TIDES 2014

Nasal, Pulmonary, Oral, Transdermal, and Microneedle Technologies for Peptide Delivery
Peptide Delivery Outline

- Peptide Properties and Delivery
- Non-invasive Technology
- Marketed Peptides in Non-Invasive Systems
- Technologies in Development for Peptides
- Peptides / Delivery Systems in Development
Goals for Non-Invasive Delivery Systems

- Improve uptake through improved convenience, compliance, ease of use
  - Must be a simple system to be adopted by physicians and patients
- Small portion of market has needle phobia (10-25%)
  - But, most can get used to simple injections
- Must maintain safety / side effect profile
  - In some cases, can improve either or both
Non-Invasive Market Preference

Simple >> Complex
Once per day > BID >>> TID

Market Preference

Patients ~ Doctors

Injection

Oral

Nasal
Buccal
Sublingual
Transdermal
Limited Non-Invasive Product Precedents

- Pulmonary
- Oral
- Transdermal
- Sublingual / Buccal
- Nasal
- Pen Injection
- Auto-injector
- Vial Syringe

Risk vs. Reward

- Commercialized Products
- Products in Development
Properties of Peptides

- Typically water soluble > 1 mg/ml
- Stability in solution is often limited
  - Hydrolysis, deamidation in aqueous solution
- Stability as solid is good when water content is low
- Synthesis < 5000 g/mol > recombinant
- Immunogenicity and safety
  - Naturally derived peptides are typically risk reduced because safety of the endogenous molecule is well understood
  - Immunogenicity a concern for analogues and non-natural
- Half-life short for natural amino acid peptides
  - Minutes to hours
**Biomolecule Delivery Constraints**

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Proteins</th>
<th>Antibodies</th>
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</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MW (kD)</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Half-life (hour)</td>
<td>100</td>
<td>100</td>
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Peptide Delivery TIDES 2014
Typical Product Life Cycle for Peptide Therapeutics

- First drug product is usually solution for injection
  - Store in lyophilized form, or store in solution at 2-8°C
- Immediate product improvements to commercial product
  - Improve product presentation (Vial / syringe to pen/injector)
  - Predictable cost, time, high probability
- Next Generation: Sustained exposure injection technologies
  - Formulations (lipids, polymer, gels, implants)
    - Moderate cost and moderate probability
  - Covalent (PEG, Fc, Albumin, Ab binding conjugates)
    - Higher cost (NCE), risk-reduced if known target / pharmacology and follow on program
- Additional considerations: Non-invasive or minimally invasive
  - Nasal, Pulmonary, oral, microneedle, implant
  - Typically a device combination product, except most orals
  - High cost and lowest probability
Life Cycle for Peptides

Risk & Cost

Pen Injection Auto-injector
Vial Syringe

Sustained Exposure Injection
Non-Invasive

Time from First Launch
+ 5 Yrs
+ 10 Yrs

05/15/14
Non-Invasive Challenges

- Compatibility of drug, formulation, device
- Predictability of in vitro and in vivo methods
- Variability in Exposure (Cmax, AUC, Tmax)
- Overall cost of the system
  - Bioavailability, novel excipient, device, manufacturing
- Maturity of the technology
  - Phase 1 PK, or late stage phase 2/3 development
  - Scale up experience, manufacturing systems
- Regulatory experience and acceptance
Mucosal Transport of Biomolecules is Limited

- Low passive diffusion across mucosal barrier
  - Some active transport systems
- Significant permeation across pulmonary epithelial lining
  - Alveoli in deep lung show good permeability to peptides
  - Efficiency of deposition in deep lung limits bioavailability
  - Overall bioavailability typically 5 to 10% versus SC
- Permeation enhancers typical for nasal, oral, buccal, sublingual
  - Bioavailability typically < 2 to 4% versus SC
- Transdermal typically involves an active penetration or permeation
  - Penetration - microneedles, microporation (ablation)
  - Membrane disruption - iontophoresis, sonophoresis
  - Bioavailability can be significant > 20 to 40% versus SC
Peptide Products: Combination Products with Trivalent Complexity

**Biology & Chemistry**
- Molecule
  - Efficacy / side effects
  - Continuous or pulsatile
  - Cost per gram
  - Physicochemical properties

**PK & Formulation**
- Delivery System
  - Process complexity
  - Bioavailability
  - Cost per unit
  - Compatibility with molecule

**Device & Handling**
- Device
  - Device complexity
  - Ease of use / acceptance
  - Cost per unit
  - Formulation compatibility
Non-invasive Program Expectations

- Pulsatile exposure compared to SC injection
  - Limited absorption phase due to permeation and penetration aid
- Much lower bioavailability than SC
  - Can be a challenge to COGs and manufacturing scale
- Increased variability in exposure
  - Can be challenging for peptides with limited tolerability window
- Handling of a device 1X to 3X per day
  - Nasal, pulmonary, transdermal, microneedle
- Increased regulatory scrutiny
  - Change in route of delivery and formulation
  - Concern for change in safety profile / immogenicity
- Significant development time and cost
  - Increased drug consumption in pharmaceutical development
  - Potential for plant and equipment capital investment prior to phase 3
PK of GLP-1s

Native GLP-1: \( t_{\frac{1}{2}} \) 2 min (IV)

Liraglutide (Victoza): \( t_{\frac{1}{2}} \) 13 hrs (SC)

Exenatide (Byetta): \( t_{\frac{1}{2}} \) 1-2 hrs (SC)

J. Eng license to Amylin 1996
FDA approved 2005
Twice daily injection

Novo
FDA approved 2010
Once daily injection
DDAVP Nasal Spray and Oral Commercial Products

- DDAVP (desmopressin acetate)
  - MW 1183, anti-diuretic
  - Synthetic analogue of natural hormone arginine vasopressin
  - Multiple generic versions available

- DDAVP Nasal Spray (Sanofi, 1984)
  - 10 mcg / spray
  - Bioavailability ~10%, half-life 55 minutes

- DDAVP Tablets (Sanofi, 1995)
  - 100 to 200 mcg / tablet
  - Bioavailability 5% vs nasal, 0.2% vs Intravenous injection
Oxytocin Nasal Spray
Commercial Product

- Nasal Oxytocin
  - MW 1007, Initial milk letdown
  - FDA approval 1960 (Novartis)
  - Removed from US market in 1997 for commercial reasons
  - Still marketed in EU / ROW as Syntocinon (Novartis, Sigma-Tau)

- Development programs
  - Significant interest from several companies in CNS indications
  - Autism, Schizophrenia, anorexia, etc…
Salmon Calcitonin Nasal Spray
Commercial Product

- Nasal calcitonin
  - MW 3432, 32 amino acids
  - Post-menopausal osteoporosis
  - FDA approval 1995 (Sandoz)
  - CHMP and FDA recommend removal from market in 2012/2013, Health Canada Mandates removal in 2013

- Mean bioavailability of 2 to 3% vs IM injection
  - Range of 0.03 to 30 % in small human PK study
Insulin Oral Inhalation Commercial Product

- **Exubera (Pfizer / Nektar)**
  - MW 5807, 51 amino acids, two polypeptide chains
  - FDA approved 2006
  - Type I and II diabetes
  - Bioavailability vs SC injection ~10%
  - First inhalable insulin approved, proved that good engineering could produce similar PK profiles to SC injection
  - Pfizer pulled from market in 2007 due to poor acceptance

- **Afrezza (Mannkind)**
  - Technosphere Insulin Inhalation System
  - Under final FDA review 2014
Non-invasive Programs in Clinical Development

- **Inhaled Insulin**
  - Dance Pharmaceuticals, founded by John Patton (Nektar)
  - Based on the Aerogen device

- **Oral Insulin**
  - Biocon technology originally licensed from Nobex based on PEGylated insulin conjugates – IN-105
    - Failed to reach primary endpoint in phase 3 study
  - Oramed – phase 2 study
  - Diabetology
  - Ora-Lyn (Generex buccal spray)
  - All technologies have bioavailability << 10% vs SC injection

- **Nasal Insulin**
  - Nasulin (CPEX) failed in a phase 2 trial in 2011 and was halted
Non-invasive Programs in Clinical Development

- **Nasal Oxytocin**
  - Retrophin, other companies
  - Clinical exploration in multiple CNS indications

- **Oral Calcitonin**
  - Tarsa Therapeutics licensed Unigene Labs product
  - Completed phase 2, in phase 3 readying for submission?
  - Oral bioavailability 1 to 2% versus SC injection

- **PTH1-34 Microneedles**
  - Zosano stainless steel microneedle system (Alza Macroflux technology)
  - Radius (3M plastic microneedle system)
  - Bioavailability 20 to 40% versus SC injection

- **Exenatide Implant (minimally invasive)**
  - Intarcia titanium implant with 6 and 12 month of exenatide (Alza Duros technology)
Prospective Non-Invasive Peptide?: Consider Indication / Patients Needs First, Then Technical Feasibility in The Space

**Molecule**
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- Device complexity
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**Biology & Chemistry**

**PK & Formulation**

**Device & Handling**

Prospective Non-Invasive Peptide?:
Consider Indication / Patients Needs First,
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