

Innovations

Cortex Pharmaceuticals, Inc. Maintaining Brain Function Goes a Long Way

Diseases such as Alzheimer's and schizophrenia can result in such a devastating loss of a person's purpose and ability to reason that remedies for these and other neurological and psychiatric disorders remain among the most critical health issues for millions of people around the world. Cortex Pharmaceuticals, Inc. in Irvine, California, engages in the discovery, development, and commercialization of novel compounds that enhance memory and cognition and thus impact a range of disorders.

Since 1993, Cortex has been arduously refining their patented AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor modulator compounds termed AMPAKINES. The AMPA glutamate receptors are one of three types of ionotropic glutamate receptors responsible for binding the excitatory neurotransmitter L-glutamate. Activation of AMPA-type receptors propagates the depolarization required to unblock the voltage-sensitive NMDA (*N*-methyl-D-aspartate) glutamate receptors, which then admit calcium into the dendritic side of the synapse and induce the long-term potentiation (LTP) shown to have predictable effects on memory. Established correspondence between the LTP and memory enhancement prompted the search for AMPA receptor activators. AMPAKINE compounds bind to one or more modulatory sites distinct from either the agonist/antagonist site or the allosteric benzothiadiazide site of the AMPA receptor complex. AMPAKINE technology was invented and developed by Dr. Gary Lynch at the University of California, Irvine. Lynch's work and expertise has since been adopted by Cortex, and a successful collaboration has been maintained.

A compound that enhances memory is an obvious therapy for Alzheimer's disease (AD) and mild cognitive impairment (MCI). In fact, it is known that the number of glutamate receptors is decreased in areas of

the hippocampus that are particularly vulnerable to AD. Interestingly, AMPAKINE compounds can differentially affect various types of brain function. "The pure cognitive function of the agent ultimately triggers LTP. It turns out that this pathway is critical...in schizophrenia," explains Roger Stoll, President and Chief Executive Officer of Cortex. Studies have shown that glutamatergic activity could underlie some symptoms of schizophrenia. Stoll points out that LTP targets are "missing in most of the drugs being used in schizophrenia." There is currently a widespread pharmaceutical search for drugs that affect the cognitive portion of schizophrenia.

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Having one family of compounds affect multiple functions of the brain can be advantageous but has also contributed to Cortex's struggle to overcome skepticism about whether enhancing the excitatory processes in the brain could be done safely. Such skepticism has led to difficulties with funding, and, although research has been going well, the process of clinical trials is too costly and time consuming for this company to pursue. To alleviate some of the burdening costs, Cortex has licensed two of its leading AMPAKINE compounds to larger pharmaceutical developers. Organon obtained the license for Org-24448 in 1999 and is currently carrying out phase II trials for efficacy in schizophrenia with this compound. Cortex established an alliance with Servier Pharmaceuticals in 2000 for the development of S18986, which is in phase II clinical

trials for the treatment of Alzheimer's and MCI.

Cortex's lead AMPAKINE compound, CX516, was successful in proof-of-principle studies and is currently undergoing phase II clinical trials. In preclinical studies, CX516 showed distinct memory enhancement in mice and monkeys, and in phase I studies, this compound showed dose-dependent memory enhancement in both young and elderly healthy subjects, resulting in enhanced performance in individuals tested for visual association, odor recognition, and visuospatial maze acquisition. In animal models, CX516 displayed synergistic effects with antipsychotic drugs used to treat schizophrenia. Such synergy shows promise and could potentially allow for a decrease in the antipsychotic dosage, alleviating some of the extra-pyramidal side effects of these drugs, e.g., involuntary body movements. CX516 is currently in phase II trials in medicated (clozapine or olanzapine) schizophrenia subjects.

CX516 is also being studied as a potential therapeutic for Fragile X syndrome and autism and is the subject of a government-funded study for narcolepsy and other sleep disorders. From preliminary results it is hoped that AMPAKINE compounds could increase attention, executive function, memory, and language in order to improve the quality of life for persons with Fragile X retardation, autism, as well as Attention Deficit Hyperactivity Disorder (ADHD). The narcolepsy studies are funded by the Defense Advanced Research Projects Agency (DARPA) in hopes of maintaining critical thinking in persons with sleep deprivation.

Though CX516 has shown promise in several studies, successors with improved functionality are likely to be the compounds of choice for specific diseases. From continued research over the last ten years, researchers at Cortex and in Dr. Lynch's lab at UC Irvine have iso-

lated more potent AMPAKINE compounds for specific activation of LTP. While most of the AMPAKINE molecules can bind to several AMPA receptor domains, they have identified specific AMPAKINES which have up to a 10-fold greater affinity for specific receptor sites, e.g., GluR1, GluR4, flip, or flop. Cortex currently has a family of more than 800 unique AMPAKINE molecules which are chemically diverse and appear to vary in selectivity across a variety of established disease-based animal behavior models for neurological and psychiatric disorders. Despite its proven effectiveness, CX516 has a short, one hour half-life and low potency, requiring multiple doses in one day. CX717, however, has a longer half-life, is 50 times more potent, and will likely be one of the replacements for CX516 once the necessary trials have been completed.

A more recent Cortex discovery is the effect of certain AMPAKINE compounds on the induction of brain-derived neurotrophic factor (BDNF). It was previously demonstrated that activation of excitatory receptors increased BDNF production in the adult brain. BDNF is widely expressed in the adult mammalian brain and has been found to promote survival of all major neuronal types affected in Alzheimer's and Parkinson's disease. Cortex researchers surmised that the activation of AMPA receptors by AMPAKINE drugs could upregulate BDNF expression. Preclinical studies with CX614 demonstrated an increase in BDNF mRNA and protein content in adult rat brains. Dr. Stoll reports, "some of our compounds are much more efficient at upregulating BDNF than others." A series of compounds, CX546, CX691, CX614, and CX691, increased BDNF expression in different parts of the rat brain. The research has shown there is more selectivity with certain structures of AMPAKINES, and Stoll claims current research is focused on "trying to find that mechanism and what triggers it." Finding the specific receptor domain that gives the greatest BDNF expression could lead to a more complete understanding of how the AMPAKINE molecules function. Further studies are expected to produce a highly specific, highly potent AMPAKINE molecule for in-

duction of BDNF. The ability to induce BDNF in various areas of the brain has potential in therapies for Alzheimer's and Parkinson's disease as well as spinal cord injuries, in which increased amounts of BDNF could restore neuronal function.

The list of possibilities for AMPAKINE drugs seems to grow as the research continues. Cortex is also investigating the use of CX516 as an intravenous drug for coronary bypass patients. Post-surgery, it is not uncommon for these bypass patients to experience symptoms of mild cognitive impairment. In order to prevent this memory loss, Cortex is in the process of producing an intravenous CX516 drug.

All of these possibilities and avenues of AMPAKINE research have to be strategically pursued in order for Cortex to survive. Roger Stoll has been with Cortex for just over a year and has directed the company's focus toward the development of AMPAKINES for Fragile X syndrome, as this rare disease qualifies for Orphan Drug application. The Orphan Drug tract allows a company to bring a potentially low-profit drug for a rare disease to market with shorter development timelines. In this way, a profit can be rendered in a shorter amount of time. Any profits for Cortex would fund the more lengthy and expensive trials for the "blockbuster" drugs like those for Alzheimer's, Parkinson's, and schizophrenia. "My charge here is to find a pathway on which we can succeed as a business," states Stoll. Cortex believes that this combined approach to developing its technology may not only create value for its company but also may bring therapeutic relief to those suffering from diseases that are currently among the most difficult to treat.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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