more modulatory roles, fine-tuning the balance between neuronal excitation and inhibition.

Positive AMPA receptor modulators strengthen excitatory transmission, enhance synaptic plasticity, and preclinical and preliminary clinical research suggested efficacy as cognition enhancers (Lynch, 2006; O'Neill and Dix, 2007). The first potentiator tested in large clinical trials was CX516 (Cortex Pharmaceuticals), which did not show efficacy in a variety of pathologies (eg Berry-Kravis *et al*, 2006). In contrast, a second-generation ampakine, CX717, normalized behaviors associated with attention deficit hyperactivity disorder (ADHD). Further testing of CX717 for ADHD was not approved by the US Food and Drug Administration due to toxicological concerns, although approval was granted to continue trials of CX717 in Alzheimer's disease. The outcome of this project is uncertain, however, given that a chemically distinct potentiator, LY415395 (Eli Lilly), failed to improve cognitive performance in an Alzheimer's disease trial (Chappell *et al*, 2007). Recently, compelling preclinical data prompted initiation of two Phase II trials in Germany to determine if CX717 reverses or prevents respiratory depression during opiate analgesia. These appear to be the only ongoing studies of efficacy for positive AMPA receptor modulators in humans, as clinical studies for similar molecules have been suspended (Schering-Plough) or the results remain undisclosed (Servier, GlaxoSmithKline).

Noncompetitive inhibitors of AMPA receptors, such as talampanel (Teva Pharmaceuticals) and perampanel (Eisai Medical Research), reduce overexcitation and potentially slow neurodegeneration. These drugs were efficacious as adjunct therapies for refractory partial complex seizures (Howes and Bell, 2007); perampanel also alleviated diabetic and postherpetic neuropathic pain and will be further tested for these indications. Results released from an in-progress study suggested that talampanel decreased mortality from glioblastoma, and an examination of its efficacy in amyotrophic lateral sclerosis is planned. Perampanel was not effective as an add-on therapy to levodopa in Parkinson's disease, however, and this program was terminated by Eisai.

Preclinical data suggest that kainate receptors represent an untapped and attractive target for drug development. A nonselective AMPA/kainate receptor inhibitor, tezampanel (NGX424; Torrey Pines Pharmaceutics), reduced both migraine pain and other symptoms in a recent Phase II trial. This clinical efficacy is likely attributable to inhibition of kainate receptors, based on preclinical evidence with more selective antagonists developed by Eli Lilly. A chemically distinct AMPA/kainate receptor antagonist, NS1209 (NeuroSearch A/S), also alleviated refractory status epilepticus and neuropathic pain in small Phase II studies, but further research into this molecule was suspended. The apparent success of the first representatives of this new class of drugs provides a strong impetus for further development and clinical testing.

It is evident from this overview that there is reason for both optimism and healthy skepticism regarding the clinical prospects of drugs targeting AMPA and kainate receptors. Cusp of a renaissance or a false dawn? Perhaps a Magic 8-Ball offers the best advice for would-be prognosticators: 'Ask again later.'

Geoffrey T Swanson[1]

[1]Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
E-mail: gtswanson@northwestern.edu

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Gene expression profiling in blood: new diagnostics in alcoholism and addiction?

The successful treatment of most diseases relies heavily upon early detection. Biomarkers with diagnostic and prognostic value are critical to the addiction field. Most individuals with alcohol or drug dependence or use problems evade detection until severe medical, legal, or social consequences arise. The short half-life of alcohol in the blood after cessation of drinking eliminates the feasibility for using blood alcohol as a biomarker. Carbohydrate-deficient transferrin (CDT) is currently the most specific serum marker of chronic, heavy alcohol use (Reynaud *et al*, 2000), but the low sensitivity of the CDT test in the general population makes it an unreliable candidate for predicting either heavy alcohol use or for diagnosing alcohol abuse and/or dependence (Alte *et al*, 2004). Except for the drugs and their metabolites, there are not biomarkers for addiction.

Advances in the field of genomics offer new diagnostic and screening potential for complex genetic diseases like addiction. The ability to simultaneously measure the level of all possible transcripts (mRNAs) provides an unbiased view of potential biomarkers. The importance of understanding gene expression changes in alcohol and drug dependence can be appreciated by the impact of expression profiling in other diseases, most notably cancer, where studies have led to improved pharmacotherapies and to a molecular classification of disease. Gene expression profiling is only beginning to be applied to psychiatric

illnesses and may also provide an accurate means to diagnose these conditions. Human brain gene expression studies of alcoholics and cocaine abusers suggest that specific patterns of gene expression may underlie addiction-related phenotypes and provides evidence that a molecular classification of alcoholism may be feasible in the future (Liu *et al*, 2006; Mash *et al*, 2007). However, in order for expression profiling to be useful in the clinical screening of dependence and consumption, the tissues or cells under investigation need to be readily accessible. A wide variety of screening tests are available that relies upon peripheral blood samples for assaying biological markers. For example, blood tests allow early detection, and in some cases prevention, of conditions such as prostate cancer, diabetes, thyroid dysfunction, and heart disease. Blood samples offer advantages over procedures such as tissue biopsy as they are fast, non-invasive, and can be repeated many times on the same individual. Blood biomarkers also offer the potential to predict disease before any detrimental symptoms are manifested. Genomic profiling of peripheral blood samples could be of great value in identifying biomarkers for complex diseases including addiction. This idea is supported by studies utilizing white blood cells to identify discrete patterns of expression associated with modeled complex disease states in animals (Tang *et al*, 2001). In addition, patterns of gene expression have been identified from blood samples obtained from a large number of healthy individuals, revealing surprising consistency in expression of genes associated with age, gender, and blood composition (Tang *et al*, 2001). Thus, it's feasible that nucleated blood cells of alcohol-dependent individuals could show changes in gene expression that will provide a 'signature' of the disease.

Discovery of reliable blood-based molecular markers of alcohol dependence and use would mark a milestone for addiction research and offer a great benefit for predicting the disease even without knowing the role of the markers in the disease process. Once biomarkers are discovered, the opportunity for early detection and intervention as well as personalized therapeutics should lead to new treatments for the disease.

R Dayne Mayfield[1] and R Adron Harris[1]
[1]Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, TX, USA
E-mail: dayne.mayfield@mail.utexas.edu

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From rapid *In Vitro* screening to rapid *In Vivo* screening in the drug discovery process

Synthetic combinatorial methods, combined with rapid assays, have fundamentally advanced the ability to synthesize and screen large numbers of compounds. Using a range of combinatorial approaches, libraries composed of tens of thousands to millions of different compounds have been produced. Combinatorial chemistry and high-throughput screening is now a universally utilized tool for drug discovery and development, but the harsh reality is that the drug discovery process remains extremely slow and enormously expensive. Drug candidates resulting from many combinatorial approaches have also often tended not to have drug-like properties and thus have a high inherent rate of attrition in the later stages of drug development because of poor physicochemical properties. Although unrelated to the advances in combinatorial approaches, it is worth noting that increased regulatory issues and unrealistic public expectations have reduced the number of approved drug entities over the past 20 years from approximately 35 per year to 10 or less.

One approach to circumvent this high attrition rate would be to use *in vivo* models directly in the discovery phase to identify candidates with desired biological profiles while simultaneously eliminating those compounds with poor absorption, distribution, metabolism, and elimination (ADME)/pharmacokinetic (PK) properties.

It is clearly unrealistic to use discovery *in vivo* models to screen the large collections of hundreds of thousands of the individual compounds currently available. A potential solution that shows promise is the use of mixture-based combinatorial libraries directly for *in vivo* testing. This offers a unique opportunity to carry out successful preliminary studies in which tens to hundreds of thousands of compounds would be screened directly in translational *in vivo* assays. This has been accomplished in early studies carried out in rats and dogs to monitor blood pressure and heart rate (Houghten, 1994) using 400 separate mixtures each of 132 000 hexapeptides. Immunological modulation by large mixtures has also been accomplished (Shukaliak Quandt *et al*, 2004). Recent studies have involved research into pain therapeutics utilizing *in vivo*