

Spotlighting Neurobiotech Developments

Central Nervous System Remains a Large Target for Novel Therapies

Gail Schechter, Ph.D.

The brain is poised to become the number-one target for drug development during the next decade. The neurotechnology market currently exceeds \$100 billion, reported Zack Lynch and Casey Crawford Lynch of NeuroInsights (www.neuroinsights.com), publisher of "The Neurotechnology Industry 2006 Report". The three sectors of the neurotechnology industry include: neuropharmaceuticals with revenues of \$93 billion and 7% annual growth; neurodevices with revenues of \$3.4 billion and 21% annual growth; and neurodiagnostics with revenues of \$13.5 billion and 11% annual growth.

There are 450 public and private companies vying for the central nervous system (CNS) markets, including Alzheimer's disease (AD), Parkinson's disease, stroke, epilepsy, pain, depression, anxiety, schizophrenia, obesity, hearing loss, and sleep disorders. The recent "Neurotech Industry Investing and Business Conference" sponsored by NeuroInsights featured scientists, executives, and investors analyzing critical factors driving the development of new drugs and diagnostics for CNS disorders to treat a host of serious nervous system disorders.

The Memory Market

Targacept (www.targacept.com) is engaged in the design, discovery, and development of a new class of drugs to treat CNS disorders by selectively modulating neuronal nicotinic receptors, or NNRs, known to play a role in memory. The company uses its in silico drug discovery engine, Pentad™, to design small molecule drugs that target specific NNR subtypes for optimal therapeutic benefit.

Targacept has a development and commercialization agreement with **AstraZeneca** for its lead NNR product candidate, TC-1734, and recently reported successful Phase IIb results for drug in age-associated memory impairment.

Saegis Pharmaceuticals (www.saegispharma.com) is targeting an array of CNS disorders that involve a cognitive dysfunction component. The company's focus is on AD, mild cognitive impairment (MCI), cognitive impairment associated with schizophrenia (CIAS), and attention deficit hyperactivity disorder (ADHD).

Several small-molecule modulators are under investigation. SGS742 is the first selective GABA(B) receptor antagonist to display cognition enhancing effects in clinical trials, according to the company. Phase II clinical studies of SGS742 for MCI showed improvements in learning and memory in patients with AD. Another trial is currently under way

for adult ADHD.

SGS518, a selective antagonist of the 5-HT6 serotonin receptor, is a member of a family of drug targets believed to be crucial in learning and memory. Saegis will soon complete a proof-of-concept Phase II trial of SGS518 in cognitive impairment associated with schizophrenia.

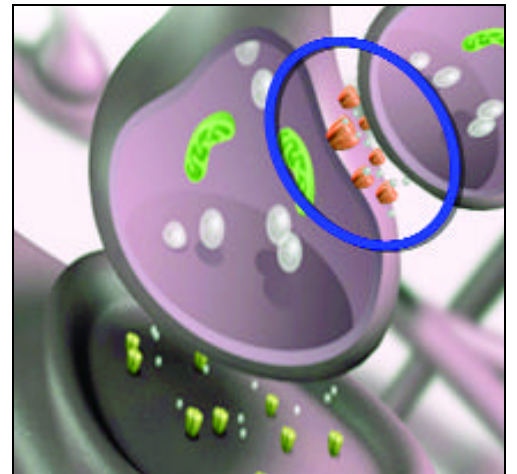
"There are many specific challenges that must be overcome in order to demonstrate efficacy of treatments for memory disorders,"

explained Rodney Pearlman, Ph.D., president and CEO of Saegis, "including flawed animal models that do not translate well to the human condition, poor understanding of disease etiology and drug mechanism of action,

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Presynaptic neuronal nicotinic receptors (NNR) modulate the release of cholinergic and noncholinergic chemical messengers. Thus, NNR can function to regulate levels of a broad spectrum of chemical messengers altering actions of a plethora of ionotropic and metabotropic neurotransmitter receptors. This expands horizons for NNR function far beyond all-or-nothing control of synaptic transmission to enable roles in modulating synaptic output over a range of stimulation frequencies.

Targacept



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Neurotechnology

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lack of quantitative and robust efficacy measures, ethical concerns related to the use of placebo controls, lengthy clinical trials to test disease-modifying drugs, and the huge expense of conducting clinical trials.”

Acumen Pharmaceuticals (www.acumenpharm.com) mission is to develop disease-modifying drugs to treat AD. The company's main therapeutic target is amyloid-derived diffusible ligands (ADDLs), which are soluble oligomer assemblies of amyloid beta 1-42 protein. These clusters are increasingly implicated in the molecular etiology of AD and as a trigger in early memory-related disorders.

Anti-ADDL strategies being developed by Acumen include injected antibodies that target soluble ADDLs before they reach receptors, small molecules that prevent ADDLs from binding to ADDL receptors, pills that prevent the formation of ADDLs, and vaccines that allow the body to generate its own antibodies that target soluble ADDLs.

Acumen entered into a research, collaboration, and licensing agreement with **Merck** (www.merck.com) to develop disease-modifying therapeutic drugs for AD and other memory-related disorders. Merck has acquired the worldwide exclusive rights to Acumen's ADDL technology for monoclonal antibodies and vaccines.

Ceregene (www.ceregene.com) focuses on the discovery and development of gene therapies for the treatment of CNS disorders. This therapeutic approach delivers natural growth factors into regions of the brain where neurons are degenerating in AD.

The company's lead target is nerve growth factor (NGF), which is known to prevent cholinergic cell death, reverse cholinergic cell atrophy, and improve memory performance in animal models of AD. Mark Tuszynski, M.D., Ph.D., and colleagues at the University of California, San Diego, conducted a Phase I clinical trial of ex vivo NGF gene delivery. Autologous fibroblasts genetically modified to express human NGF were placed into the forebrain of several patients with mild AD. “Study results suggested preliminary safety and efficacy, although this approach is not clinically prac-

tical due to time-limited effectiveness,” Jeffrey Ostrove, Ph.D., president and CEO of Ceregene, explained. “Therefore, attention is now focused on in vivo NGF gene delivery using an adeno-associated viral (AAV) vector.”

The Ceregene pipeline includes CER-110 (AAV-NGF) in Phase I for AD, CER-120 (AAV-Neurturin) in Phase I for the treatment of Parkinson's disease, and CER-130 (IGF-1) for the treatment of amyotrophic lateral sclerosis.

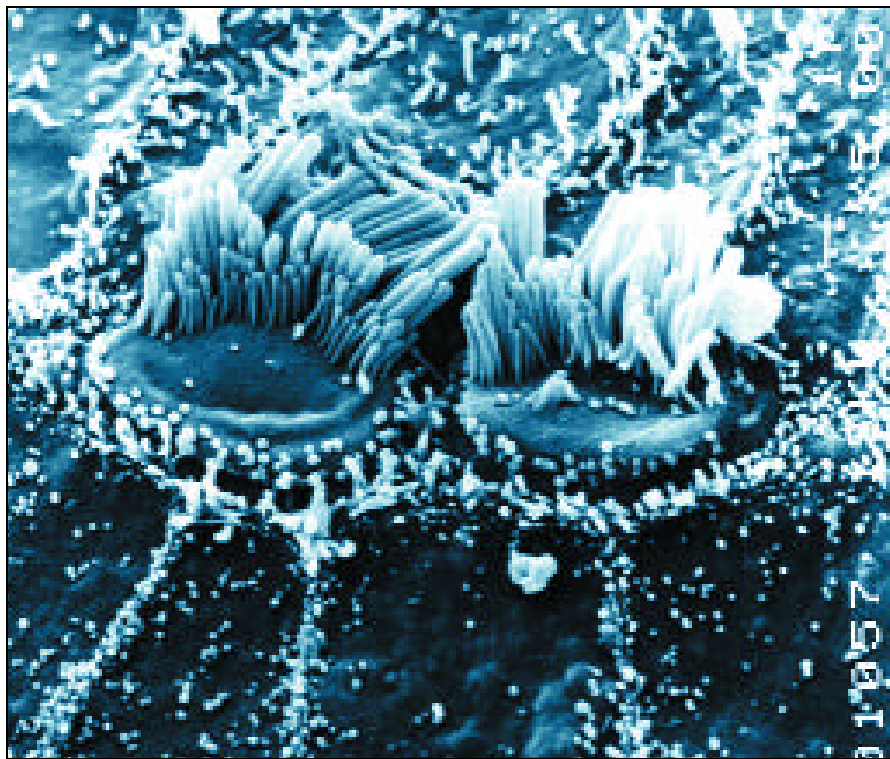
Neuropsychiatry

Jazz Pharmaceuticals (www.jazzpharmaceuticals.com) has three new products, one recent acquisition, and \$345 million in funding. Products include Xyrem® (sodium oxybate) for patients with narcolepsy who suffer from excessive daytime sleepiness. In a Phase II trial of patients suffering from fibromyalgia, Xyrem also relieved pain and improved functioning. Antizol® (fomepizole) injection is indicated as an antidote for ethylene glycol (such as antifreeze) or methanol poisoning. Cystadane® (betaine anhydrous for oral solution) is the first agent for the treatment of homocystinuria, a rare genetic disorder.

Matthew Fust, senior vp and CFO, reported that the company recently completed its acquisition of Orphan Medical. Jazz is actively looking to expand its internal portfolio of products and development projects through in-licensing, acquisition, and co-development partnering transactions.

Amarin (www.amarincorp.com) is developing medications for major neurodegenerative disorders. The company's drug, Miraxion, is synthesized from eicosapentaenoic acid, an omega-3 fatty acid, which is believed to stabilize cell membranes and mitochondrial integrity of stressed neurons, thereby preventing or slowing progression of neuronal degeneration.

Amarin currently is conducting large Phase III clinical trials of Miraxion in the U.S. and Europe to treat Huntington's disease. The company recently acquired an oral formulation of apomorphine to treat Parkinson's disease, which will broaden its neurology portfolio. Miraxion also was studied in a Phase II trial of depressed



Adult guinea pigs were deafened with a systemic combination of two ototoxic drugs: kanamycin sulfate (aminoglycoside antibiotic) and ethacrynic acid (loop diuretic). Five days later the animal's cochlea was injected with a 5-mL bolus of an adenovirus encoding an shRNA against p27Kip1, a cyclin-dependent kinase inhibitor. Eight weeks later the animals cochlea was dissected and prepared for scanning electron microscopy. These two new auditory hair cells were observed in regions that normally contain inner hair cells. This work was done in collaboration with Tatsuya Yamasoba at the University of Tokyo.

Sound Pharmaceuticals

patients who failed to respond to current treatments, both as an adjunctive therapy and a monotherapy.

“As a result of encouraging clinical trial results, Amarin intends to further evaluate the clinical benefits of Miraxion in depression and will seek a development and marketing partner to accelerate this program,” said Rick Stewart, CEO of Amarin.

Predix Pharmaceuticals (www.predixpharm.com), which recently merged with EPIX Pharmaceuticals, is focused on the discovery and development of novel, highly selective, small molecule drugs that target GPCRs and ion channels.

Using its drug discovery technology, Predix has advanced several drug candidates to clinical trials. The lead clinical-stage drug candi-

date, PRX-00023, a novel long-acting 5-HT_{1A} agonist, completed enrollment for a Phase III trial in patients with generalized anxiety disorder. PRX-03140, a highly selective, small molecule agonist of a specific GPCR known as 5-HT₄, completed Phase I trials indicating that the drug penetrated the brain and was well tolerated in patients with AD.

BrainCells (www.braincellsinc.com) applied the phenomenon of therapeutic neurogenesis to the field of psychiatry for the indication of treatment-resistant depression. The company is pursuing improved antidepressants by targeting small molecule drugs that specifically modulate the neurogenesis cascade leading to the development of new neurons.

Neurogenesis has been shown preclinically to play a role in the antidepressant efficacy of Prozac and other antidepressant medications. The goal of current research is to provide greater sensitivity, specificity, and predictive value in the treatment of depression and related mood disorders. Specifically, the neurogenesis-based approach to disorders of mood and anxiety may enable the discovery and development of next-generation antidepressants with greater efficacy, fewer side effects, and faster onset of action.

“The company is deploying its neurogenesis platform for profiling and selection of drug candidates,” noted Jim Schoeneck, CEO of BrainCells. “We believe that the platform represents a major improvement in the predictive power of preclinical models for CNS disorders, in particular depression and mood disorders, which will facilitate a paradigm shift in CNS drug discovery.”

NeuroNova (www.neuronova.com)

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va.com) is developing novel drugs to induce therapeutic neurogenesis. The drug development program is aimed at stimulating growth processes in the brain that lead to the formation of new endogenous neurons. NeuroNova uses its integrated platform of drug discovery technologies for neurogenesis—the Neurogenesis Qualifier—to identify therapeutically relevant drug targets and to develop new drugs for these targets.

The company's three leading drug candidates are sNN0029 for an undisclosed orphan drug indication, and sNN0031 and sNN0465 for Parkinson's disease. Preclinical proof-of-concept has been demonstrated in animal models. Using ICV administration to deliver neurogenic drugs resulted in dose-dependent neurogenesis in vivo. Clinical trials are planned for 2006.

"We believe therapeutic neurogenesis can revolutionize the treatment of several currently incurable neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease, as well as certain orphan drug indications," states Anders Haegerstrand, M.D., Ph.D., CSO of NeuroNova.

Sound Pharmaceuticals (www.soundpharmaceuticals.com) is developing medications to prevent and treat hearing loss. Currently, there are no FDA-approved drugs that protect or restore hearing loss due to noise damage, ototoxic drugs, or aging.

The company is focusing on the role of cyclin-dependent kinase inhibitor 27 (p27Kip1), an enzyme shown to regulate cellular proliferation by interrupting the cell cycle. This research demonstrates for the first time that hair-cell regeneration is possible in mammals, and that cell-cycle regulation is important in controlling hair-cell regeneration.

Sound received a DARPA grant from the DoD to develop its novel regenerative therapies. Jonathan Kil, M.D., president and CEO of Sound, said that "based on promising research with p27Kip1, the company is currently optimizing its lead compound for further testing and expects to develop its patented formulations into oral drugs that will provide protection and regeneration."

Transplantation Therapy

StemCells (www.stemcellsinc.com) developed human CNS stem cells (HuCNS-SC) for transplantation therapy, using a proven methodology to isolate rare stem and progenitor cells from human fetal tissue.

"A sequence of steps must be accomplished to make stem cells work: isolate the cells, create all three CNS cell types (neurons, astrocytes, and oligodendrocytes), deliver the cells to the brain, avoid adverse events, and promote normal biological function," stated Martin McGlynn, president and CEO of StemCells.

StemCells received FDA clearance for Phase I testing of its HuCNS-SC to treat Batten disease, and the company is initiating enrollment of children with this rare, fatal, genetic lysosomal storage disease. This is reportedly the first FDA-allowed trial to use a purified composition of human neural stem cells as a potential therapeutic agent in humans. Stereotactic placement of HuCNS-SC in appropriate sites in the brain offers the prospect of replacing missing enzymes, protecting against neuronal loss, and improving neurological function not only in Batten disease, but also in more common adult CNS disorders such as spinal cord injury and stroke.

StemCell Sciences (www.stemcellsciencesltd.com) is focused on technologies to grow, differentiate, select, and purify embryonic stem cells. The company's intellectual property includes technologies to permit the genetic selection of unlimited quantities of highly purified stem cells and their differentiated progeny for use in genetic, pharmacological, and

toxicological screens. These technologies can also be used to provide pure populations of appropriate cell types (which were not exposed to animal products) for transplantation therapy.

"The company has an established track record of collaborations with academic centers and commercial companies. Success requires multiple technologies and a globally integrated initiative. Our technologies, commercialization programs and collaborative partnerships with scientific pioneers continue to offer significant growth opportunities and the most realistic route to delivering medical benefits for those who suffer currently incurable diseases," said Peter Mountford, Ph.D., president and CEO of StemCell Sciences.

Conference panelists, presenters, and partici-

pants alike were clearly favorably disposed toward neurotechnology, in spite of the unique challenges confronting CNS product development. Representatives from both venture capital and big pharma reported being open to funding neurotechnology, especially when a company's products have already demonstrated proof-of-concept, are further along in clinical development, and have a clear commercialization path. High-risk is mitigated by the potential for significant reward. After all, today's risks may be tomorrow's breakthroughs.

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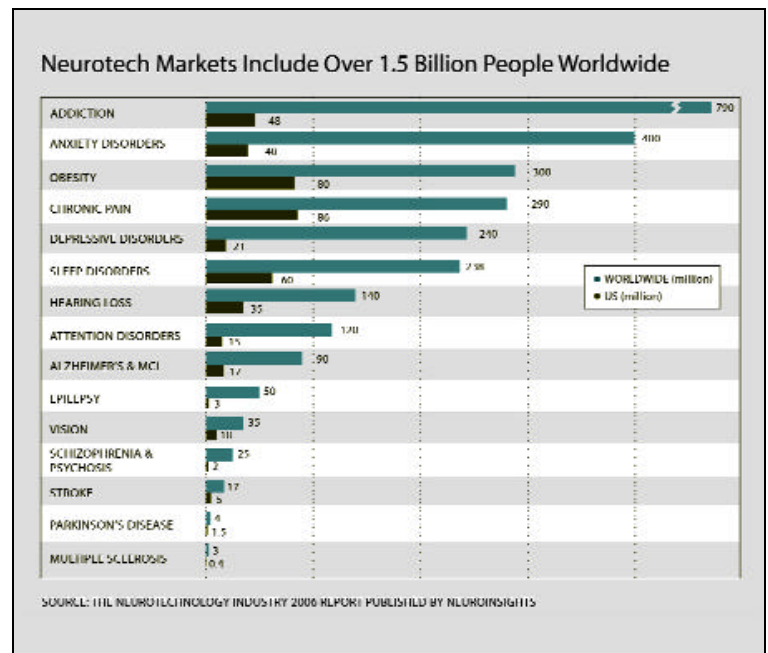
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Brain-related disorders currently afflict more than 1.5 billion individuals worldwide. There is unprecedented demand for novel treatments that prevent, delay, or cure a wide range of neurological and psychiatric illnesses. NeuroInsights