**Samidorphan: Discovery of a Medication with Potential to Treat CNS Disorders.**

Samidorphan was discovered at Rensselaer Polytechnic Institute in the laboratories of Professor Mark Wentland as part of an effort to identify orally available, long-acting modulators of opioid GPCRs as medications to treat cocaine use disorder in humans. **Samidorphan** is a high potency ($K_i = 0.052$ nM) mu opioid receptor antagonist that first appeared in the literature in 2005. A 2009 publication provided further details on the design, crystallography and structure-activity relationships of samidorphan.

In 2006, Rensselaer signed a license agreement granting Alkermes Inc. exclusive rights to a library of Rensselaer's opioid compounds. Alkermes has subsequently sponsored multiple clinical trials involving the use of samidorphan to treat CNS disorders. In a recent publication, Alkermes described the human pharmacokinetic properties of samidorphan where they found the oral bioavailability and elimination half-life of the drug to be 69% and 7-8 h, respectively.

ALKS 3831, an oral medication combining samidorphan with olanzapine, is currently in late-stage development. Olanzapine is an established antipsychotic agent that can cause significant weight gain. The role of samidorphan is to mitigate this olanzapine-associated weight gain. The NDA for ALKS 3831 was recently reviewed by two FDA Advisory Committees who voted in support of ALKS 3831 for the treatment of both schizophrenia and bipolar I disorder. It is anticipated that an FDA decision on the ALKS 3831 NDA will be announced by June 1, 2021. See the following press releases from Alkermes for additional information:

- [FDA Advisory Committee Votes in Support of ALKS 3831 for the Treatment of Schizophrenia and Bipolar I Disorder](#)
- [FDA Accepts Alkermes' Resubmission of New Drug Application for ALKS 3831](#)

In addition to samidorphan, other compounds from Rensselaer's patent estate that have entered clinical trials are ALKS 37, ALKS 7106 and ALKS 7119.

Collaborators for this opioid GPCR modulator research program are:

- Dr. Jean Bidlack and coworkers at the University of Rochester
- Discovery and development personnel at Alkermes, Inc.

Acknowledgments: This research was supported by the National Institute of Drug Abuse of the National Institutes of Health under award numbers DA012180 and KO5-DA00360. Funding from AMRI, Inc. is also gratefully acknowledged.