

## **Opportunities for Therapeutic Development of 2DG A Novel Anticonvulsant Drug**

2DG (2-deoxy-D-glucose) is a chemical analogue of sugar currently in preclinical development as a novel anticonvulsant and antiepileptic compound for treatment of epilepsy. 2DG differs from normal glucose only by removal of a single oxygen atom. As a close chemical analogue of sugar, 2DG is taken up into cells by glucose transport mechanisms, but unlike normal sugar cannot undergo metabolism and acts as a reversible inhibitor of glucose metabolism (glycolysis).

The therapeutic effects of 2DG were discovered during investigation of mechanisms of the ketogenic diet (replacement of carbohydrates in the diet with fats and proteins), which can produce improvement in seizure control in as many as 40% of intractable patients. 2DG has novel acute and chronic anticonvulsant properties which are unlike any current drugs. 2DG acutely suppresses epileptic discharges in multiple experimental models of epilepsy and prevents the progression of the chronic effects of seizures, which can include susceptibility to additional seizures, memory loss, and cognitive dysfunction. 2DG has a distinctive spectrum of acute efficacy in preclinical screening models, and no anticonvulsant drugs on the market have disease-modifying properties which can favorably alter the consequences and prognosis for patients with epilepsy. Glycolytic inhibition is a novel anticonvulsant mechanism. 2DG modifies acute processes of activity-dependent synaptic vesicle release, and also favorably modifies activity-dependent expression of neural genes in the brain contributing to the adverse chronic consequences of seizures. Because regions of the brain producing seizures have increased needs for energy and metabolic demand for sugar, 2DG preferentially accumulates in epileptic regions during seizures. This activity-dependent delivery property potentially enables novel methods of administration to optimize anticonvulsant action while minimizing dosing and side effects, including post-seizure administration and combination with device therapy and electrical stimulation through implanted brain electrodes which are currently in development and clinical trials.

With a record of safe use for decades in human clinical imaging, favorable preliminary toxicity studies, and a unique spectrum of protection in preclinical animal models of epilepsy, 2DG appears to have potential as a therapy for epilepsy with novel mechanisms of action compared to currently available anticonvulsants. The Wisconsin Alumni Research Foundation (WARF) holds the intellectual property rights for 2DG and has granted NeuroGenomex, Inc. (NGX) an exclusive license for human therapeutic development of 2DG. NeuroGenomex is currently seeking funding for completion of Phase I/II clinical trials.