development trends for peptide therapeutics

THE FIRST COMPREHENSIVE QUANTITATIVE ANALYSIS OF PEPTIDE THERAPEUTICS IN CLINICAL DEVELOPMENT
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Compile everything known about every peptide that has ever been tested in a human, then analyze and develop compelling insights.
Peptide Database

Data collected

- Chemical information
- Molecular Pharmacology (target, MoA)
- Clinical Status/Phase Transition
- Therapeutic Indications
- Companies

Inclusion

- Synthetic peptide of any length
- Recombinant peptide <50aa
- Hybrid molecule/conjugate with discrete peptide domain

Exclusion

- Epitope-specific vaccines
- Bacterial fermentation products
- New formulations/uses of an already-included peptide

Insulin is excluded

531 compounds in the dataset
Up to 60 data points/parameters per compound
Data from publicly available information sources
Therapeutic Peptide Timeline

Cumulative peptide approvals

Peptides entering clinical study

Peptides entering clinical study: 5-year trailing average
Peptide Therapeutics

64 Therapeutic Peptides approved in US and/or Europe

- Most recent peptide drug approvals:

163 Peptides in Active Development
## Peptide Diversity

<table>
<thead>
<tr>
<th>Type</th>
<th>Analog</th>
<th>Native</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>31aa / 4114 M.W.</td>
<td>8aa / 1046 M.W.</td>
</tr>
<tr>
<td>Conjugated?</td>
<td>Yes - lipid</td>
<td>No</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>GLP1R</td>
<td>AT1R</td>
</tr>
<tr>
<td><strong>Target Class</strong></td>
<td>GPCR-B</td>
<td>GPCR-A</td>
</tr>
<tr>
<td>MoA</td>
<td>Agonist</td>
<td>Agonist</td>
</tr>
<tr>
<td>Therapeutic Area</td>
<td>Metabolic</td>
<td>Critical care</td>
</tr>
<tr>
<td>RoA</td>
<td>s.c. weekly</td>
<td>Continuous i.v.</td>
</tr>
<tr>
<td><strong>IND → Approval</strong></td>
<td>~ 10.5 years</td>
<td>~3.5 years</td>
</tr>
</tbody>
</table>
Properties of Development Peptides

- Number of amino acids
- Conjugated vs. Non-conjugated
- Molecular Targets
- Duration of Development
- Likelihood of Phase Progression
- Top-Selling Peptide Drugs
Size and Conjugation

Area of pie chart is proportional to % conjugation in each time period

Length of Peptides Entering Clinical Trials

Amino Acids
- 2 to 10
- 11 to 20
- 21 to 30
- 31 to 40
- 41 to 50
- >50
- Unknown

Fused/conjugated/complexed to protein
Lipidated
PEGylated/conjugated to other synthetic polymer
Radiolabeled
All other/unknown conjugates
Conjugated to Peptide

8% conjugated
24% conjugated
34% conjugated
Molecular Target Classes

Target Classes of Peptides Entering Development

- **2010-present**
  - GPCR
  - Catalytic and other Ig-family receptors
  - Anti-microbial targets
  - Ion channels
  - Ion channels
  - Intracellular targets/unknown
  - Other extracellular targets

- **2000s**
  - GPCR
  - Catalytic and other Ig-family receptors
  - Anti-microbial targets
  - Ion channels
  - Intracellular targets/unknown
  - Other extracellular targets

- **1990s**
  - GPCR
  - Catalytic and other Ig-family receptors
  - Anti-microbial targets
  - Ion channels
  - Intracellular targets/unknown
  - Other extracellular targets
GPCR Modalities

GPCR Modalities for All Development Peptides

1990s

2000s

2010-present

- GPCR-A agonist
- GPCR-A antagonist
- GPCR-B agonist
- GPCR-B antagonist
Molecular Targets

All-Time Top Targets for All Development Peptides

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 receptor</td>
<td>53</td>
</tr>
<tr>
<td>GnRH receptor</td>
<td>22</td>
</tr>
<tr>
<td>SST receptors</td>
<td>17</td>
</tr>
<tr>
<td>MC receptors</td>
<td>15</td>
</tr>
<tr>
<td>AMY receptors</td>
<td>12</td>
</tr>
<tr>
<td>NPR-A</td>
<td>11</td>
</tr>
<tr>
<td>Ghrelin receptor</td>
<td>10</td>
</tr>
</tbody>
</table>

By Decade

<table>
<thead>
<tr>
<th>Decade</th>
<th>1990’s</th>
<th>2000’s</th>
<th>2010’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH receptor</td>
<td>6</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>AMY receptors</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>TRH receptors</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>MC receptors</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>GLP-1 receptor</td>
<td>53</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>PTH1 receptor</td>
<td>15</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>MC receptors</td>
<td>15</td>
<td>6</td>
<td>5</td>
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<td>SST receptors</td>
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<td>6</td>
<td>5</td>
</tr>
<tr>
<td>GnRH receptor</td>
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<td>4</td>
</tr>
<tr>
<td>CXCR4</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ghrelin receptor</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CD36</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: each peptide is assigned a single target in the database
Clinical Development Time

Peptides approved since 2010

- Tesamorelin
- Lucinactant
- Pasireotide
- Carfilzomib
- Linaclotide
- Teduglutide
- Lixisenatide
- Albigrutide
- Dulaglutide
- Afamelanotide
- Etelcalcetide
- Plecanatide
- Abaloparatide
- Oxodotreotide
- Semaglutide
- LJPC-501

Median development time for peptides approved since 2010: ~10.4 years
Clinical Development Time

Peptides that Entered the Clinic since 1990

N=35 approved peptides
Median duration of development: ~8 years
Likelihood of Approval

Sources: CMR 2016; FRI Peptide Database (PTX DB)
NBE: new biological entity; NCE: new chemical entity
Top-Selling Peptide Drugs, 2017

2017 Sales ($M)

Victoza, Saxenda (liraglutide)
Copaxone (glatiramer)
Trulicity (dulaglutide)
Forteo (teriparatide)
Sandostatin (octreotide)
Acthar (corticorelin)
Lupron, Eligard (leuprolide)
Somatuline (lanreotide)
Kyprolis (carfilzomib)
Zoladex (goserelin)
Linzess (linaclotide)

$ Millions
Current Phase 3 Peptides

- Forigerimod
- Omiganan
- NGR-hTNF
- Timbetasin
- Difelikefalin
- Glepaglutide
- Dusquetide
- NA-1
- Vosoritide
- Setmelanotide
- Murepavadin
- Relamorelin
- Dasiglucagon
- Efpeglenatide
- APL-2
- Voclosporin
- PXL-01
- ACT-1
- Rapastinel
- Elamipretide
- Reltecimod
- BL-8040
- TDM-621
- B2A

Glepaglutide
Source: Zealand Investor Slides

Rapastinel
Current Phase 3 Peptides

Presented at PTS, 2006-present

• Forigerimod
• Omiganan
• NGR-hTNF
• Timbetasin
• Difelikefalin
• Glepaglutide
• Dusquetide
• NA-1

• Vosoritide
• Setmelanotide
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Forigerimod

Elamipretide
What next?
#1: Technology-Driven Progress

Continue to Develop and Apply Technology to Defy Conventional Wisdom

- Short half life $\rightarrow$ Innovative HLE strategies
- Parenteral administration $\rightarrow$ Oral delivery
- Peripheral restriction $\rightarrow$ Cell- and brain-penetrating peptides
- Polypharmacy

Sources: TRULICITY website; *Lancet* 2018 (doi: 10.1016/S0140-6736(18)32260-8)
It’s astonishing that to this day, we’re still discovering hormones that we didn’t know existed.

— Brian J. Feldman, endocrinologist, Stanford University

“Hormones reveal the secret life of fat cells”, C&EN 96, Oct 6, 2018
Opportunities for Discovery?

“New” Endocrine Organs

Adipokines
- Adiponectin
- IL-6
- MCP-1
- TNF-α
- Resistin
- Visfatin
- WAT
- Adipocyte
- Blood vessel

Cardiokines
- Natriuretic peptides [19-24]
- Ghrelin [26-28]
- Relaxin [26]
- Neuregulin-1 [26]
- Galanin [32]
- Endothelins [37]
- Glucagon-like peptide-1 [25, 26]
- Adrenomedullins [29, 30]
- Apelin [31]

Sakarai and Kizaki, *Int. J. Endo*, 2013
Takahashi and Herzig, *Peptides*, in press
Summary

- Peptide therapeutics are diverse, despite perceptions of niche application
- Technological advances → broader utility and new applications
- New discoveries (targets, hormones) → continuing opportunity

- Stay tuned: More breakthroughs to come!
Acknowledgements

Contributors to Peptide Database

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