Samidorphan: Discovery of a Medication Currently in Multiple Phase 3 Clinical Trials:

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 (CONH$_2$) 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 September, 2006 Rensselaer signed a license agreement granting Alkermes Inc. exclusive rights to a library of opioid compounds discovered by our team. Alkermes has announced positive results of a phase 3 clinical study of ALKS 5461 (samidorphan in combination with buprenorphine) for treatment of patients with major depressive disorder. On 8/21/17, Alkermes announced the initiation of the rolling submission of the New Drug Application (NDA) for ALKS 5461 to the U.S. Food and Drug Administration (FDA). The FDA has granted Fast Track status for the drug. The following press releases from Alkermes provide additional information:

Alkermes Announces Positive Topline Results From FORWARD-5 Pivotal Phase 3 Study of ALKS 5461 for Major Depressive Disorder

Alkermes Initiates Rolling Submission of ALKS 5461 New Drug Application for Major Depressive Disorder

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