

Neuro Investment

Investment research on companies developing neuro/psychopharmaceuticals

No. 75 SEPTEMBER 2001

Sector Overview

With all due respect to the office and the complexity of the decision, President Bush's ruling on federal funding for stem cell research was a masterstroke of political expediency bereft of scientific merit. There is no logic to the notion that embryos already destroyed prior to August 9 are valid sources of stem cells, but embryos destined to be discarded after August 9 are not. It was good for **Geron**, which has a strong US patent position (albeit under challenge) and for a number of lesser known international companies like **BresaGen** and **ES Cell**, who were fortunate enough to have destroyed their embryos early. But the notion that we have all the cell lines needed (and we strongly doubt that those sixty-four alleged cell lines are all viable) is absurd. Knowing so little about these cells, how to grow them and differentiate them into useful cell progeny, there is no way to be sure how long they last, what flaws they hide, and how many will be enough. To place Leonard Kass at the head of the commission charged with overseeing this research is like putting Savonarola in charge of the town book fair. Our congratulations to the United Kingdom, which is busily reinventing itself as a sanctuary for cell researchers of all nationalities, races, and creeds. Meanwhile, the political debate will continue in Washington.

NI Neuroscience Stock Index 205.22

1 month(August 215.34) **dn 4.7%**
3months(June 242.80) **dn 15.48%**
2001 (12/29/00 266.03) **dn 22.86%**

Tier A Recommendations **dn 19.3%**
Tier B Recommendations **up 32.4%**

Disorders of Memory: Mild Cognitive Impairment

Memory weaves the fabric of human awareness. Without memory, we would live in moments which flare into life and then extinguish themselves. Learning, and thus survival itself, would be impossible. While memory can be amazingly resilient, we are increasingly vulnerable to disorders of memory as we age. The spectrum of memory dysfunction ranges from the subtle losses in wordfinding and processing speed that impact almost all of us from age forty on, all the way to the extreme memory impairment displayed by advanced Alzheimer's patients. The scale is enormous, for in the United States alone, there are almost 60 million people age fifty-five or over. While four to five million of them have Alzheimer's, we estimate that fifteen to twenty million suffer from lesser, but still impactful, degrees of memory impairment. The spectrum of memory disorders thus constitutes the fourth largest CNS patient population, after depression, anxiety, and the hodgepodge of disorders comprising 'excessive daytime sleepiness.'

Learning itself involves a range of cognitive activities and processes, and across the whole phylogenetic range of species, the capacity for new learning starts to ebb from the time of sexual maturation on. One must attend to and focus on the environment in order to take in new information, be able to hold it in 'working memory' in order to have it begin to then be consolidated. With age, the mechanisms by which memories are initially encoded and built, deconstructed for storage, and then located and reassembled for recall, gradually deteriorate. The increases in longevity offered by modern medicine and lifestyles are pushing the envelope of the neural wiring with which humans are equipped. Cognitive slippage that might have been mildly annoying in the past takes on more ominous importance. While the adage 'use it or lose it' holds much validity, and both physical and mental exercise help maintain cognitive 'tone', there is an inevitable if subtle loss of certainty and grip. The intellectual sands seem to shift under one's feet as keys become elusive, names teeter upon the tip of one's tongue. As time passes, for some the anxiety turns into fear that this is the harbinger of a slow slide into dementia.

Such is not necessarily the case. But, unlike most disorders we discuss, there is controversy regarding the delineation of what is normal decay and what is pathological disorder, and whether the promise of treating the latter is offset by the prospect that many might try to forestall the former. The FDA has been reluctant to widen the range of memory disorder definitions in such a way that people might then have access to a 'smart drug', used as a cognitive enhancer rather than as disease remediation. There are numerous diseases and disorders which are age-related, but the FDA has

continued on page 3

Recommendations

A (*nearterm revenues, growth potential, and relative safety*)

Cephalon (59.22, recommended 1/99 @ 9.0): Sold off after an upbeat conference call wherein a 22% gain in Provigil sales over 1Q was announced. Fueling the growth is increased utilization by psychiatrists, a trend that continues. Psychiatrists write 31% of the scrips for Provigil, most of them for depression. 27% of 1H Provigil scrips were for depression, compared to 13% in 2000. In fact, 80% of Provigil use is now off-label. Gabitril sales also improved impressively, up 19% over 1Q. A 300pt sleep apnea Provigil trial will finish later this year, while Gabitril trials in bipolar, anxiety, neuropathic pain, and spasticity have started or will by early 2002. We continue to be somewhat annoyed at management's statement that they will release news about trials only if they are successful. Cephalon is staying with its prediction of being profitable this year. Target is 100.

Titan (9.75, recommended 4/00 @31.00) No news, so the stock price wallowed in a more ugly fashion than expected .

Novartis remains committed to the Zomaril program, and well they should, since it continues to be a valuable asset. Novartis is still putting money into a clinical trial intended to show Clozaril is superior to Zyprexa, and if they are willing to keep investing in a drug that will never be a first line therapy, they certainly will support one that could be. We hope that Novartis will release more data from the completed Phase III during the fall so that some of the rumors can be laid to rest. Year-end target is 20.

Neurocrine Biosciences (39.33, recommended 9/97 @9.5):

After a news-filled July, a breather on events during August. More insomnia drug trial data is imminent. There is increased anticipation of an insomnia partnership over the next six months. It has weathered the recent storm quite well thanks to strong analyst support. But after all, if one could own but one CNS company, this would be the one to choose. Target is 60.

NPS (33.62, recommended 2/01 @ 40.44) Other than comments from observers noting that the success of Lilly's osteoporosis drug provides validation for NPS, there has been total silence from NPS. Its price oscillated with the sector and market. Target of 60.

B (*more speculative and longer term, with both high potential and risk*)

Cortex (2.55, recommended 2/99 at 2.75). Cortex is review in full in this issue. Still waiting for Organon's initiation of Ph II schizophrenia trials, and we expect news during September, after Europe returns from vacation. Preparations continue for the initiation of a major MCI trial this winter, designed by Cortex and Servier. A small Alzheimer's trial at NIH produced some surprisingly good impact upon ADAS-cog scores, and a fixed-dose trial is going to be started as a result. With so many

potential targets for Ampakines lying fallow for now, we believe Cortex is going to accelerate its timeline for seeking a North America partner for MCI/dementia. Target is 5.

Pharmos (2.70, recommended 4/00 @4.94): The initiation of the US arm of the Phase III is delayed until early 2002. Pharmos states that the FDA required another preclinical experiment to be carried out. Pharmos continues to enroll patients slowly but steadily into the Euro arm of the TBI Phase III. The LE-T program is going to require a 2400pt Phase III, much larger than expected, and Quintiles found a piece of data missing from the UK submission for Lotemax. It does not appear that Bausch & Lomb is a competent partner. But in spite of them, Lotemax and Alrex sales continue to grow in the US faster than the market itself. Target is 6.

NeoTherapeutics (3.72, recommended 4/01 @ 5.69) NEOT took another large step back towards fiscal respectability when they repurchased the \$5 million in NeoGene convertible warrants they had issued last year, for \$5.5 million. The only remaining reset/convertible warrants are held by Societe Generale (\$2 million). A \$2 million financing was also done with another reputable investor, Summit Capital, who had bought more than 700,000 shares on the open market. We expect NEOT to announce that all 500 pts have been randomized to drug/placebo at any time. The trial sites expanded and enrollment continues in the spinal cord and Parkinson's trials, while NeoOncoRx is in late-stage talks to inlicense two more cancer drugs. Target is 16.

Interneuron (5.00): No news, the initiation of the Trospium Phase III is the next expectable event. Target is 12.

A note about copyrights. The unauthorized reproduction or electronic transmission of NI is not permitted, no matter how worthy the cause. A corporate/institutional subscription is intended as a single-site license. It does not allow the placement of NI excerpts on a company intranet, nor the unauthorized reproduction of an issue or excerpt for inclusion in a corporate information packet or website. If those options are needed, we welcome the opportunity to discuss suitable and reasonable licensing arrangements.

News and Developments

Synaptic's Multiple Personality Disorder

Synaptic has reinvented itself once again. Born as a target-identification company, it briefly anointed itself as a genomics firm after key corporate partners dropped joint programs. Now it has decided to become a drug discovery and development company. Their first target is depression, for which they claim to have identified a novel target, obesity could be the second. No one has ever doubted their scientific expertise, but this is not an easy role to take or target to address. To fund their efforts, Synaptic entered into a deal with a group led by Warburg Pincus. Synaptic would raise a total of \$41 million in two tranches (shareholder approval pending for the second), the WP group would own 41% of the company. Given their lack of drug development, they will rely upon CROs for much of the preclinical and clinical work, which is not an inexpensive option. Overall, a steep price to pay for a second childhood. •

CNS Company News

On the theme of second chances, **Merck's** Substance P antagonist program is back for Phase III in depression. When last heard from, the initial lead compound had failed after its much ballyhooed inauguration as the antidepressant of the future... Finland's **Orion Pharma** partnered its antianxiety agent (via 5HT_{2a}/5HT_{2c} antagonism) deramciclone with **Pharmacia**, receiving \$30 million upfront. The drug, already in a European Phase III, will go into a US Phase III trial...**Shire's** ADHD challenges expanded as the FDA declared **Celgene/Novartis'** monoisomer version of Ritalin approvable, boasting improved duration and potency... **Janssen** has signed a deal with **Biofrontera** to look at neurogenomic patterns associated with nicotinic receptor activity in Alzheimer's. This is an attempt to identify patient subgroups more likely to be responsive to Reminyl's nicotinic activation. This kind of pharmacogenomic pattern identification will be the first generation of return from the massive investment in genomics research...**NeuralStem** and **MetriGenix** (a **GeneLogic** spin-off) have agreed to develop and market neurochip assays combining NeuralStem's gene expression data and the MetriGenix 3D microassay. It will be marketed to CNS companies seeking to do high-throughput testing of compounds against novel genomic targets...**NeuroSearch** has dropped its GABA-A sedative program due to competition (especially from Guilford)...**Forest** is taking NTII's memantine into a second Phase III for diabetic neuropathy...and **Gliatech** has been given conditions by the FDA for a ADON-L return, including tougher statistical standards for the MRI reread analysis now ongoing.... •

Memory Disorders continued

not taken the position that cardiac disease, hypertension, impotence, and arthritic distress are to be expected with age and therefore are undeserving of pharmacotherapy. Instead, they have approved drugs to forestall the effects of aging, at times inviting misuse. The obvious example is Viagra, approved as a treatment for male impotence, often instead utilized as a potency-enhancer.

We have always been puzzled by the parsing out of cognition as somehow less worthy. It intuitively seems connected to the stigma often attached to disorders of the mind. But while one can argue that many psychiatric disorders are difficult to quantify, such is not the case for cognitive efficiency, which is highly measurable. For example, age-related decline is clearly manifest on several subtests of the *Wechsler Memory Scale-III*, perhaps the most comprehensive memory assessment tool available. One subtest involves the reading of two short stories, recall checked immediately and after a delay. To obtain an average (compared to peers) score at age 17, one must achieve a score of 26. At age 45, to be defined as average, 20 items will suffice. And at the age of 75 (excluding those with a dementia), recalling 14 items produces an 'average' score. Thus a 75 year old individual who is 'average' retrieves roughly half the information recalled by the teenager. This is not just a cosmetic change that should be accepted as a part of normal development. In a world where we slice open faces and bellies to remove excess fat, inject toxin to smooth the lines time has etched, ingest Viagra and hormones to restore the libido of youth, and hair loss and 'crow's feet' warrant Propecia and Botox, the toll that cognitive decline takes on functional efficiency and one's sense of personal efficacy deserves to be addressed.

To the credit of the FDA, the CNS Division did agree this past June that the category of Mild Cognitive Impairment should be considered a diagnostic category separate from Alzheimer's, and a valid target for drug therapy trials. This will not be the last heard of this issue, for all companies seeking to treat Alzheimer's hope that they can extend their market into Mild Cognitive Impairment, and any firm targeting MCI will be more than happy to sell their drug to greying boomers trying to regain a sense of intellectual sharpness. The enormous scale of this potential market, which even today would exceed ten million individuals in the US alone, demands an immaculate safety profile. Since MCI is viewed as relatively benign, virtually no adverse event risk will be tolerated in a drug seeking approval for MCI. The efficacy hurdle has been made easier to surmount, but these firms can expect that longterm safety studies covering the gamut of risks will have to be part of their NDA package.

Memory Disorders continued

The Diagnostic Muddle

Memory disorders constitute a spectrum that begins with Age Associated Memory Impairment (AAMI), shifts to Mild Cognitive Impairment (MCI) in the midrange, and progresses to the dementias at the extreme. One working definition for AAMI, an even more ambiguous category than MCI, is that it involves a one standard deviation decline in memory performance compared to a thirtysomething normative group--i.e. worse than 84% of individuals in their thirties. This involves the subjective 'not feeling as sharp as I once did.' MCI involves memory impairment compared to one's age cohort, being at least one standard deviation below their peers, but without significant impairment in other areas and no loss of capacity for basic daily functions. If there is a broader range of decline, or if ADLs are suffering, this presumes dementia, not MCI. There is much debate as to whether MCI is simply a precursor to dementia or is itself a disorder. MCI patients do not show cholinergic system deficits on autopsy, but other researchers claim that some MCI patients have evidence of tau protein or amyloid pathology consistent with AD. One of the problems with this differentiation is that patients who present themselves for assessment may already be in the more severe, pre-dementing stage, and thus not surprisingly 'convert' to Alzheimer's at a high rate, 12-15% per year (the rate of conversion for the elderly population as a whole is 1-2%). But one AD expert we consulted states that in a less skewed, self-selected sample, the conversion rate is 5%. MCI is a risk factor for Alzheimer's, but does not appear to always lead to it. This complicates the process of assessing whether a drug slows the progression into Alzheimer's, since multiple outcomes are possible. What is clear is that for most people, MCI distressingly diverges from the cognitive changes associated with 'normal aging.' Estimates tend to place the number of individuals with MCI in the US as roughly commensurate with the number of patients with Alzheimer's, four to five million at present. Adding in the vast range of patients with real or perceived AAMI would at least double that total. The estimated cost of dementia in the US approaches \$100 billion per year now. With projections of the number of US dementia patients reaching 16-18 million by mid-century, the societal burden could become totally overwhelming. To treat memory disorders at an earlier stage may or may not alter disease progression, but in our view is a valid and valuable goal in itself.

The Neurobiology

In our past reviews of cognitive/memory enhancement, we broke down the processes intrinsic to cognitive 'sharpness' into three segments: arousal, attention, and memory. We are going to utilize a different framework in this issue, one which focuses more heavily, albeit not exclusively, upon the third component, memory per se. But arousal and attention are essential, they provide a permissive environment for learning, for if one must attend to a stimulus at some level (even for the implicit learning of a motor skill) in order to learn it. This is an area of neural functioning whose deficits often fall into the category of attention deficit disorders, which we have discussed separately.

Arousal refers to the overall level of activation present, sometimes labeled cognitive 'tone.' The reticular system of the brain receives sensory input and then sends out activating signals via the reticular activating system. These signals reduce the threshold of intensity required for the cortex to respond to a stimulus. This system involves many neurotransmitters: the noradrenergic system has extensions throughout the brain and may be the fundamental modulator of cortical 'tone' via the release of norepinephrine. A widespread network of histaminergic circuits emanates from the hypothalamus, and these also modulate the overall level of activation. The amygdala, which integrates emotional arousal into experience is also hard wired in. The greater the amount of emotional arousal, the more likely an event is to be remembered, adaptively in many contexts, less so in the case of posttraumatic stress disorder (PTSD). Dopaminergic connections also play an important role in focused attention—the selection of something in the environment upon which one focuses their cognitive apparatus. Again, there is a maladaptive potential detour, because it is the dopamine-fueled amplification of drug-induced stimulation (and memory thereof) that contributes to the process of addiction. Cholinergic pathways connect to the thalamus and hippocampus, and are also intrinsic to learning/memory. In oversimplified form then: one must be sufficiently stimulated and awake to have the potential to attend to stimuli; the emotional valence of a specific stimulus engages selective attention upon one element out of the multitude of stimuli that barrage us at any given moment; and the activation of learning areas allows us to process and store what has been attended to, and enter it into memory. This is crucial to short term memory, the learning of new material itself.

The development of longterm, long-lasting memory appears to go on in parallel, and this second system utilizes different pathways and ultimately moves the

memory out of downtown hippocampus into the cortical suburbs. It does so via long-term potentiation (LTP), a process of upregulating the excitability of neuronal circuits in response to input. This repeated stimulation defines what is significant and worthy of remembering, and what is superfluous, to be discarded.

The Molecular Puzzle

While the hippocampus is the part of the brain wherein memory processing occurs, but once a memory has been assembled and consolidated, memory storage itself is via a circuit, not via a 'place' in the cortex. It is the activation of complex patterns of neurons (whose communication status is binary, polarized or depolarized, on or off) interconnecting through the variety of brain areas (connecting sensory, cognitive, and emotional aspects of an experience), that provides for memory in its enduring form. It is similar to how a computer assembles digital data into the representation of a page, an image, or even a sound—close enough to the original that it is recognizable, albeit imperfect.

The sequence by which experiential stimulation leads to the formation of memories is still the object of intense study. Several pathways have been shown to be contributory, as is not surprising, since experiential learning involves association between two events, termed coincidence detection. Thus the simultaneous activation of different pathways is crucial to learning/memory--there is no sound of 'one hand clapping.' The molecular cascade that leads to memory formation offers several targets for potential intervention, and each of the scientific groups pursuing this area tend to preferentially focus on one or two. The cascade involves:

Presynaptic neurotransmitter release: By blocking autoreceptors or reuptake, neurotransmitter levels are increased, thereby increasing their impact upon postsynaptic activity. The enhancement of retrograde neurotransmitters like nitric oxide would in theory also permit increased release. The reuptake strategy is epitomized by the use of cholinesterase inhibitors, such as **Pfizer's** Aricept, **Novartis'** Exelon, and **Shire's** Reminyl, with **Axonyx's** more potent Phenserine completing Phase II soon. Intended for Alzheimer's, the first three provide modest, time-limited improvement in a minority of patients. As the disease progresses, even that initial improvement dissipates. The use of cholinesterase inhibitors is complicated by the fact that as blocking reuptake leads to a temporary increase in neurotransmitter level, autoreceptors then detect that level and shut off presynaptic release. The University of Pittsburgh researcher Steven DeKosky has also reported that the cholinergic system appears relatively intact in MCI patients, casting further doubt upon the utility of

cholinesterase blockers in MCI. Aricept is being used (as is Vitamin E) in a large-scale NIH-sponsored study of the progression from MCI to dementia, but that three year trial has a long way to go. Since blocking the autoreceptor should permit continued neurotransmitter release, acetylcholine levels also can be increased by antagonizing the muscarinic M2 autoreceptor (**Memory Pharma**). GABA-B modulation can also increase the release of several neurotransmitters (**David Pharma**), which produces an activity-dependent upregulation of synaptic activity. The modulation of the CB1 endogenous cannabinoid receptor also is a potential target for improving memory, recent papers in *Neuron* and *Nature* showed that it can have an effect upon LTP. Thus far, **Pharmos**, who has an unmatched pipeline of cannabinoid-based analogs, has not announced any intention of pursuing cognitive enhancement.

Postsynaptic neurotransmitter effects: LTP is a product of neuronal stimulation, specifically the activation of NMDA receptors by glutamate, allowing calcium to enter and depolarize the neuron, this process is a high-level target for intervention. Simply seeking to open NMDA channels across the board would be neurotoxic, thus the trick is to activate specific LTP-relevant subtypes (**Eureka's** work with the NR2B subunit), the glycine co-receptor (**NPS**, apparently dropped by its partner **Janssen**), the d-serine co-receptor (**Memory Pharma**), the kainate receptor (**David Pharma**) or the AMPA receptor, whose activation (**Cortex, Lilly**) **promotes** the expanded opening of the NMDA ion channel (**Eureka, Sention**). The d-serine hypothesis has been partly confirmed by Harvard's Joseph Coyle (in schizophrenia), while **Cortex's** Ampakines have shown early proof of principle in Alzheimer's and schizophrenia. The downregulation of inhibitory GABA receptors is being pursued by **Neurogen** and **Merck**, though this appears to not impact LTP per se, but instead addresses attention/alertness/arousal. It should be noted that **Shire's** Reminyl is said to also serve as an allosteric modulator of postsynaptic ACh receptors (i.e. it does not activate the receptor directly, but promotes its opening, similar to how **Cortex's** Ampakines modulate NMDA receptor opening), which should allow the ACh in the synapse to have more effect postsynaptically. **Targacept** is using nicotinic ACh receptor modulation as a vehicle to treating AD/MCI. This could operate both presynaptically (which causes increased release of other neurotransmitters, including dopamine) and postsynaptically, where the increase in cholinergic activity should be cognition-enhancing. **Merck** has (via its acquisition of **SIBIA**) two compounds which are active at the nicotinic receptor. But nothing has been heard of them in more than two years, when they were in Phase II trials, which does not augur well.

In terms of other major neurotransmitter approaches, D1 (dopamine-1) agonism/activation is a vehicle for downstream enhancement of a variety of other neurotransmitters, including acetylcholine, norepinephrine, and dopamine. **NeuroSearch** saw enough evidence of cognitive improvement in Alzheimer's patients using its D1 agonist that they plan to take that program through Phase III themselves. The upregulation of dopamine and norepinephrine would have an impact upon attention, and boosting acetylcholine levels selectively in the septal region (as occurs with their drug) might address the cholinergic deficits seen in AD, without involving the side effects associated with broadspan cholinergic upregulation. **Drug Abuse Sciences** has incensed **Abbott's** D1 agonist ABT-431 as a cocaine craving drug, but also is exploring the idea of using it at much lower doses as a cognitive enhancer, perhaps via aerosol delivery. A paper recently published in the *Archives of Neurology* found that high-dose ABT-431 induces dyskinesia in Parkinson's patients just as easily as does L-dopa. Whether that risk would also be incurred with low dose ABT-431 in the non-Parkinsonian brain is debatable, but since pre-Parkinson's is symptomatically silent and undetected for many years, satisfying the FDA regarding D1 agonist safety in MCI will be a challenge.

Further downstream are a variety of intracellular targets. Receptor activation leads to the entry of calcium, which then activates second messengers such as adenylyl cyclase, via calmodulin. Metabotropic receptors, specifically mGluRs, had once been thought to participate as well, but it does not now appear that they are essential to LTP. A pathway that does appear critical involves the sequence of second messenger transmission following receptor activation. The second messenger cAMP is produced from ATP (the basic cellular energy store). The level of cAMP available is regulated by the enzyme phosphodiesterase (PDE). It is cAMP which is central to the LTP pathway, because it produces cAMP kinase, or PKA, and PKA activates the gene transcription regulator CREB1. By inhibiting PDE4, cAMP levels can be increased, leading to enhanced CREB1 levels. The *Journal of Neuroscience* recently published a paper suggesting that aging neurons have reduced levels of cAMP, and that increasing those levels to those seen earlier in development enhances regenerative processes and neurite growth.

However, the modulation of cAMP has been problematic because it is so ubiquitous, and its modulation by PDE4 overly nonspecific in its impact. PDE4 receptors are found throughout the body, and indeed are targets in a variety of antiinflammatory drug strategies (**GlaxoSmithKline**, **Celgene**, **Icos**, **Pfizer**, **Inflazyme**). And the prototype PDE4 inhibitor, **Bayer's**

Rolipram, caused emesis, and was terminated. **Memory Pharma** and **Helicon** are both pursuing subtype selective (there are at least fifteen variants) PDE4 inhibitors which would only act on types found in the cortex. Helicon claims to have a patent governing the modulation of CREB, and has identified a number of compounds which activate it. CREB1 triggers the expression of genes that produce proteins (including BDNF and tPA) that contribute to synaptic growth, while also displacing CREB2, which inhibits protein expression. This growth, and the LTP amplification of signals along its path, propels the process of longterm memory consolidation. It is that new configuration, with its own constellations of synaptic connections, that constitutes the circuit of a new memory. The discovery that neurogenesis, the production of new cells, occurs in the adult brain (*NI May 2001*), raises an intriguing question as to how those new cells interface with established memories. Speculatively, perhaps new cells are utilized in the formation of new memory circuits, rather than disrupting circuits already in place.

The flip side to the well-established coin of LTP is LTD, longterm depression. High-frequency stimulation is interpreted as significant, and leads to LTP. Low frequency stimulation on the other hand is interpreted as irrelevant, and those circuits become underresponsive, habituated to a stimulus which is not likely to be meaningful. Thus what is encoded into memory depends on a bidirectional filtering process born of organismic salience. There is simply too much going on in the environment for everything to be a focus of attention and suitable for memory storage. One appealing explanation for how the hippocampus 'gates' relevant, storable stimulation as opposed to the irrelevant has been proposed by Daniel Alkon (**NeuroLogic**). He has defined a parallel memory potentiation circuit that involves cholinergic activity and intracellular signalling. The intracellular sequence leads from the protein calexcitin to carbonic anhydrase, activating ryanodine receptors which in turn release intracellular stores of calcium (much as post-synaptic stimulation causes calcium influx). This calcium release causes GABA-A receptors to turn excitatory (instead of their usual inhibitory role) in an activity-dependent fashion. This amplifies the signal generated by the cholinergic input and simultaneously, by input at the aforementioned glutamate receptors. Alkon notes that this activity creates the 'theta' frequency of hippocampal activity, observable via EEG. This dual channel theta pattern may be optimal for the generation of associative learning, longterm potentiation set to neural music.

There has been much activity in the nutraceutical industry devoted to cognitive enhancement. Ginkgo

biloba increases blood flow, while Vitamin E is an antioxidant which is frequently used to reduce neurotoxic oxidative processes. Annual sales for ginkgo biloba, which has marginal effects on cognitive tests, but has been skillfully marketed by nutraceutical firms, are estimated to be in the \$1 billion range. The antiinflammatory effects of NSAIDs like ibuprofen have been touted as staving off the gradual diminution of cognitive capacity, and the selective COX-2 inhibitors (Celebrex and Vioxx) are being tested for their effect upon cognition. The antiinflammatory compounds developed by **Inflazyme** inhibit the production of TNF-alpha, but because of their effect upon PDE4, some may also be memory-enhancing, and have been licensed to **Helicon Therapeutics**).

There is a class of compounds, called nootropics, the best known of which is piracetam. They have a modest positive effect upon cognition, but their mechanism of action has been obscure. It has been suggested that they are low-potency enhancers of LTP via AMPA controlled channel activity. They have been studied for the past 20 years in Europe, but the findings have been equivocal. They have thus failed to garner any development interest from pharmaceutical firms, and indeed have been ignored in the US. A more potent piracetam-like compound has been inlicensed by **David Pharma** from its Russian developer.

One trend in the memory field is to rummage through Big Pharma 'attics' in search of memory-enhancing compounds. Big Pharma has literally thousands of compounds which have been explored, sometimes extensively, for a variety of indications before being sidelined for reasons of inefficacy, adverse events, or bureaucratic shortsightedness. These old compounds are being raided by companies seeking MCI drugs, testing them in more advanced models of memory than were previously available. **David Pharma**, **Helicon**, **Memory Pharma**, and **NeuroLogic** have all acquired compounds via this route, some of which already have gone through extensive toxicology studies and even human trials.

Programs to follow: Currently Prioritizing MCI

Axonyx: In April 2001, Axonyx took an option to license a Thomas Jefferson University researcher's work on the peptide Gilatide. Gilatide interacts with the exendin-4 receptor, activating the cAMP-CREB pathway. Administered intranasally, it provided improved memory performance in animals up to two weeks post-administration. Further preclinical studies are ongoing. Being a small peptide, the delivery issue is complicated, and if Axonyx were to develop this as an intranasal drug, there would be much work to be done regarding consistent dosing and absorption. Axonyx

states that it hopes to file an IND within 12-18 months.

Cortex: UC-Irvine's Gary Lynch developed AMPA modulating compounds that cause NMDA gated ion channels to remain open longer (by removing magnesium blockage), thereby strengthening the signal. This is activity-dependent however, there must already be some type of synaptic input impinging upon the channel in order for it to be amplified. This avoids the inevitable side effects that would come from an indiscriminate upregulation of NMDA activity. The lengthening of the signal duration in turn leads to an enhancement of LTP. All of this work has been licensed and developed by Cortex Pharmaceuticals. There are at least three generations of Ampakine molecules comprised of several hundred compounds. Cortex has identified at least eight AMPA receptor variants (which are differentially expressed in various areas of the brain), and has molecules that selectively modulate those subtypes. Ampakine activity also upregulates the transcription factor cfos, and leads eventually to increases in the neurotrophic proteins BDNF and NGF. These likely play a role in synaptic growth.

Beyond its extensive testing in rodents, the Ampakine platform is the best characterized cognition and memory enhancement platform in terms of human exposure. European trials in healthy young and elderly volunteers began in 1995, and improvement on a limited array of memory tasks was shown. These effects in elderly subjects showed significant improvement at the highest dose, where the recall of nonsense syllables began to approach the level displayed by healthy young volunteers. This supplied the preliminary support for taking Ampakine into MCI. **Servier** has partnered with Cortex for MCI (Cortex retaining American rights) and a 200pt Phase II trial of CX516 will begin around year end, data to be available mid-2003. A NIH researcher has just produced data from a 14 pt escalating-dose study which surprisingly found a statistically significant benefit at four and six weeks. Six weeks of treatment produced a mean decrease in ADAS-cog scores of approximately 4 points. A fixed dose trial should begin later this year. Cognition was also improved in a 19pt Phase IIa study of chronic schizophrenics (also receiving clozapine) conducted by Don Goff at Harvard/MGH. A thorough neuropsychological assessment showed statistically significant improvement in attention, memory and problem-solving. Goff has now embarked on an expansion of that study to a total of 80 patients, while **Organon** is about to initiate Phase II trials with a later generation Ampakine in schizophrenia. **Shire** is initiating a 114 pt Phase II of CX516 in adult ADHD, to be completed mid-2003. This is in reference to Ampakine impact upon attentional processes,

enhancing the cognitive potential for learning. All of the human data provided thus far has been for CX516, the first-generation Ampakine, but we expect that later generation analogs, 10-100 times more potent, may be likely to be commercialized. To this point, Ampakines, which at very high doses would in theory present some risk of being epileptogenic, have not been associated with any significant adverse events. Cortex appears to have a time-advantage in the race for an MCI therapeutic, with a launch possible in 2006.

Cortex must keep an eye on **Lilly**, the Big Pharma company most interested in AMPA modulation. Lilly has compounds which, in head to head testing with first generation Cortex molecules, were more potent, though not necessarily more efficacious. However, Cortex has patents on the use of AMPA modulators for memory and cognition, thus Lilly would have to license the right to market their molecules for that indication.

David Pharma: Started by Big Pharma veterans, David Pharma has inlicensed three molecules, two of which have already had human trials. Two of the compounds came from **Ciba-Geigy** (now **Novartis**). The third came from a Russian company, and like many compounds being explored by Eastern European researchers, is related to the extensive nootropic family (e.g. piracetam) which never went far due to limited potency and the lack of patent protection. This analog is 1000 times more potent, and also appears to have neuroprotective effects beyond the cognition-enhancing effects. The lead compound from Novartis operates on GABA-B receptors pre and postsynaptically. Levels of several neurotransmitters (glutamate, serotonin, norepinephrine) are upregulated, and kainate receptors (the third family of glutamate receptors) are activated. The premise is that this amplifies channel opening and hence LTP. It had been given to 100 pts by the outlicensor, thus it has an extensive database in place, including positive effects in primate memory models. David Pharma is aiming for a Phase II study in MCI beginning later this year, data to be available late next year. The piracetam-analog is in a Phase I/II trial outside the US, in TBI/stroke patients, due to its combination of cognitive and neuroprotective effects. Its target will be chosen mid-2002.

Helicon Therapeutics: Formed in 1997 around the work of Tim Tully at Cold Spring Harbor Laboratory, Helicon is working farther 'downstream' than anyone else. Tully focused upon role of CREB induced gene expression in synaptic formation, and Helicon states that it holds the patent upon direct CREB-modulation in the service of memory enhancement. The trick of course

would be upregulating CREB only where it is needed for memory upregulation, rather than precipitating wildfire gene expression elsewhere. They have adapted an **OSI Pharma** high-throughput screening process to assess the effect of compounds upon CREB, and have identified ten compounds from a library licensed from a larger pharma company. While they have not commented on whether these compounds include any with previous human trial exposure, we suspect that is the case. Another three candidate compounds have just been inlicensed. This is downstream of the PDE4 being utilized by **Memory Pharma** (see below). Helicon is also addressing PDE4 itself, having signed a deal with **Inflazyme**, who has developed a range of specific PDE4 inhibitors. Since Inflazyme is primarily interested in inflammatory bowel disease and asthma, Helicon has licensed the work and compounds that appear CNS-specific. Tully has also identified a 'substantial' number of genes associated with memory formation, which constitute a range of future drug discovery targets.

Memory Pharmaceuticals: Memory Pharma has been constructed around the Columbia University research orchestrated by Eric Kandel, who won the Nobel Prize for his exploration of the molecular processes central to memory formation. The most advanced inhouse program involves the inhibition of PDE4 (phosphodiesterase 4), which as was discussed earlier, is an enzyme which cleaves cAMP. By inhibiting the processing of cAMP, more cAMP is available to upregulate CREB1 and triggers synaptogenic/neurotrophic gene expression. It is a step upstream from Helicon, indirectly going after CREB-mediated gene expression. The model for PDE4 upregulation came from **Bayer** (from which Memory Pharma's CEO also came, having run their dementia research programs). Bayer had developed an antidepressant called Rolipram, a PDE4 inhibitor found to be effective in depression and memory models. Unfortunately, the therapeutic index was 1.0, the dose at which memory enhancement was seen was also the dose at which nausea/vomiting were induced, an experience most people would prefer to forget. Memory Pharma has developed three families of Rolipram analogs, comprising 600 compounds in total. They have also identified a variant of the PDE4 subtype almost exclusively found in the area of the hippocampus most closely associated with memory functions, and not found peripherally. Thus the side effects associated with across-the-board upregulation of PDE are avoided. Memory is testing these compounds in a variety of models, including its proprietary 'Cognostics' screening for assessing impact upon LTP. They have identified one drug candidate, by November they expect to choose a lead for preclinical development. aiming for human trials around the end

of next year. A less advanced memory enhancement program involves the development of a selective D5 (dopamine) agonist. No one has yet developed a pure D5 agonist (nor has Memory, they do have compounds 10:1 preferential for D5 over D1). The premise is that since D5 is concentrated in the hippocampus and absent from the periphery, that it might offer focused effects with an acceptable side effect profile. In their assay system, these compounds have a similar magnitude of effect as do the PDE4 activators. Memory's quality of science, and the Big Pharma pedigree of its management, marks it as a longerterm entrant to watch.

NeuroLogic: NeuroLogic is developing the work of NIH researcher Daniel Alkon, and has an ambitious plan to develop therapeutics for MCI, ADHD, AD, and an Alzheimer's diagnostic test (now in Phase III). The Alkon learning-enhancement molecules operate as modulators of the ryanodine receptor, which is a receptor inside the cell governing the release of intracellular calcium (thereby amplifying the effects of calcium entering the neuron as it depolarizes and 'fires.' The molecules may be analogs of the calyculin protein, which is the endogenous modulator for the ryanodine receptor. The ryanodine receptor triggers the carbonic anhydrase cascade, which Alkon states turns inhibitory GABA receptors into excitatory ones, further amplifying neuronal excitation. This process enhances learning in rodent models, in a process which is initially parallel to, but ultimately synergizes with, NMDA receptor based LTP. At first glance, we speculated that by reducing GABA inhibitory effects, this would amplify neuronal excitation in a fashion similar to what **Neurogen** and **Merck** are doing with GABA inverse agonists. This may enhance attentional focus and sets the context for initial learning, and indeed these drugs have been described as 'attentional mediators.' But, just as Ampakines are upstream post-synaptic modulators of longterm potentiation, it appears that these compounds are intracellular, upstream modulators of a process parallel to LTP. Alkon has postulated that ryanodine activated release of calcium stores triggers a signalling pathway via ras and MEK to MAPK, resulting in gene transcription. NeuroLogic is using imidazole analogs, including histamine variants, as carbonic anhydrase activators, and states that it is ready to enter Phase II trials in 2002. NeuroLogic is little-known but ambitious (it is setting up a Switzerland based research arm), and is another entrant that should be monitored.

Sention: Founded in 1999 around the work of two well-regarded Brown University neuroscientists, Leon Cooper and Mark Bear, Sention recently changed its name from **Nemogen** (for aesthetic reasons) and is about to announce a CEO (none had been in place) and their

first VC financing (via MPM and Burrill). The founders have a body of published work that primarily deals with the modulation of NMDA and AMPA receptors to alter LTP and LTD. But while Sention has a lead compound for which they are now discussing an IND with the FDA, they are unclear as to the mechanism of action, saying only that it upregulates consolidation in animals. They have an early-stage pipeline of cognition enhancers, and 17 employees. The addition of a hand-on CEO will be an important step for Sention, which up to this point has struck us as rather disorganized.

Programs To Watch: Potential MCI Targets

Drug Abuse Sciences: DAS will soon start preclinical dosing studies for DAS-431 (formerly Abbott's ABT-431) D1 agonist, with the aim of initiating clinical trials sometime next year in memory disorders. They believe that low doses will avoid dyskinetic effects and be optimal for cognitive enhancement. **NeuroSearch** and **Prana** are also exploring D1 agonist utility in cognitive enhancement.

Gliatech: Gliatech's Perceptin (GT2331) is an antagonist of the H3 (histamine) receptor. This is an autoreceptor, whose activation causes a reduction in the release of histamine, leading to decreased arousal. By blocking the autoreceptor, cognitive arousal is enhanced. Levels of other neurotransmitters pertinent to arousal/attention, including norepinephrine, serotonin, and dopamine, are also modestly enhanced. Perceptin has been in Phase II for ADHD, its progress slowed by Gliatech's other preoccupations. Cognitive enhancement could be a second target if successful.

NeoTherapeutics: Though Neotrofin has been focused upon Alzheimer's, given its stimulation of endogenous neurotrophic factors, MCI is a possible next target, provided that the Alzheimer's trial shows positive results. This not only reflects Neotrofin's demonstrated effect upon neurotrophin expression (via an alternate cGMP to PKC pathway), but also the indications that some other mechanism of action is at work, since earlier data showed improvement on a memory task two hours after just one dose of Neotrofin. This suggests that the drug may cause changes in neurotransmitter availability or synaptic responsivity, since even though neurotrophin levels themselves do rise within minutes, one would not anticipate significant structural changes (such as axonal sprouting and new interconnections) so quickly. The nature of that mechanism has yet to be explicated, all traditional neurotransmitter systems have been explored and found nonparticipatory.

Neurogen: Neurogen and its partner **Pfizer** have taken a selective GABA-A inverse agonist NGD-97-1 into Phase II for Alzheimer's, data to be available mid-late 2002.

The premise is that since activation of that receptor subtype accounts for the diminution in cognitive efficacy (decreased attention and learning) seen with such drugs as benzodiazepines, 'reversing' its activity via an inverse agonist would enhance those capacities. This is dissimilar to **NeuroLogic's** carbonic anhydrase program, since the latter operates on intracellular GABA-A receptors, and in an activity-dependent fashion. It is unclear how the Neurogen program would translate into longterm memory consolidation. Since GABA-A activation is powerfully anxiolytic and often soporific, they will need excellent subtype selectivity, which had better be purely connected to cognition, or else sleep impairment or anxiogenicity might be anticipated. There had been mixed signals regarding the choice of target, Alzheimer's or cognitive enhancement, and the fact that they chose Alzheimer's, a less face-valid choice, may mean that the side effect profile might not pass muster for the relatively more benign MCI choice.

Longterm Prospects

Setting aside cholinesterase inhibitors like Aricept, which we doubt will be effective in MCI, the first efficacy trials for novel memory enhancers will provide data in 2003, from **Cortex** and **David Pharma**. If **NeoTherapeutics** succeeds in its Alzheimer's Phase III, Neotrofin will immediately join the list of nearerterm candidates. **NeuroLogic** and perhaps **Helicon** could follow soon thereafter, while **Memory Pharma** or **Axonyx** are unlikely to have any efficacy data until 2004. Longerterm, drug discovery strategies will also target new genes found to be associated with enhanced LTP, and many of the companies we have discussed have genomics programs aimed at identifying such genes. The *Journal of Neuroscience* just published a report from scientists at the Robert Wood Johnson Institute of a gene (Rab3A) which appears to be necessary to the facilitation of synaptic activation by BDNF. As other genetic triggers and facilitators are discovered, they will offer new drug targets. With the number of individuals over 55 in the US alone now approaching 60 million and growing, the potential market for an effective, safe memory enhancing drug would easily reach the billions of dollars now, even assuming limited penetration and pricing. The massive cost of caring for those no longer fully functional and independent makes preserving cognition in a greying population a necessity, not a luxury. The payoff could be as big as any in the neuro realm. As this becomes apparent to the Market, these companies will become a fresh focus for 'boomers' already notorious for not aging gracefully, fixed upon retaining their vitality in all spheres as long as possible. If they will spend billions out of pocket for unproven nutraceuticals, the potential for a validated memory-enhancing drug is enormous.

Company Focus: Cortex Pharmaceuticals

We have followed Cortex closely since 1995. In past times it has teetered on the fiscal brink, but over the past three years it has acquired key corporate partners (**Organon**, **Servier**, **Shire**) and has taken its cognition enhancing platform farther than any of its competitors.

Research Targets

The Ampakines (developed at UC Irvine by Gary Lynch and colleagues) are a family of molecules which have their effect upon the AMPA family of glutamate receptors. Glutamate is the major excitatory neurotransmitter, and AMPA are the second major family of receptors to which glutamate binds (NMDA receptors are slightly more numerous). Cortex has developed several hundred Ampakine compounds which are selectively activating for various AMPA receptor subtypes. This allows them to finetune which areas of the CNS and thus which disorders are targeted by each variant. Cortex has a dominant patent position in AMPA-upregulation for the treatment of cognitive/memory disorders and the enhancement of neurotrophin expression, although **Lilly**, the Big Pharma company most active in the AMPA modulation field, is challenging one of Cortex's European patents. We believe that this challenge is unlikely to succeed, and that if Lilly does advance its own molecules, it will have to pay Cortex for the privilege.

Ampakines modulate the activation of NMDA receptors. When those receptors are activated, Ampakine activity causes those ion channels to remain open longer, lengthening the bioelectrical signal and thus strengthening its effects. This leads to an amplification of LTP (longterm potentiation), and the improved consolidation of memory. Beyond this first-stage, rapid effect upon calcium channel opening, there is a second stage of intracellular effect. Ampakines trigger the c-fos gene, which in turn initiates the synthesis of other proteins, including the production of natural nerve growth factors, including BDNF and NGF. This aids the growth of dendritic spines which create more complex synaptic connections. Ampakines thus appear to modify complex cortical networks of synaptic circuits. The downstream effects of Ampakine action are to cause the release of BDNF and NGF. This at the very least pertains to the growth of new synaptic connections, and raises the possibility of neuroregenerative effects. Whether Ampakines have effects on levels of other trophic factors, or upon stem cell proliferation, is being assessed via an ongoing six-month exposure Ampakine rat study. In this study, which should be completed this fall, rats are given drinking water with or without an Ampakine, while both groups live in an enriched

environment (which in itself spurs stem cell proliferation). BrdU will then be given (which binds to mitotic brain cells) and the animals sacrificed. If the Ampakine group shows more BrdU binding, that would mean that cell mitosis was increased by Ampakines, and would indicate Ampakines spur cell proliferation.

The Ampakine prototype molecule is CX516. It has a high therapeutic index: in animal studies, significant toxic effects were not encountered until a dose 70 times the therapeutic dose was reached, at which point seizures occurred. CX516 is a short-lived molecule whose short-duration of action was of concern to some potential partners, but its duration of action extends beyond its short half life. The effects of Ampakines upon LTP lasts much longer than the brief lifespan (60 minutes) of the molecule's effect upon individual AMPA receptors. In one study, animals given CX516 for 8 days showed persistent effects both in terms of neuronal firing rate and behavioral changes for 10-14 days following cessation of drug administration. Cortex has identified over 200 other Ampakines, two subsets of which are being fast tracked as the next generation of Cortex molecules. CX691 is from a group of molecules 100 times more potent than CX516, and has shown effects in memory and schizophrenia animal models. This greater potency likely reflects greater subtype specificity. Molecules in the third generation have a potency 1000 times that of CX516.

- **Mild Cognitive Impairment:** The best-documented effect of the first generation of Ampakines is on long term potentiation, LTP. As was discussed earlier in this issue, memory storage depends upon the unique patterning of 'turned-on' synaptic circuits that comprises the substrate of a memory. Ampakines promote connections so that they stay 'on' longer and at higher amplitude, and memory formation is enhanced. The effects of various Ampakines differ according to which of the many subtypes of receptors are involved. Some subtypes are particularly common in the hippocampus, vital to memory formation.

In 1995, our first review of Cortex focused on the application of Ampakines to cognitive/memory enhancement, and this continues to be the main basis for our interest. In 1995, Cortex ran three Phase I studies in Europe, testing CX516 in healthy volunteers. The drug group showed improvement of 12%-60% on some learning tasks. No significant side effect or safety concerns emerged. Most importantly, one of the studies involved healthy elderly subjects. On a nonsense syllable recall task, elderly patients receiving placebo recalled an average of only 1.25 syllables out of 10 after five minutes. Those receiving 900 mg of CX516 could recall an average of 3, some recalling 4 or 5, near the level

attained by healthy young adults. Last year, the privately held French firm **Servier**, having conducted inhouse research of its own on AMPA modulation, partnered with Cortex on the mild cognitive impairment/dementia range of targets, Cortex retaining US rights. The key hurdle that had to be passed was for the FDA to give its blessing of MCI as a diagnostic entity and therapeutic target in its own right, which came this past June. Based on the FDA's assent, Cortex and Servier are now designing a Phase II trial that will assess primarily symptomatic endpoints of change in memory and other cognitive domains. This is infinitely simpler than having to prove that treating MCI would slow the progression into Alzheimer's, though clinical and adaptive measures will be secondary endpoints.

At year-end, that 200pt Phase II will start in the US, enrolling patients over a span of one year, drug to be administered for four weeks. Data should be available, about two years from now. Based on the range of human data now available, we expect that CX516 will prove efficacious. It is the side effect profile that will be critical, because the FDA is quite aware that a drug approved for a relatively benign, nonacute indication like MCI could be utilized by millions, not just with MCI, but an equal or greater number seeking improvement in age related cognitive decline. There will be zero tolerance for adverse effects. To this point no significant adverse events have been reported.

We were anticipating that Cortex would hold on to its US rights in MCI (and dementia) until this Phase II produced data, in order to maximize their leverage. While it could still play out that way, the likelihood of a deal prior to that time has increased. This is due partly to the slow timeframe of the Servier sponsored trial, Cortex does not want to have to wait until 2004 (trial completion plus 6-12 months of negotiation) to finalize a deal and receive the cash that will allow them to more actively pursue other targets. But the timing is also right for MCI because of the heightened profile it is enjoying in the press and in the sights of Big Pharma. Those companies are now appraising the candidates, and 2002 might be a fruitful timeframe in terms of lining up a partner as these companies try to deepen their inlicensed pipelines. That deal, whenever it occurs, will be the most important and richest in Cortex's history, because it is the US where boomers are most likely to flock to anything that promises an extension of youthful vitality now in ebb.

- **Alzheimer's:** Given the impact upon memory and the production of possibly regenerative trophic factors, Alzheimer's is another natural target. For the past three years or so, a National Institute of Health researcher has ran a small, idiosyncratically designed, painfully slow

Phase IIa trial in Alzheimer's patients. We had given up hope of ever hearing anything, but he finally produced data from an escalating dose 19 pt study which showed a surprising effect after six weeks of CX516 administration. Drug group patients in this double blind study showed ADAS-cog score decreases averaging 4 points, a statistically significant magnitude of improvement even in such a small population. The dosing was very inconsistent with considerable variation in the final, maximum tolerated dose. NIH will begin a 30 pt fixed dose trial later this fall, data available at some point in the distant future. This target is also licensed (US rights retained) to **Servier**. Obviously, the extension of positive MCI data into less impaired AAMI patients might accompany an extension into more impaired Alzheimer's patients. This does not address the basic pathology of Alzheimer's, but it is a potential avenue to symptom improvement.

- **Schizophrenia:** There is a growing consensus that schizophrenia involves an imbalance between the dopaminergic and the glutamatergic neurotransmitter systems. Harvard's Joseph Coyle found that giving d-serine (which activates another NMDA co-receptor) produced positive effects in schizophrenics, and there has been considerable work done (**Allelix/NPS** and **Janssen**) on utilizing the glycine site co-receptor for the same purpose. But it is the modulation of the AMPA receptor that has progressed the furthest in this area. By enhancing glutamatergic activity, Ampakines at least help address the cognitive deficits (decreased motivation, attention and problem-solving) of schizophrenia, often referred to as 'negative symptoms', and there is some evidence that they may also help adjunctively with the positive symptoms. Some Ampakines decrease motor hyperactivation in animals that have been given amphetamines, a crude dopamine-based model of schizophrenia. The fact that Ampakines ameliorate these effects without direct dopamine-system effects points to the likelihood that there is indeed an interaction between the systems that can be modulated from either direction.

Animal studies indicate that Ampakines work synergistically with current antipsychotics. A 19 pt Phase II study conducted by Harvard's Don Goff found that combining CX516 with Clozaril resulted in improved attention, learning/memory, and problem-solving, compared to schizophrenic patients receiving Clozaril alone. In January 1999, **Organon** partnered with Cortex on the schizophrenia target, and has gone through extensive evaluation of various Ampakine compounds to choose one of the later-generation candidates to take into Phase II in schizophrenia. That long-awaited announcement, and the \$2 million

milestone it will bring, has been imminent for months, but should arrive by the end of September.

- **Depression:** Depression emerged as a potential target when another company conducting due diligence found that Ampakines cause alterations in REM sleep similar to those produced by antidepressants. This was the second target indication chosen by **Organon**, and the one prioritized by **Lilly** in their program, in their quest for a faster acting antidepressant. The premise is that if BDNF can be increased faster in the amygdala than it is by standard SSRIs, that might provide more rapid therapeutic onset. Animal studies in depression models also indicate potential value. The mechanism by which Ampakines work appears to be in via glutamatergic tracts which control activity in an area of the brain (the serotonergic dorsal/medial raphe) wherein antidepressants exert their effects. Thus the area that SSRIs and tricyclics affect directly, is modulated indirectly by Ampakines through glutamatergic circuits. It is also possible that Ampakine induced trophic factors might contribute to neurogenesis, a process which is now believed to result from the utilization of current antidepressants and lithium. **Organon** exercised its option on the depression target this past January. Development for this target is slow, because **Organon** wants to find a high potency molecule that will involve a low 'cost-of-goods' and hence better profit margin. This program is unlikely to reach the clinic until 2003.

- **Attention Deficit Disorder:** The Goff schizophrenia Phase II trial produced preliminary data which showed improved attention in schizophrenics, a population who tend to have difficulty therein. This spurred interest in Ampakines as possible therapeutics for ADHD, and **Shire** took an option on worldwide rights for CX516 for ADHD. **Shire's** ADHD franchise is under fire from several competitors, and they need to develop successors to **Adderall**. They initiated a 114 pt Phase II trial in adult ADHD this past June, involving a four week exposure to CX516. Data will be available sometime late next summer. **Shire** has given mixed signals about the intensity of its interest, it took them quite a while to move ahead. If successful, CX516 would be a candidate to be the first nonscheduled ADHD medication, compared to the current roster, all of which are tightly controlled on Schedule II.

- **Other Potential Targets:** Cortex has received an SBIR grant to fund its research into the use of Ampakines in stroke, wherein the neurotrophic and cognitive enhancement effects would in theory be useful. The same applies to Traumatic Brain Injury (TBI), but while there is a group at **UCLA** interested in trying Ampakines in a post-TBI group, nothing has gone forward. **Servier** licensed rights in MS, but a group in New York has gone

nowhere in terms of moving ahead with an MS-dementia trial they had proposed. Rodents display heightened sexual pursuit on Ampakines, and **Servier** inlicensed the rights to the use of Ampakines in sexual dysfunction (decreased sexual desire). But since no one in France will admit to diminished libido, that may be difficult to pursue. ALS was the fourth target licensed by **Servier** (Cortex retains North America rights for all the **Servier** targets). A small Italian firm indicated interest in developing an Ampakine for autism, based on the premise that autism reflects a dopamine system disturbance addressable via the glutamate system, but nothing has happened.

The theme is a consistent one: for all of these other targets, Cortex has depended upon the good intentions and execution of independent parties who are neither disciplined nor organized in their followthrough. Waiting for others to carry the ball when they do not have the same vested interest is counterproductive. Cortex, tired of having its hands tied fiscally, may accelerate its outlicensing of US rights in MCI/dementia, so that it can then push these other programs ahead by itself.

Risks and Competition

Cortex has enormous competition In all of its major targets; MCI, schizophrenia, dementia, depression, and ADHD. **Lilly** has put considerable effort into AMPA modulation and has developed a number of potent molecules. We believe that the Cortex patent position is a strong one and will be upheld by the European review of **Lilly's** challenge to a Cortex patent, but that will only be confirmed by the hearing early next year. There has been lingering skepticism in the field about Ampakine potency and magnitude of effect. But compared to many of the molecular platforms heralded in the biotech spin factories, Ampakines have a considerable body of data in both humans and animals, and this data makes a compelling case for Ampakine utility, as a stand-alone treatment for AAMI/MCI, and as an adjunctive treatment for schizophrenia and Alzheimer's. The MCI competition includes companies retooling old drugs which have some clinical history and others that are earlier on in their elucidation, and may intervene at more impactful loci in the memory process. In terms of schizophrenia, we suspect that Ampakines would serve as adjuncts to antipsychotic drugs, and the **Memory Pharma** d-serine program could eventually be a competitor. The antidepressant field is too crowded to detail, but the advent of **Forest's** monoisomer Celexa (escitalopram) and the possibilities raised by **Merck's** resurrected Substance P, **Neurocrine Biosciences** and **Neurogen's** CRF-antagonists, and **Innapharma's** injectible peptide mandate caution when considering

Ampakine prospects. In terms of ADHD, besides the current crop from **Novartis**, **Shire**, and **Alza**, **Celgene/Novartis'** monoisomer 'Ritadex' (just deemed 'approvable' by the FDA), **Gliatech's** Perceptin, and **NeuroLogic's** carbonic anhydrase activators all must be seen as threats. Even **Cephalon's** Provigil, while wounded, is not demised as an ADHD alternative. Thus it is in MCI and as a schizophrenia adjunct that we see the biggest prospects for Ampakines, while we remain curious about the platform's potential use in some of the earlier-stage targets not yet thoroughly explored.

Finances

There were times in the past Cortex counted its cash on hand in the thousands, not millions. But those days are over, thanks to the corporate partnerships now in place. With under five million dollars in the bank, this is still a lean operation, and Cortex continues to be very limited in their ability to pursue projects inhouse. The next fiscal milestone will come from **Organon** when the schizophrenia program goes into Phase II, and based on past milestones, we expect the payment to be around \$2 million. **Organon** royalties would be in the low double digits on eventual sales. During 2002, **Shire** will decide whether to advance SPD420/CX516 for ADHD. The more important event would be if the US rights for MCI/dementia were to be licensed to a Big Pharma company, providing Cortex with significant cash for R&D expansion. **Lilly** would seem a natural candidate given their AMPA interests, but thus far they seem more inclined to fight (i.e. their patent challenge) than ally. Cortex's move onto AMEX earlier this year marked the end of their Bulletin Board exile. While the share price has not yet permitted significant institutional participation, a major deal would change that.

Prospects

We tend to like companies that have a strong patent position for a platform of compounds modulating a range of therapeutic targets. **Pharmos'** cannabinoids and **Neurocrine Biosciences'** CRF program fit that bill, and so do Cortex's Ampakines. The Cortex pipeline rests upon this technology alone, but it is one which has demonstrated proof of principle and basic safety over six years of human testing. The Company's management is consistently straightforward, with a refreshing lack of hype. Next year may see an MCI US deal and a **Shire** licensing, which could bring Cortex back onto institutional radar screens. More significant clinical data will come in 2003, when data from the **Servier** MCI trial and **Organon's** schizophrenia Phase II should be released. **We assume only an Organon Phase II initiation and milestone in our year-end target of 5.**

Corporate Overview: Cortex Pharmaceuticals

15241 Barranca Parkway Irvine, CA 92618 1-949-727-3157

Chief Executive Officer: Vincent Simmon PhD

Products: Pharmaceuticals for schizophrenia, depression, Alzheimer's, mild cognitive impairment, ADHD, stroke/TBI

Corporate Alliances: Organon, Servier, Shire

Cash on hand: US \$ 4.88 million (as of 3/31/01)

Burn Rate: US \$1.2 million/yr

Shares Out: 16.62 million

Cash per share: US\$0.29

Fiscal Year (6/30) Net (loss):

2000 US\$ (0.01)

1999 US\$ (0.12)

Category	Product	Target	Stage	Comments
CNS Disorders	CX516	Mild Cognitive Impairment	Ph II	Servier partnered, Phase II begins January 2002
	CX516	ADHD	Ph II	Phase II ends mid-2002, Shire can then exercise option
	Ampakine	schizophrenia	Phase II	Organon go/no go decision imminent
	Ampakines	depression	preclinical	Organon exercised option
	CX516	Alzheimer's	Ph II	second NIH trial starts soon
	Ampakines	stroke	preclinical	SBIR grant received
	Ampakines	TBI	preclinical	
	Ampakines	multiple sclerosis	preclinical	
	Ampakines	sexual dysfunction	preclinical	Servier licensed
	Ampakines	autism	preclinical	Italian researchers interested

The contents of this publication are based on sources that are believed reliable, but accuracy cannot be guaranteed. This is not an offer to buy or sell securities, the information and opinions are intended for informational purposes only, and are not intended as investment advice. The companies discussed September carry significant investment risk. Readers should review information thoroughly with a registered investment advisor or stockbroker. The publisher and its directors or employees September have positions in and make purchases or sales of securities discussed in this publication. All rights are reserved. Duplication of the contents of this publication without the written permission of Neuroscience Stock Reports Inc. is strictly prohibited. Copyright 2001.

PRODUCT DEVELOPMENT TABLE

	R&D	Preclinical	I	II	III	NDA	Mkt	Comments
Axonox	1	3	1					<i>Phenserine data soon</i>
Boston Life Sciences	2	3		1	1			<i>Altropane trials expanded</i>
CeNeS	2	3		2			3	<i>Neuropathic Pain Ph II started</i>
Centaur	5	3		3				<i>Stroke Phase II/III starting</i>
Cephalon	3	3	2	4		1	3	<i>Gabitril supplemental trials underway</i>
Cognetix	9	1						<i>Finalized round of VC financing</i>
Cortex	2	1	1	3				<i>Awaiting Organon decision/milestone</i>
Curis	3	2		2	1			<i>hedghehog deal with Elan</i>
Diacrin	2	8		5				<i>Parkinson's trial duration failed</i>
D-Pharm	2	2		2				<i>valproate prodrug partnered with Shire</i>
Elan Pharma	3	4	1	2	2	1	5	<i>waiting for ziconotide approval</i>
Genset	5	1						<i>Famoxin trial delayed until 2002</i>
Gliatech	3	2	1		2		2	<i>MRI data available end of September</i>
Guilford	5	5	1		1		1	<i>NIL-A failed in PD Phase II</i>
Interneuron	1	3			3		1	<i>Trospium Ph III imminent</i>
MitoKor	7	4						<i>Acquires Apollo</i>
NeoTherapeutics	3	2			1			<i>AD Trial fully enrolled</i>
NPS	10	9	3	1	1			<i>Partnered mGluRs with AstraZeneca</i>
Neurobiological Technologies			1	2	1			<i>Forest starting second neuropathy PhIII</i>
Neurochem	2	2	2					
Neurocrine Biosciences	7	3	1	4				<i>Glaxo partnered CRF programs</i>
Neurogen	3	4	2	1				<i>GABA agonist in Ph II for dementia</i>
NeuroSearch	2	3	2	4				
Pharmos	2	2		1	2		2	<i>US PhIII application in preparation</i>
Shire	1	2	2	1	2		4	<i>raised \$400 million in spending money</i>
StemCell	4							<i>Sold remainder of Modex state</i>
Synaptic	9	3						<i>Sold 41% of company to Warburg-Pincus</i>
Titan	2	3	1	4	1			<i>Zomaril program extended one year</i>

Published by Neuroscience Stock Reports Inc. Editor and Publisher: Harry M. Tracy Ph.D
P.O. Box 458 Rye, NH 03870 Telephone (603)964-9640 (24 hr/day operator coverage)
Fax (603)964-7561 e-mail: neuroinv@neuroinv.com Website: www.neuroinvestment.com
Published 12 times per year.

Individual subscription: 1 yr-US\$420 2 yrs-\$720 3 month trial- \$130
Institutional subscription: 1yr-US\$590 2yrs-\$1020 3month trial- \$160
Outside US and Canada, add \$30/year fax delivery (US only) add \$25/year
Payments accepted via US check, Mastercard, Visa, American Express e-mail delivery add \$25/year

NEUROPHARMACEUTICAL COMPANY SUMMARY

company		8/31/01 price(\$US)	change% 2001	market cap (\$USmil)	52 wk high/low	shares (mil)	cash (\$USmil)	corporate alliances	principal product targets
Axonyx	AXYX	3.56	-41.8%	54.47	14/3.0	15.3	6.05	Ares Serono	Alzheimers
Boston Life Sciences	BLSI	2.15	-29.7%	44.51	10.12/2.16	20.7	15	Pfizer	neurodegeneration, cancer, Parkinsons dx
CeNeS	London Stock Exchange							Allergan, Bayer	pain, MS
Centaur	Zurich BB					17.63	20.40	AstraZeneca	Parkinsons, stroke, AIDS-dementia, AD
Cephalon	CEPH	59.22	-6.5%	2826.57	73.92/36.37	47.73	420.80	Schwarz TAP, Lundbeck	Alzheimer's, sleep disorders, cancer
Cognetix	privately held							Medtronic	epilepsy, stroke, schizophrenia
Cortex	COR	2.08	35.9%	34.53	4.5/1.41	16.60	4.88	Organon, Shire, Servier	Alzheimers, depression, schizophrenia, MCI
Curis	CRIS	6.05	-31.9%	190.94	27.25/3.0	31.56	58.98	Aegera, Stryker, Elan	neuroregeneration, bone repair, urinary tract disorders
Diacrin	DCRN	1.80	-64.0%	32.24	9.62/1.05	17.91	52.30	Genzyme	neurodegeneration, diabetes, epilepsy
Elan Pharma	subsidiary of Elan PLC							AHP, Pfizer, Idun	Alzheimer's, MS, Parkinson's, epilepsy
Genset	GENXY	1.22	-90.3%	29.67	29.62/1.08	24.32	35.70	Abbott, Sanofi, SignalGene	Alzheimer's, obesity, schizophrenia
Gliatech	GLIA	3.90	-3.9%	37.75	26.87/1.5	9.68	11.30		Alzheimers, surgical scarring, cognition
Guilford	GLFD	12.05	-33.1%	328.00	35.99/12.37	27.22	179.02	Amgen	cancer, Parkinsons, drug delivery, ischemia
Interneuron	IPIC	5.00	290.6%	234.20	10/1.16	46.84	34.88	Pfizer	stroke, anxiety, cirrhosis
MitoKor	privately held							AHP, Pfizer	Alzheimer's, Parkinsons stroke
NeoTherapeutics	NEOT	3.72	-9.7%	68.86	10/2.22	18.51	18.61	Pfizer	Alzheimer's, neurodegeneration
Neurobiological Technologies	NTII	4.49	12.3%	90.29	11.13/1.56	20.11	11.04	Merz, Forest, Lundbeck	neuropathic pain AIDS-dementia, Alzheimer's
Neurocrine Biosciences	NBIX	39.33	18.8%	1002.92	46.0/14.25	25.50	146.30	Wyeth-Ayerst Janssen, Taisho Glaxo	anxiety, insomnia glioblastoma, depression
Neurogen	NRGN	18.98	-46.0%	330.63	41.0/16.12	17.42	92.98	Pfizer, Cubist	anxiety, insomnia, depression, obesity
NeuroSearch	NEUS:CO	19.52	-25.6%	126.10		6.46	33.51	Shire, Glaxo, Abbott, Organon	Parkinsons, anxiety, depression, stroke
NPS	NPSP	33.62	-30.0%	999.52	58.0/15	29.73	241.26	Amgen, Janssen, Lilly, AstraZeneca SmithKline	hyperparathyroidism stroke/TBI, osteoporosis, pain
Pharmos	PARS	2.70	69.8%	146.77	4.56/1.46	54.36	214.30	Bausch & Lomb	TBI/stroke, ophthalmology
Shire	SHPGY	43.42	-5.7%	6678.00	65.87/35.75	153.80	303.30	NeuroSearch, Janssen, Cortex	Alzheimer's, ADHD, stroke, epilepsy
StemCells	STEM	3.10	24.0%	64.79	11.67/1.47	20.90	9.40		neurodegeneration
Synaptic	SNAP	5.45	6.4%	59.62	8.0/3.56	10.94	23.52	Grunenthal, Kissei	depression, anxiety,
Titan	TTP	9.75	-72.4%	269.30	65.3/11.35	27.62	113.10	Novartis, Schering	psychosis, cancer, neural implants