Changing Lives Through Delivery Technologies

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Oral Peptide Delivery Update

AsiaTIDES Kyoto Japan
01 March 2017

Christopher A. Rhodes
# Peptide and Oral Delivery Technology Evolution

**Semaglutide** - Long-acting Peptide and Permeation Enhancer & **Linaclotide** - Stable Peptide for Local Oral Delivery

| Microneedles and Long-Acting Peptides Others???
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**Microneedle Advances Applied to Oral Delivery** (Rani, MIT)

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**New Delivery Approaches**

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**Improvements in Peptide Structure**

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Common Challenges for Oral Delivery of Peptides

- Variability in exposure (Cmax, AUC, Tmax)
- Food effect on permeation enhancing technologies
- Low bioavailability impact on cost and mfg scale
- Stability of peptide in standard oral formulations
- Maturity of the technology (commercial or clinical?)
- Scale up experience, manufacturing systems
- Regulatory experience (some new excipients)
Peptide and Oral Delivery
Technology Evolution

- **Semaglutide** - Long-acting Peptide and Permeation Enhancer
- **Linaclotide** - Stable Peptide for Local Oral Delivery
- **Salmon Calcitonin Octreotide, CR845** in Permeation Enhancing Systems

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- New Delivery Approaches

Improvements in Peptide Structure
Peptides in Permeation Enhancing Technology for Systemic Delivery

• Many technologies evaluated in last 20 to 40 years
• Most focused on permeation enhancing excipients
  • Mechanistic focus on transiently opening tight junction
  • sCT focus from Unigene, now Enteris and Tarsa Therapeutics
  • Octreotide focus from Chiasma
• Some exceptions
  • Emisphere technology – SNAC excipients
    • Mechanism somewhat unclear – not tight junction opening
    • Potentially exposing hydrophobic surfaces to enhance absorption
  • Generex – liposomal buccal spray formulation
• Summary – despite significant effort
  • Bioavailability still substantially less than 5% versus SC injection
sCT Oral Formulation Program
Tarsa Therapeutics (Enteris / Unigene)

- Originally supported by Novartis to phase 3
- Unigene and Novartis developed oral tablet formulation
- Bioavailability ~ 1% vs SC
- Phase 3 study: 200 microgram
- Phase 3 results published
- FDA accepted for review Oct 2015
- Initiated development 1990 or so
- Citric acid, lauryl carnitine

sCT Oral Formulation
Tarsa Therapeutics (Enteris / Unigene)

• Challenges for oral delivery
• Tmax and Cmax variability
• Short absorption window
• Significant food effect

Ref: Osteoporos Int, Volume 25, Issue 11, pages 2649-2656
Octreotide Oral Formulation
Chiasma Phase 3 program

- Bioavailability ~ 0.5% vs SC
- Phase 3 study: 40 mg QD and BID (80 mg)
- Food effect – 90% reduction in exposure

Ref: J Clin Endocrinol Metab, July 2012, 97(7):2362–2369

Octreotide
MW 1019.2 g/mole

Ref: J Clin Endocrinol Metab, July 2012, 97(7):2362–2369
Cara Therapeutics CR845
Enteris Oral Delivery Technology

- Kappa opioid analgesic
- Peripherally restricted
- IV in phase 3
- Oral in phase 2

Difelikefalin
MW 679.85 g/mol

CR845 Demonstrated 16% Oral Bioavailability

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**Improvements in Peptide Structure**
Linaclotide Example
Peptides for Local Oral GI Delivery

- Take advantage of peptide properties – no oral absorption
- Ironwood focused on GI disease (as well as others)
  - Inflammatory bowel disease, chronic constipation, etc…
  - Platform focus on guanylate cyclase-C agonists
- Linaclotide shows no oral bioavailability
  - Immediate release capsule formulation, standard excipients
  - 290 micrograms sprayed onto microcrystalline cellulose pellets
  - Technology focused on stability of peptide and process technology
  - Amorphous peptide dissolves quickly in gut
  - RT stability for 2 years

C59H79N15O21S6
MW 1526.8 g/mole
12.3 Pharmacokinetics

**Absorption**
LINZESS is minimally absorbed with low systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma are below the limit of quantitation after oral doses of 145 mcg or 290 mcg were administered. Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (Cmax), and half-life (t1/2) cannot be calculated.

**Distribution**
Given that linaclotide plasma concentrations following therapeutic oral doses are not measurable, linaclotide is expected to be minimally distributed to tissues.
Peptide and Oral Delivery
Technology Evolution

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**Microneedles and Long-Acting Peptides**

Others???

**Microneedles Advances Applied to Oral Delivery**

(Rani, MIT)

**New Delivery Approaches**
Peptides with Long Half-Life in Permeation Enhancer Technology

- Peptides for chronic disease move to longer half-life
  - GLP-1 is a good example (all human half-lives by SC injection)
  - GLP-1 native half-life ~1-2 minutes
  - Exenatide half-life 1 to 2 hours (BID administration) 10 to 20 ug dose
  - Liraglutide half-life 13 hours (QD administration) 1 to 2 mg dose
  - Semaglutide half-life 165 hours (weekly administration) 0.25 to 1 mg

- Oral delivery of long-acting peptide relies on low dose
  - Novo has done a good job at optimizing albumin binding to lower dose
GLP-1 Peptide Half-Life Optimization for Delivery

Native GLP-1: t½ 2 min (IV)

Exenatide (Byetta): t½ 1-2 hrs (SC)

Liraglutide (Victoza): t½ 13 hrs (SC)

Semaglutide: t½ 165 hrs (SC)

Vilsbøll T et al. JCEM 2003;88:220-224


Semaglutide for Oral Delivery
Novo Optimized GLP-1 Analogue

• Bioavailability ~ 0.25% vs SC
• Phase 2 study: 2.5 to 40 mg orally
  • 40 mg Oral compares to 0.25 to 0.5 mg SC
• Standard permeation enhancing technologies (Emis SNAC)
• Likely to experience food effect – may not be as important
• Novo relying on ability to manufacture recombinant GLP-1 cost effectively (North Carolina manufacturing plant)
• Structure is similar to Liraglutide with some important changes
Semaglutide Structural Differences to Liraglutide (Once daily GLP-1)

94% sequence homology to human GLP-1 with modifications at a.a. 8, 34, 26

Fatty acid side chain optimized for enhanced albumin binding affinity

Linker optimized to move the albumin bound fraction (99%) away from albumin to enhance activity
\[ {}^3\text{H}\]-Semaglutide SC ADME

- Ozempic FDA, EU approved
- Once weekly SC
- 0.5 to 1.0 mg dose
- Oral phase 3 completed

### Peptide and Oral Delivery Technology Innovation

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Oral Delivery Innovations

- Greatest leap forward is from engineers
- **Microneedle as an approach for oral delivery**
  - Capsule formulation / device containing pH activated microneedles
  - Rani Therapeutics (dissolving microneedles)
  - Bob Langer and MIT group
- **Addresses two of the three major issues of oral delivery**
  - Biologic protected from gastric fluid until released (stability)
  - Microneedles poke hole in lumen of gut and directly deliver drug (BA)
- **Risks**
  - Technology risk – very early exploratory studies, limited PK data
  - No safety data – safety of regularly penetrating lumen of gut
  - Drug loading, device complexity, manufacturing complexity
Rani Therapeutics
Dissolving Microneedle Approach

- Microneedle is crystalline solid
  - Peptide stability is good
- Enteric coated capsule is used
  - pH trigger as expected
- Microneedle and capsule release mechanism are new
- Bioavailability >50% vs SC
- Large biologics possible
- Long half-life opportunity
- Phase 1 late 2018

Rani Therapeutics comes from Mir Imran’s Incube Labs
www.ranitherapeutics.com
MIT Group
Metal Microneedles

- Microneedle is solid or hollow
- Novo collaboration

MIT Group:
Bob Langer, Daniel Blankschtein, Daniel Anderson, Avraham Schroeder, Carlo Traverso, Baris Polat, Carl Schoellhammer

Ref: Traverso et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:362–367, 2015
Oral Peptide Delivery Summary

- Bioavailability still quite limited (e.g. 2% sCT)
  - Even for small peptides (octreotide)

- Permeation enhancers are still primary approach
  - Leads to sharp and narrow PK profiles
  - Unless molecules are engineered to long half-life (Novo)

- Promise of microneedle approach is significant
I am fortunate to work with a really strong team

Thanks to our collaborators, clients, colleagues, friends, advisors