RESEARCH/PROJECT NAME: Benzodiazepine Prodrug/Enzyme Combinations for Intranasal Seizure Rescue Therapies

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CURRENT STATUS/TIMING: We are presently in the early preclinical stage of drug development. We are about to undertake toxicology studies, which, if successful, will enable us to test our drug formulations in dogs and, ultimately, humans. If all is successful, we anticipate having a marketable product by late 2022.

OVERALL GOAL: Our goal is to introduce an organic solvent-free intranasal spray formulation that will facilitate rapid absorption of benzodiazepines, enabling preventative or rescue therapy for seizure emergencies.

PROJECT SUMMARY: Epileptic seizure emergencies require rapid response. Benzodiazepines (BDs) are the drugs of choice for treating this condition, but their routes of administration either involve significant delay (IV route requiring trained medical personnel) or are unacceptable to all but the youngest of patients (rectal route). The nasal route is of great interest, but the low water solubility of BDs has been a barrier to development. Formulations containing organic (chemicals similar to alcohol) additives have been pursued, which may lead to commercial intranasal sprays in the near future. However, the organic additives may cause irritation and the products under development exhibit either relatively slow or variable absorption. In our research, we are taking a new approach to intranasal drug delivery by using water-soluble prodrugs of BDs, which are chemicals that differ slightly from the active drug, but are converted to the active drug, often by an enzyme. We envision a spray system in which prodrug and enzyme are mixed in the spray, followed by rapid conversion to the active BD and absorption across the nasal tissue. This system, if successful, may rapidly ameliorate or even prevent seizure emergencies.

In this this presentation we will discuss our strategy, highlighting diazepam (Valium). We synthesized avizafone, a lysine prodrug of diazepam. We the showed that an enzyme from the fungus *Aspergillus Orizae* rapidly coverts avizafone to diazepam at supersaturated concentrations in water, without crystallizing, much as sugar can supersaturate in water for a long time before it crystallizes into rock candy. We also showed that supersaturated diazepam could cross cell membranes very rapidly. These experiments support the development of an intranasal spray system. In the near future, we will synthesize other prodrugs of diazepam, and also prodrugs of midazolam (Versed), another drug used to treat seizure emergencies. For each prodrug, we will search for the corresponding converting enzymes, and carry out the same tests as just described. By this means we can determine the optimal combinations of prodrug and enzyme for intranasal diazepam and midazolam. Toxicological studies and studies in dogs will set the stage for trials in humans.