Using Macrolides to Address Multiple Therapeutic Needs – Inflammation, Diabetic Gastroparesis and Cancer

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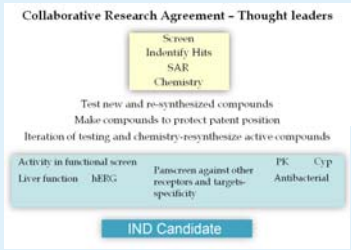
Abstract

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.

Macrolides – Beyond Antibacterials

- Macrolides are "preferred" oral druggable molecules that provide the pharmacophore for many therapeutic targets that have even larger market potential then 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

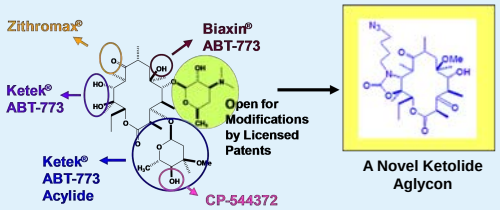
Cempra's Strategy



Non-Antibacterial Applications

- Several companies have developed non-antibiotic macrolides by modifying the N-dimethyl of the desosamine at the 5 position of the macrolide ring to decrease antibacterial activity
- All these compounds have one methyl group that does keep some antibacterial activity and therefore the potential for induction of resistance
- Cempra has aglycon chemistry for designing new structures at the 5 position, thus designing out antibacterial activity and decreasing CYP3A4 interaction

Historic Breakthrough in Macrolide Chemistry



1. PCT International Application filed March 5, 2004 (published Sep. 3, 2004, WO 2004/080391)
2. PCT application nationalized in United States, Europe, Canada and Hong Kong
3. Second Office Action received in US application; response due before July 22, 2008

What is Motilin?

- Is a GI peptide released by enterochromaffin cells in the upper small intestine
- Related to family of peptides that includes ghrelin, growth hormone peptide (secretagogues)
- Found in plasma preceding contractions
- Regulates motility between meals as well as postprandial
- Induces the migrating motor complex (MMC), hunger contractions, and cleaning contractions
- Disturbance in motilin function results in diseases

Therapeutic Potential of Motilin Agonists

ORAL

- ***gastroparesis***
- reflux disease
- ***pseudo-obstruction***
- gallstone prevention
- constipation

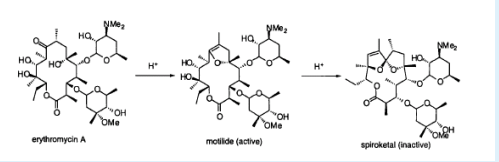
INTRAVENOUS

- ***emergency surgery***
- postoperative ileus
- prevent bacterial translocation
- ***endoscopy***
- ***duodenal intubation***

15% of diabetics are affected by gastroparesis – unmet need
Effect of destruction of nerves in autonomic nervous system
Up to 30% in Type 2 diabetics

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"



Erythromycin, a Motilin Agonist, Accelerates Gastric Emptying in Diabetic Gastroparesis

Erythromycin mimics exogenous motilin

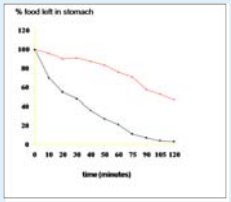
Itoh Z… *Am J Physiology* 1984

Erythromycin is a motilin receptor agonist

Peeters TL… *Am J Physiology* 1989

Erythromycin improves gastric emptying in diabetic gastroparesis

Janssens J… *New Engl J Med* 1992



Gastric Emptying in Patients with Diabetic Gastroparesis

Activity of Cempra's Motilin Leads

Fraction of Maximal Response to Motilin

Sample ID	Concentration (mg/mL)	
	4.35×10^{-4}	4.35×10^{-2}
Erythromycin	0.67	0.96
Clarithromycin	0.46	1.00
852	0.73	1.02
921	-0.02	1.02
637	0.03	0.03

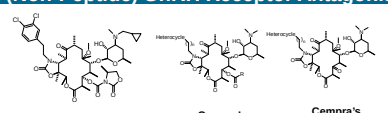
Why Focus on Motilin Agonists?

- Market opportunity because of lack of prokinetics
  - o 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 LHRH 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

Macrolide (Non-Peptide) GnRH Receptor Antagonist



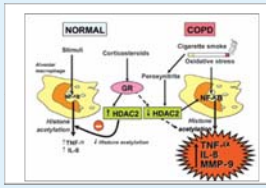
Abbott has shown that a macrolide analog can be a potent GnRH receptor antagonist and lower plasma LH responses in castrated rats.

Cempra's chemistry program can find similar,potent GnRH receptor antagonists without antibacerial actvity.

Anti-inflammatory

- Current, effective anti-inflammatories are mostly injectable proteins
- Macrolides are known to be anti-inflammatory, - oral and safe
- Macrolides are currently used for augmenting steroid sensitivity in COPD and cystic fibrosis pneumonia
- Recent publications show that macrolides can act directly to modulate NFκB and thus decrease TNFα production

Anti-inflammatory - COPD



Barnes, PJ. Reduced HDAC in COPD. Chest, 125: 151-155,2006

Proposed mechanism of corticosteroid resistance in COPD patients. Macrolides are believed to increase HDAC2, which enhances the activity of corticosteroids.

Anti-inflammatory - Screening Results

- Identified 6 hits that are more potent than erythromycin
- Re-synthesizing these hits and their analogs to determine the structure/activity relationships (SAR)
- Partner after achieving in vivo activity

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