somatic cells). They are autologous, NWL claims that they are deliverable via IV or implantation; in animal models, they migrate and interwire functionally; and are not tumorigenic. NWL states that they produce more neurites than do neural stem cells, with greater length and more complex branching. The jury is still very much out on whether reprogrammed cells will function as planned in the clinical context. SCI is a secondary target for this program.

A subtype of cells that have received attention are olfactory ensheathing cells, which in animal models, appear to proliferate and increase axonal growth. Jonas Frisen (a **NeuroNova** co-founder) did work at Karolinska on these cells, and the conditions under which they can make headway through glial scars. That group has found that chondroitinase ABC, which is discussed in this report, improves regenerative capacity. The use of olfactory-source cells has also spurred for-profit programs overseas, which has been offering such implants to patients in spite of the lack of clearcut validation, or longterm safety data. There are the usual anecdotal rave reviews, but as noted below, there are some adverse event issues that mandate caution. A USC group has used olfactory sheathing neurons to provide what they believe is a permissive environment for endogenous Schwann cells to access the spinal cord and provide myelination. **Weizmann Institute** researchers have reported that combining adult stem cells with a vaccine containing myelin-derived peptide improved recovery in a mouse model performed better than either therapy alone.

There are many obstacles still to be overcome in this branch of cell transplantation therapy. The survival of such cells is always a concern, and neither initial human trial involves the co-administration of neurotrophins. One report is that cell implantation leads to the increased production of calpain and caspase-3, and downregulation of one or both might be necessary for optimal survival. Even if the survival issue is surmounted, there may be unforeseen consequences to the successful regeneration of cells. For example, a previous animal study found that undifferentiated stem cells tend to become astrocytes when implanted, rather than neurons or oligodendrocytes. The problem with this is that astrocytes themselves release neurotrophic factors, particularly NGF. NGF can cause sensory neuron sprouting, and in animals, precipitatesallodynia, a potentially serious neuropathic pain symptom. By adding the transcription factor neurogenin-2, the cells were steered into an oligodendrocyte fate, not only reducing allodynia, but improving functional outcome. This is not only relevant to SCI, but may also speak to a question pertinent to all CNS cell therapy: to what degree one can depend on local signals to direct 'raw' stem cells to become what is needed.

Retinoid X agonists, used in oncology, appear to enhance the differentiation of cells into oligodendrocytes, of potential use in SCI and MS. The addition of a HDAC inhibitor like valproate has been reported to increase the differentiation of implanted cells into neurons--from 5% to 20%, which in itself shows the difficulties attendant to the technology. Thus the task involves using the right cells that differentiate optimally on location. Local signals are not enough, they lead undifferentiated cells down a path that is not only insufficiently regenerative, but one that incurs a serious adverse effect. Even when neural stem cells are available, local signals might keep them from migrating to the area of injury, where they are needed. Netrin-1's previously noted growth inhibition effects may include action as a repulsive factor, repelling stem cells from the injury. Neurogenic or cell replacement therapies thus may also have to utilize attractant factors, or repress these repulsive factors, in order to deliver cells where they have to go.

Regulatory caution led to a very lengthy hold on **ReNeuron**'s stem cell program for stroke, though that finally did make it into the clinic. ReNeuron has a secondary program aimed at SCI. Related to the cell replacement issue is the interference that may be presented by neural adhesion molecules (NCAM). Generally associated with guiding early development, these molecules are expressed after SCI, and may interfere with the migration of new cells to where they are needed, or conversely, interfere with astrocyte migration that could add to scarring. **Pharmaxon** is developing a small peptide, PR-21, which apparently pursues the latter approach, though the mechanism is not clear. It mimics a NCAM, and in animals, reduces glial scarring and improves motor function, inferring axonal growth. It continues in preclinical toxicology testing.

Remyelination

Providing myelin for damaged axons could in theory be an avenue to improving signal transmission. This is tempered by the observation that myelin produces factors that suppress axon growth and sprouting, thus this would be ill-suited for acute treatment, and its later utility would depend on what the timeframe for axonal growth turns out to be. One would need to allow for, and promote, such growth before turning to the remyelination of axons already 'on site.' **Acorda** had done work with M1 antibodies, which promote remyelination. Preclinical

studies of murine M1 antibodies (sHlgM46 and SHlgM22) indicated strong myelinating effects. These antibodies have been humanized, but M1 has been on the backburner due to a lack of financial resources. The same is true for the neuregulin/GGF2 program acquired from **CeNeS** (after being initially developed by **Cambridge NeuroScience**). GGF2 is involved in forming oligodendrocytes, which raises the question of whether resulting myelin formation would be boon or bane. This is a cell regeneration therapy, but in contrast to those described below, which are aimed at regrowing lost connections themselves, GGF2/NRG2 would be aimed at providing remyelination to axons that are still connected, but are not effectively conducting impulses. **Acorda** has chosen cardiology as their first priority for the GGF program. Then there are the cell replacement approaches to remyelination, e.g. **Geron**'s, as were previously discussed. **SanBio** has refocused its cell therapy efforts to their use as neurotrophin producers and, in the case of SCI, oligodendrocytes for remyelination. The former, in the treatment of stroke, has become their top programmatic priority (**Dainippon** has an option).

Walls, Tunnels, and Bridges

The challenge of reconnecting spinal cord circuits is not just one of crossing a gap, it also means growing through a barrier of scar tissue, a literal wall. Spinal cord injury creates scar tissue, containing proteoglycans, especially chondroitin, block fiber extensions both physically and chemically. These barriers are thus targets, their dismantling would serve to open the path for axons seeking to cross the death zone of injury. Scar tissue contains RGMs, Repulsive Guidance Molecules identified as potent blockers of axonal incursion. Just as other factors guide axons via attraction, these factors guide them by deflection away, in this case away from the scar tissue that borders the area of injury. Thus inhibition of RGMs would be another possible tactic. Myelin and chondroitin contribute to this physical barrier, but they are also connected to the aforementioned chemical barrier, since both activate Rho (as does Nogo). Protein kinase C is involved in the pathway that links myelin and chondroitin to Rho, and could be another target.

Chondroitinase ABC is an enzyme that 'dismantles' the chrondroitin/proteoglycan structure that is the physical 'backbone' and boundary for neuronal networks. In its variant as scar, this structure also provides both a boundary to damage, and a limit to repair, restricting regenerative axonal sprouting. Chondroitinase has shown positive effects in a mouse model of SCI, and also upregulates the production of the pro-regenerative factor GAP-43. A SUNY research team has developed nanospheres containing chondroitinase ABC that release the enzyme for two weeks, but that is still in animal studies. It has also been found in animal studies that applying a MMP9-inhibitor to the area of SCI reduces the astrocyte migration that fosters scarring, and reduces chrondroitin production. Thus, this might be way to prevent excessive glial scarring. The chondroitin target is the focus of a program that has been in stasis at **Acorda**. The challenge of completing Fampridine-SR's development and market launch has largely monopolized Acorda's energies. There are difficulties attendant to the chondroitinase target, particularly given the fact that chondroitinase itself rapidly degrades, requiring frequent replacement. An Emory University group published work in *PNAS* that shows that chondroitinase can be stabilized via the addition of the sugar trehalose, and implanted in tiny straws, providing up to six weeks duration of activity in removing/preventing scar tissue.

Chondroitinase analogs could be synergistic with a Nogo or rho antagonist tactic, yielding more potent regeneration. Case Western Reserve's Jerry Silver, who has done a great deal of work on proteoglycans, has done animal studies using cABC plus Zymosan, which is believed to stimulate macrophages. He reported that combining the two was synergistic, exceeding either one given alone. He also showed that the resultant axonal growth was functional in terms of carrying signals. A Silver-affiliated group has also identified a binding site for proteoglycans, PTPRS, which when bound, block neurite growth. This is another potential target for intervention.

Additionally, the proteoglycan/chondroitin complex does not only represent a physical barrier to regeneration, it also has intracellular effects via the EFGR pathway. **Alseres** had access to early-stage work involving inhibitors of that pathway, but did nothing with it.

SCT Therapeutics (formerly **Neuraxo**) programs include an off-patent iron chelator, renamed Cordaneurin, which they believe can inactivate an enzyme that contributes to collagen formation, and antibodies against extracellular collagen aggregates. A Phase I/IIa trial, aimed at enrolling 40 patients was to begin in 2007, but it has remained in preclinical testing, as the company has restructured.

Even if the complex interweaving of regenerative versus inhibitory processes can be sorted out, one must still ensure that the axons join and form synaptic connections that are functional, rather than broadcasting the CNS equivalent of static. It is a bit like digging a tunnel from both sides of the English Channel; if the tubes do not align perfectly, they are useless. Endogenous guidance factors present in the nervous system help guide developing axons to their

appropriate targets (and as noted above, factors also steer axons away). However, some animal studies have raised questions as to whether simply boosting the number and diameter of axonal 'sprouts' necessarily translates into improved nerve conduction and functional outcome. But assuming it is useful to increase the myelination, number and/or diameter of axonal sprouts, that is a relatively 'local' change. This begs the metaphor of bridges, because one would also need to increase the length of the axons themselves if one were trying to bridge a relatively wide gap of scar tissue. This distance issue is more pertinent here than it is in post-stroke cortical regeneration, for example, because in the spinal cord, one cannot develop a network of local compensatory circuits that work around a damaged area. At some point one must (especially in complete cord transections) eventually cross the gap from one undamaged area to another. The gap to be crossed in the human spinal cord can be as large as 12-18mm, which on the cellular level, is an immense journey. This has led to speculation by some that one cannot rely upon either endogenous or implanted cells to extend over that distance without some type of supportive structure or matrix. Collagen, gel foam, stromal cells, and polymer fibers have been used experimentally as bridges.

Since these materials are space-occupying, this begs the question of how one can place such matrices within the finite space of the spinal canal, already occupied by the spinal cord and (at the site of injury) scar tissue. **New World Laboratories** has thus chosen to avoid SCI as a context for their RMx blood-based regeneration matrix, but **InVivo Therapeutics** apparently does not see this as an issue, prioritizing SCI as the raison d'être for their polymer and hydrogel technologies. InVivo was cofounded by MIT's Robert Langer, who is generally considered the foremost authority on biocompatible polymers, which gives InVivo some instant credibility. InVivo is developing three products for SCI:

1) a biocompatible polymer which is used in acute SCI to deliver anti-inflammatory drugs inhibiting nitric oxide synthase, all in the service of neuroprotection.

2) a biocompatible hydrogel which releases methylprednisolone locally for the treatment of acute SCI (begging the question of whether avoiding myopathy will then reveal steroidal benefit).

3) a scaffold seeded with autologous neural stem cells, to regenerate/repopulate the spinal cord in acute or chronic SCI.

These three tactics raise more questions than they answer: Is there space for polymer and hydrogel insertion? Instead of mimicking neuroprotection, did methylprednisolone-induced myopathy mask it? And how will these autologous cells, other than avoiding immunogenicity, fare in comparison to other cells in development?

Rehabilitation Facilitation

A Quebec company (**Nordic Life Science**) has received DoD funding for a clinical trial of a triple-combination of approved drugs intended to trigger 30-45 minute episodes of involuntary motor system activation in SCI patients with complete transections. The intent is to use this activation as a means of providing stepping movements which can hopefully be used in rehab programs. 'Spinalon' combines L-Dopa, apomorphine or carbidopa, and buspirone, and this brief dopaminergic activation is reminiscent of the use of apomorphine to awaken coma patients.

Programs to Watch

It primarily a cohort of smaller companies that have picked up the gauntlet regarding SCI treatment. At some point, when some clinical and commercial success has been demonstrated, we expect that Big Pharma's growing interest in rare disorders will eventually extend to SCI. Novartis, which has also moved into Fragile X as a CNS orphan disorder of interest, in the Big Pharma exception. At present, the programs of greatest interest in SCI include:

BioAxone BioSciences: In a 48pt open-label PhI/II program using four doses of Cethrin, 43% overall showed functional gains of two ASIA grades or more, from a start point at ASIA A, some improved up to Level D. In the 3mg cohort, the mean improvement was 27.3 points, compared to 10 points for historical controls. Importantly, Cethrin patients continued to show improvement over the 12 months of the study, which suggests regenerative effects, in addition to neuroprotective effects documented in animals. No adverse event or tolerability problems have been noted thus far. Having regained their control of Cethrin from **Alseres**, BioAxone has reconstituted itself, and is reassembling the clinical development team that ran the previous trial. Now they are raising the money to fund Phase IIb. This tactic could be very complementary to the cell therapy programs discussed herein.

Axerion Therapeutics: Blocking the action of three growth inhibitors simultaneously has intuitive appeal, although they all share a common lineage, and there is some debate in the field as to whether focusing only on myelin-derived inhibitors is sufficient, since there are other inhibitory pathways. This tactic prevents a loss of (regrowth) function, but does not inherently accentuate protective/regenerative processes. There is also some disagreement as to the optimal

timeframe for intervention, Axerion choosing to delay treatment-onset. Axerion needs to raise money in order to advance this program, which is a second priority for them, behind their Alzheimer's program.

Geron: Geron was first into the clinic with a cell therapy for SCI. They recently reported that the first two patients receiving two million cells injected into the lesion site showed no adverse events. Perhaps most importantly, no immunoreactivity has been seen, even thirty days after immunosuppression was stopped. A total of ten patients are to be enrolled in this trial.

StemCells: A pilot study of their neural stem cells in SCI has been initiated in Switzerland, and will provide a fascinating parallel to the Geron program as both progress.

Novartis: Novartis has continued Schwab's work on Nogo inhibition. They have developed two neutralizing antibodies against Nogo-A, and report that after eight weeks, animals showed axonal sprouting and improved motor function. One, ATI-355, is now in Phase Ib, with no adverse effects reported.

NeuralStem: NeuralStem's current plan is to make SCI their second indication, having begun the Phase I for their neural stem cells in ALS. The plan for SCI is to implant a variety of cells intended to 'rewire' the area, not just oligodendrocytes aimed at remyelination. In a rat model, human neural stem cells that they implanted increased 3-4 fold over six months.

Acorda Therapeutics: Acorda owns a wide array of IP for SCI, including antibody programs addressing axon growth inhibitors, guidance factors, and remyelination programs. All of these have remained static for a couple of years, and they would like to partner them, given that Ampyra and their cardio/GGF program will continue to consume most of their resources.

SanBio: If their stroke cell therapy shows promise, SCI would be their next indication of choice.

InVivo Therapeutics: An unorthodox biocompatible matrix device/payload approach from a company with an impeccable pedigree in the polymer matrix realm. Phase I for the lead program is expected this year.

Summary

Even more than most CNS disorders, the combination of factors at work in fostering or blocking regeneration mandates that the optimal treatment of SCI will be multimodal. Unfortunately, while the FDA has started paying lip service to the concept of testing novel polytherapies in the treatment of 'life-threatening' disorders, they appear to be primarily thinking about oncology. It is unlikely that the Neurology division will be soon able or willing to wrap its collective mind around such multimodal testing. Thus for now, each component will have to prove itself to the FDA as a monotherapy. One could employ an acute care combination of antiinflammatory cytokines and a neuroprotectant, to be accompanied and/or followed by therapies aimed at axonal growth. Optimal therapy could include several components in sequence, including suppression of myelin and/or the growth inhibitors therein produced. Cethrin is used on an acute basis very soon after injury, while other growth promoters may be applicable up to weeks after the injury--although there is no consensus as to whether later intervention will be as effective. Longterm treatment may eventually involve cell replacement, which cannot be done acutely due to inflammation, and replacement may utilize supportive scaffolding to bridge gaps of cord injury. In patients with more extensive transections, there may not be enough physical space around the scar to permit sufficient innervation, and that group would also require something that would break down the scar barrier.

Given that significant spinal nerve tracts are likely to remain irretrievable and irreplaceable, none of the therapies under development at this point are likely to produce full recovery in patients who have a complete loss of function. But improvements in day to day function are likely to within reach, allowing SCI patients increased independence, and reducing their reliance upon the most intensive and expensive of chronic care regimens. The impact and profile of successful therapies will eclipse the absolute size of the patient population. Given that SCI tends to devastate individuals early in their lifespan, and the costs that lifelong disability incur, successful therapies will receive premium reimbursement. Seven years ago we predicted that, "*in the next five to ten years, we expect very substantial progress to be made in the undoing of paralysis formerly thought to be a life-sentence*." As has generally been the case, this timeframe has turned out to be overly optimistic, partly because funding remains elusive for these companies, partly because the combination of pharmacological and structural interventions necessary for successful rewiring around or through the area of damage has yet to be defined. So the statement is still true today: In the next five to ten years, clinically meaningful interventions for SCI will be developed and validated.

SCI Programs in Development

Company	Compound	Phase	Target
Acorda Therapeutics		preclinical	M1 antibodies
Acorda Therapeutics		preclinical	GGF2/neuregulin
Acorda Therapeutics		preclinical	chondroitinase
Apogenix		discovery	fusion protein
Asubio	SUN13837	PhII	bFGF mimetic
BioArctic Neuroscience	SC086	preclinical	biodegradable device/FGF-1
BioAxone	Cethrin	PhII	Rho inhibitor
BrainStorm Cell Therapeutics		preclinical	stem cells
Genentech		discovery	LILRB2
Geron		PhI	ES stem cells
Harvard/Children's Hospital	Mst3b	discovery	neuroregeneration
InVivo Therapeutics		preclinical	anti-NOS via biocompatible polymer
InVivo Therapeutics		preclinical	steroid via hydrogel
InVivo Therapeutics		discovery	hNSC-bearing matrix
KeyNeurotek	KN38-7271	PhII (TBI)	CB1/2
Lilly		Preclinical	Lingo-1
Maprég	MAP4343	preclinical	pregnenolone derivative: microtubule repair
NeuralStem		preclinical	stem cells
Neuraxo	Cordaneurin	PhI/II	chelator
Neuréva	glial cell grafts	preclinical	inhibiting inhibitors
NeuroNova		preclinical	neurogenesis
New World Laboratories	nWL-nSCc	preclinical	stem-like cells
Nordic Life Science	Spinalon	Ph I/II	dopaminergic/buspirone combo
Novartis	ATI-355	PhI/II	Nogo
NsGene	neublastin	preclinical	neurotrophin
Oxford BioMedica	Innurex	preclinical	retinoic-acid beta 2 gene tx
Pharmaxon	PR-211	preclinical	NCAM
Proneuron	ProCord	PhII	T-cells
Regenesance	RGS2064	PhI	complement inhibitor
ReNeuron		PhI (stroke)	stem cells
SanBio	SB618	preclinical	oligodendrocytes
Sangamo Biosciences		preclinical	oligodendrocytes
SCT Therapeutics (Neuraxo)	Cordaneurin plus	preclinical	chelator+matrix+growth factor
StemCells		preclinical	stem cells
StemCyte		preclinical	umbilical cells and lithium
Sygnis	GCS-F	PhII (stroke)	neuroprotection
TetraLogic Pharmaceuticals	necrostatins	preclinical	necrosis inhibitor
Weizmann Institute		discovery	stem cells/vaccine

BioAxone BioSciences

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Founded: 2000 (as BioAxone Therapeutic, re-formed as BioAxone BioSciences in 2011)
Funding Raised: Undisclosed (raised US$18 million as BioAxone Therapeutic)
Investors: Founder, angels (Previous investors: T2C2/Bio2000, Solidarity Fund QFL, Investissement Desjardins, Medtech Partners, Innovatech of Montreal, Medtech Partners, Neuroscience Developments, Lothian Partners)
Number of Employees: Undisclosed
Summary: Rho antagonist for SCI

Platform/Programs

Rho Antagonists/Spinal Cord Injury: Rho proteins modulate signal transduction within the growth cone itself, controlling axon growth and cell proliferation. Blocking Rho promotes neuroprotection and axon growth, upstream of nogo. Rho inhibition is most directly applicable to spinal cord injury, and both in vitro and in vivo studies have shown axonal growth after Rho antagonism. Cethrin is a recombinant version of c3-transferase that, in combination with a fibrin sealant, antagonizes Rho. It is neuroprotective (reducing apoptotic cell death 50%), and reduces TNF-alpha, thus reducing inflammation and scar formation. They claim that it is effective in promoting growth, with at least a 24 hour post-crush window.No treatment related adverse events were seen from this locally-administered therapeutic. In a 48pt (mean time to treatment was 52 hrs post-injury) open-label PhI/II program using five doses of Cethrin, 43% of the patients showed functional gains of two ASIA grades or more, from a start point at ASIA A (complete loss of function below the level of injury). Some improved up to Level D, where at least half of the muscles innervated from below the injury have regained significant capacity. In the 12 patients with cervical injuries (thoracic injury patients tended to show little benefit, and were included primarily to assess safety), the mean improvement over twelve months was 27.3 points for the 3mg group, 21.3 points for the 1mg group, compared to 10 points for historical controls. Historical control data suggests about 10% of ASIA A patients show this level of ASIA-category improvement, and it usually occurs fairly early in the post-injury period. In contrast, the Cethrin patients continued to show improvement over the 12 months of the study, which suggests the gradual expression of regenerative effects, and argues against this being purely a placebo phenomenon, more likely to reflect regeneration. Motor function and sensory improvement were all noted. No adverse event or tolerability problems were noted. Even though historical control comparisons must be viewed with some skepticism, these results are striking, and unmatched by any competitors thus far. **Boston Life Sciences/Alseres** partnered this program in 2007, but while they did some work on the preclinical package, they never mustered the resources to launch the promised Phase IIb trial. In 2010, BioAxone regained the rights to Cethrin, and re-formed itself as BioAxone BioSciences in 2011.

Partners

None

Prospects

Rho is a road less traveled in the realm of growth-inhibiting factors, wherein more attention has been paid to Nogo and lingo. It is possible that Cethrin's rho antagonism might work additively or synergistically with another of these trophic programs, and it would be complementary to cell-replacement strategies. BioAxone had been a holding company of late, with Cethrin its only asset, albeit one with patent protection to 2026. However, the founder has now reconstituted the company, reassembling the staff which put together the previous clinical trial and dealt with regulatory matters. The SCI data, noncontrolled though it was, showed a magnitude of clinical benefit that has not been provided by any other SCI therapeutic agent in human testing. BioAxone hopes that this will garner enough funding to carry out the clinical trial that Alseres never conducted, using what is a very different (and improved) clinical plan. Between the preliminary evidence of impressive benefit, and Cethrin's strong safety profile, this is an underappreciated program, and a very inexpensive way to stake a position in SCI using a product that has already demonstrated human 'hint of concept.'

CNS Company Product Development Table

Company	R&D	Preclinical	Ph I	Ph II	Ph III	NDA	Mkt	Comments
Acadia Pharmaceuticals	4	6	1	1	1			Pimavanserin sz PhIII underway
Accera		2					1	Axona on medical food market
Acorda Therapeutics		2		1			2	EU OK with Ampyra
Addex Pharmaceuticals	5	2		3				Founding CEO stepped down
Affectis	1	2		2				Partnered with Elan
Afraxis		2						Phase I delayed to 1Q:12
Alexza Pharmaceuticals			2	3		1		AZ-004 decision approaching
Allon Therapeutics		1		2	1			Pivotal PSP trial enrolling
Alseres		3		1	1			Terminal condition
Biogen-Idec	2	2	2		4			BG-12 data very positive
BioTie		1	3	5	1			Merged with Synosia
BrainCells	2	1		3				CEO left for Depomed
Catalyst Pharmaceuticals	2	1		1				CP-115 potent in preclinicals
CeNeRx BioPharma		1	1	2				Depression Phase IIb underway
Cephalon	2	2		1	1	3	3	Being acquired by Teva
Ceregene		2		2				PD PhII funded by MJFF
CoLucid		2		1				COL-144 Phase II positive
Corcept	1		1		2			Cushing's data positive
Cortex Pharmaceuticals	2	2		3				Looking for acquirer or partner
Cypress Biosciences				3			1	BioLine Rx took back sz drug
Depomed			2		1		2	Planning Gralise launch
D-Pharm		2		2				Stroke PhIII underway
Elan Pharmaceuticals	2	2	2	1	2		2	Partnered with Proteostasis
Embera Therapeutics			1	1				Raising money
EnVivo Pharmaceuticals	2	1	1	2				Phase IIb sz data positive
Evotec AG	3	3	2	3				Psychogenics alliance
Intra-Cellular Therapies	3	1		2				Takeda partnered PDE program
Jazz Pharmaceuticals		3	1	2	1		3	Waiting on the FDA
Link Medicine	2	1	1					PD program in Phase 1b
Lundbeck	4	3	3	3	2		5	Positive Lu31-30 data
MediciNova				3				Raised money
Medivation			2		2			HD failure
NeurAxon		4		1				NXN-188 in partnering talks
Neuren Pharma	2			2				TBI PhII enrollment slow
Neurocrine Biosciences		2	1	2	1			Initial TD data positive
NeurogesX			1	1		1		Qutenza trends unimpressive so far
NeuroNova	2		2					Ph I/II data midyear
NeuroSearch	4	5	5	7	2			Another Huntexil PhIII needed
Newron Pharmaceuticals		2	1	3	1			Santhera buyout fizzled
Noscira	3	4	3					Two AD drugs in clinic
NsGene	2	2	1	1				Biogen-Idec continuing for now
Paion		1	2	2	1			Awaiting DSPA results late-2011
Prana Biotechnology	1	1		1				AD biomarker study to begin
Proximagen	2	3		3				Outlicensed sabcomeline
Seaside Therapeutics		1		1	1			STX209 in Fragile X Phase III
Somaxon Pharmaceuticals							1	Silenor sales teams rented

Company	R&D	Preclinical	Ph I	Ph II	Ph III	NDA Mkt	Comments
StemCells	4		1	1			SCI trial started
Stem Cell Therapeutics				2			Raised $2 million
Sygnis		4		1			AX200 trial slow to enroll
Targacept	3	2	2	3			Raised $86 million for TC-5619
Titan Pharmaceuticals					1	1	Probuphine PhIII advancing
Trophos	1	2		1	1		Actelion has option on buyout
Vanda Pharmaceuticals				1		1	Fanapt sales minuscule
XenoPort		2	1	1		1	Fumarate prodrug potential
Zalicus	2	1	3	2		1	T-type CA drug ready for clinic
Zogenix					1	1	Sumavel sales modest

CNS and the Market

The biggest movement over the past month was for **Catalyst Pharmaceuticals**, whose impressive preclinical effect (in a model of infantile spasm) for its antiepileptic candidate CP-115 boosted the stock price more than 60%, and reduces its reliance upon the vigabatrin-in-addiction schema. **Elan** was up, boosted by the EU's acceptance of the jcv test as a means of stratifying MS patients in terms of risk of PML if given Tysabri. **Biogen-Idec** continued what has been a very impressive 2011, driven by positive news for its MS franchise, both from BG-12's clinical data and, like Elan, the inclusion of jcv testing in the EU label for Tysabri.

Titan's statistical shot-across-the-bow from the FDA on Probuphine let some of the air out of its recent bubble. **Avanir**'s bubble also deflated a bit over the past month, as the reality of Nuedexta's slow sales start has hit home.

Midyear, the companies with the strongest gains in 2011 are: **Elan Pharmaceuticals** (104.4%), **Catalyst Pharmaceuticals** (89.9%), **Jazz Pharmaceuticals** (69.5%), **BioTie** (60%),**Titan Pharmaceuticals** (52.9%), **Zalicus** (49.7%), and **Prana** (49.6%).

The largest declines have been experienced by: **NeurogesX** (-72.3%), **NeuroSearch** (-52.6%), **StemCell Therapeutics** (-46.4%), and **Cortex Pharmaceuticals** (-41.25).

NI Neuroscience Stock Index

148.61

1 month (June 149.56) dn 0.64%.
3 month (April 138.74) up 7.11%
2011 (12/31/10 131.10) up 13.36%

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Global Neuropharmaceutical Companies		6/30/11 price	Change 2011	market cap (mil)	52 wk high/ low	shares (mil)	cash (mil)	Partners	Indications
Acadia Pharmaceuticals	ACAD	1.63	35.8%	82.80	3.30/.65	50.80	45.70	Allergan, Meiji Seika	psychosis, cognition
Acorda Therapeutics	ACOR	32.31	18.5%	1292.08	37.29/20.43	39.99	225.30	Biogen-Idec	MS, spasticity, regeneration
Alexza Pharmaceuticals	ALXA	1.82	45.6%	124.92	3.64/0.86	68.64	47.60		agitation, insomnia
Alseres Pharmaceuticals	ALSE.PK	0.08	-33.3%	1.83	.39/.06	22.9	0.25		SCI, PD
Avanir Pharmaceuticals	AVNR	3.36	-17.6%	408.68	5.80/1.31	121.63	105.1		PBA, pain
Catalyst Pharmaceuticals	CPRX	1.88	89.9%	44.93	2.25/.86	23.90	11.50		addiction, epilepsy
Cephalon	CEPH	80.00	26.2%	6386.40	77.59/54.15	79.83	1160.20		regeneration, EDS, cancer
Corcept	CORT	3.99	3.4%	322.23	5.07/2.76	80.76	59.20	Lilly	depression, Cushing's
Cortex Pharmaceuticals	CORX.OB	0.10	-41.2%	7.89	0.21/.06	78.86	3.28		AD, ADHD, apnea, schizophrenia
Elan Pharmaceuticals	ELN	11.71	104.4%	6910.07	11.41/4.25	590.10	422.50	Biogen-Idec, JNJ, Proteostasis	MS, Alzheimer's
Jazz Pharmaceuticals	JAZZ	33.35	69.5%	1523.09	34.97/7.51	45.67	65.10		FMS, OCD
Medivation	MDVN	21.42	41.2%	742.42	25.50/8.43	34.66	195.00	Pfizer, Astellas	AD, cancer
NeuralStem	CUR	1.50	-29.2%	71.54	2.89/1.06	47.69	8.50		ALS, PD
Neurocrine Biosciences	NBIX	8.05	5.4%	452.73	9.30/4.98	56.24	124.90	GSK, Abbott, BI	endometriosis, TD
NeurogesX	NGSX	1.76	-72.3%	31.45	7.55/1.55	17.87	34.70	Astellas	pain
NuPathe	PATH	7.33	-19.1%	106.65	10.22/5.06	14.55	32.50		migraine
Prana Biotechnology	PRAN	1.87	49.6%	37.87	4.50/1.09	20.25	6.34		AD, PD
Repligen	RGEN	3.63	-22.6%	112.53	5.35/3.11	31.00	61.50		bipolar, SMA, imaging
Shire Pharmaceuticals	SHPGY	94.21	30.2%	18531.11	96.77/56.60	196.70	193.30		ADHD, genetic disorders
Somaxon	SOMX	2.13	-32.4%	96.06	5.48/2.04	45.10	43.30		insomnia
StemCells	STEM	0.53	-50.9%	72.67	1.27/.51	137.12	21.60		Batten's, PD, SCI
Targacept	TRGT	21.03	-20.6%	700.30	30.47/17.80	33.30	300.35	AstraZeneca, GSK	depression,sz, pain
Titan Pharmaceuticals	TTNP.PK	1.82	52.9%	107.84	2.22/.87	59.25	0.80		psychosis, addiction
Transcept	TSPT	10.95	48.0%	147.39	11.88/5.84	13.46	63.30	Purdue	insomnia, OCD
Vanda Pharmaceuticals	VNDA	7.14	-24.5%	206.35	10.32/6.04	28.90	194.00	Novartis	schizophrenia, insomnia
XenoPort	XNPT	7.12	-16.4%	251.12	11.34/5.66	35.27	93.10	GSK, Astellas	pain, RLS
Zalicus	ZLCS	2.38	49.7%	222.77	3.21/1.01	93.60	55.60	Covidien	pain, inflammation
Zogenix	ZGNX	4.01	-29.3%	136.24	6.90/3.50	33.98	26.30	Desitin	migraine, pain
		6/30/11 price	change 2011		52 wk high/ low		cash (mil)	Partners	Indications
Addex Pharmaceuticals	ADXN.SW	11.00	12.1%		11.95/8.78			Merck, JNJ	Sz, pain, migraine
Allon Therapeutics	NPC.T	0.34	-10.5%		0.77/.33				AD, sz
BioTie	OMX: BTH1V	0.8	60.0%		0.82/.30			Lundbeck	addiction, depression
Evotec	EVT.F	2.69	-6.6%		3.47/1.82			Pfizer, Boehringer, Ono	AD, pain, screening
Lundbeck	LUN.CO	136.00	28.3%		137.8/82.40			Paion	depression, stroke
Neuren	NEU.AX	0.01			0.04/.02				
NeuroSearch	NEUR.CO	45.00	-52.6%		125/47			GLilly,JNJ, Abbott	depression, obesity, HD
Newron	NWRN. SW	5.80	2.1%		8.70/5.03			Merck Serono	PD, RLS
Paion	PA8.BE	2.25	0.4%		2.90/1.80			Lundbeck	stroke, pain
Proximagen	PRX.L	132.00	-14.3%		159.65/60				migraine, PD, cognition
ReNeuron	RENE.L	4.80	-25.6%		11/3.85				stroke, PD
StemCell Therapeutics	TSX-V:SSS	0.08	-46.4%		.20/.05				stroke, MS, TBI
Sygnis	LIOK.F	2.10	0.0%		3.22/.58				stroke, cognition