Abstract

Macrolides – Beyond Antibacterials

- Macrolides are "preferred" oral drug molecules that provide the pharmacopeia for many therapeutic targets that have even larger market potential than antibiotics
  - Anti-inflammatory (COPD)
  - Intestinal motility – gastroparesis (Diabetes)
  - GnRH antagonist (endometriosis, uterine fibroids, precocious puberty, prostate and breast cancer)
- Cempra’s 500+ macrolide library is being screened against these targets

Erythromycin and its analogs have non-antibiotic activities that can be optimized to yield products for treating inflammatory diseases, endometriosis, uterine fibroids, precocious puberty, prostate and breast cancer and intestinal motility in diseases such as diabetic gastroparesis. Cempra is screening its library of 510+ macrolides in functional assays for motilin receptor activity, anti-inflammatory activity and GnRH receptor antagonism. The screening is being accomplished in partnership with international experts in each field. Cempra has found that its macrolide library provides great diversity. In the motilin screen three structural series of hits were found that show a structure-activity relationship. Part of the success of macrolides in treating infections has been credited to their anti-inflammatory properties. This useful side-effect has been captured for treating COPD patients. Chronic use of macrolides with antibiotic properties is not recommended because of resistance induction. Using Cempra’s disruptive chemistry technology, macrolides with no antibacterial activity will be developed for these non-antibiotic uses. Macrolides have a history of being orally bioavailable and safe, and these new programs could provide useful alternatives to traditional injectable drugs.

Erythromycin – As a Motilin Agonist

- Optimizing the side effects to produce a useful drug
- Erythromycin at acid pH becomes anhydroerythromycin that induces intestinal motility "belly cramps"

Therapeutic Potential of Motilin Agonists

- ORAL: gastroparesis, reflux disease, pseudo-obstruction, gallstone prevention, constipation
- INTRAVENOUS: emergency surgery, postoperative ileus

- Prevent bacterial translocation
- Endoscopy
- Duodenal intubation

15% of diabetics are affected by gastroparesis – an unmet need. Effect of destruction of nerves in autonomic nervous system can be up to 30% in Type 2 diabetics.

Why Focus on Motilin Agonists?

- Market opportunity because of lack of prokinetics
  - Current treatment: Metoclopramide, erythromycin and domperidone
  - Ghrelin agonists have been less promising than anticipated
  - Widespread use of erythromycin as prokinetic
- Powerful effects of motilin receptor stimulation

LHRH Antagonists - Background

- Luteinizing hormone-releasing hormone (LHRH), secreted from the hypothalamus, binds to the LHRRH receptor in the pituitary gland, stimulating the release of gonadotropins, luteinizing hormone, and follicle-stimulating hormone
- LHRH antagonists inhibit gonadal functions and are useful for treating endocrine-based conditions such as endometriosis, uterine fibroids, and precocious puberty, as well as several steroid-dependent malignancies, including cancers of the prostate and breast
- Several peptide antagonists are known – e.g., luprolide and its analogs
- Oral, safe product is desirable

Activity of Cempra’s Motilin Leads

<table>
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<tr>
<th>Sample ID</th>
<th>Concentration (ng/mL)</th>
<th>Maximal Response</th>
<th>Fraction of Maximal Response to Motilin</th>
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Cempra – Summary and Goals

- Established a world-class team, experienced in drug discovery and development
- Developed a product pipeline in antibacterials
- Leveraged its macrolide library to identify candidates for drug development in the areas of diabetic gastroparesis, COPD, prostate cancer
- Will have clinical candidates for partnering

Histoplastic Breakthrough in Macrolide Chemistry

Erythromycin mimics exogenous motilin

In: J. Am. J. Physiology 1984

Erythromycin is a motilin receptor agonist

In: Peeters TL… J. Am. J. Physiology 1989

Erythromycin improves gastric emptying in diabetic gastroparesis


Using Cempra’s disruptive chemistry technology, macrolides with no antibacterial activity will be developed for these non-antibiotic uses. Macrolides have a history of being orally bioavailable and safe, and these new programs could provide useful alternatives to traditional injectable drugs.