Samidorphan: Discovery of a Medication to Treat Central Nervous System Disorders

At Rensselaer Polytechnic Institute, the main goal of Mark Wentland's research group is to design, synthesize and characterize oral, long-acting modulators of opioid G protein-coupled receptors (GPCRs) as medications to treat cocaine abuse and other central nervous system disorders in humans.

A common structural feature of the large majority of opioids is a phenolic-OH group (see prototypic opioid pharmacophore below) that plays a crucial role in molecular recognition via H-bonding to a histidine residue of a mu opioid GPCR. For many opioids, however, this OH group is responsible for poor oral bioavailability and/or short half-life via O-glucuronidation.

In 2001, we published the first report that a carboxamide group (CONH₂) was an effective replacement for this prototypic phenolic-OH group of opioids. In addition to high affinity binding to opioid GPCRs, certain carboxamido-substituted opioids have much improved pharmacokinetic properties (relative to their phenolic-OH counterparts) as a consequence of high metabolic stability. Since 2001 our research group has focused on capitalizing on this discovery to achieve our main goal. Our first-generation opioid modulator in this series was 8-carboxamidocyclazocine (8-CAC). Optimization of 8-CAC then provided samidorphan (formerly referred to as ALKS 33). Samidorphan first appeared in the scientific literature in 2005. Our publications describing these discoveries as well as a wealth of structure-activity relationship data are cataloged in PubMed.

In 2006, Rensselaer signed a license agreement granting Alkermes Inc. exclusive rights to a library of opioid compounds discovered by our team. Alkermes has subsequently sponsored multiple Phase 1, 2 and 3 clinical trials involving the use samidorphan to treat CNS disorders. On 1/31/18, Alkermes announced that a New Drug Application has been filed with U.S. Food and Drug Administration seeking approval to market ALKS 5461 (samidorphan in combination with buprenorphine) for treatment of patients with major depressive disorder. On 4/16/18, Alkermes announced that this NDA was accepted by the FDA for review and that FDA action is expected by 1/31/19. The following press releases from Alkermes provide additional information:

Alkermes Announces FDA Acceptance for Review of New Drug Application for ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder

Alkermes Submits New Drug Application To U.S. FDA For ALKS 5461 For The Adjunctive Treatment Of Major Depressive Disorder

Alkermes Receives Fast Track Designation for ALKS 5461 for Major Depressive Disorder

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![Pharmacophore](prototypic_opioid_pharmacophore.png)

![8-CAC](8-CAC.png)

![Samidorphan](Samidorphan.png)

**Prototypic opioid pharmacophore**

**8-CAC** \([Kᵢ(μ) = 0.31 \text{nM}]\)

**Samidorphan (ALKS 33)** \([Kᵢ(μ) = 0.052 \text{nM}]\)
Alkermes also announced positive results of a phase 3 clinical study of ALKS 3831, a novel oral atypical antipsychotic drug candidate designed to be a broad spectrum treatment for schizophrenia. Other phase 3 clinical trials are progressing. ALKS 3831 is composed of samidorphan in combination with the established antipsychotic drug, olanzapine. See the following press release from Alkermes for additional information:

Alkermes Announces Positive Preliminary Topline Results From Phase 3 Antipsychotic Efficacy Study of ALKS 3831 for Treatment of Schizophrenia

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 our opioid GPCR modulator research program are:
Dr. Jean Bidlack and coworkers (University of Rochester)
Drs. Elliot Ehrich, Dan Deaver and coworkers (Alkermes, Inc.)

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