



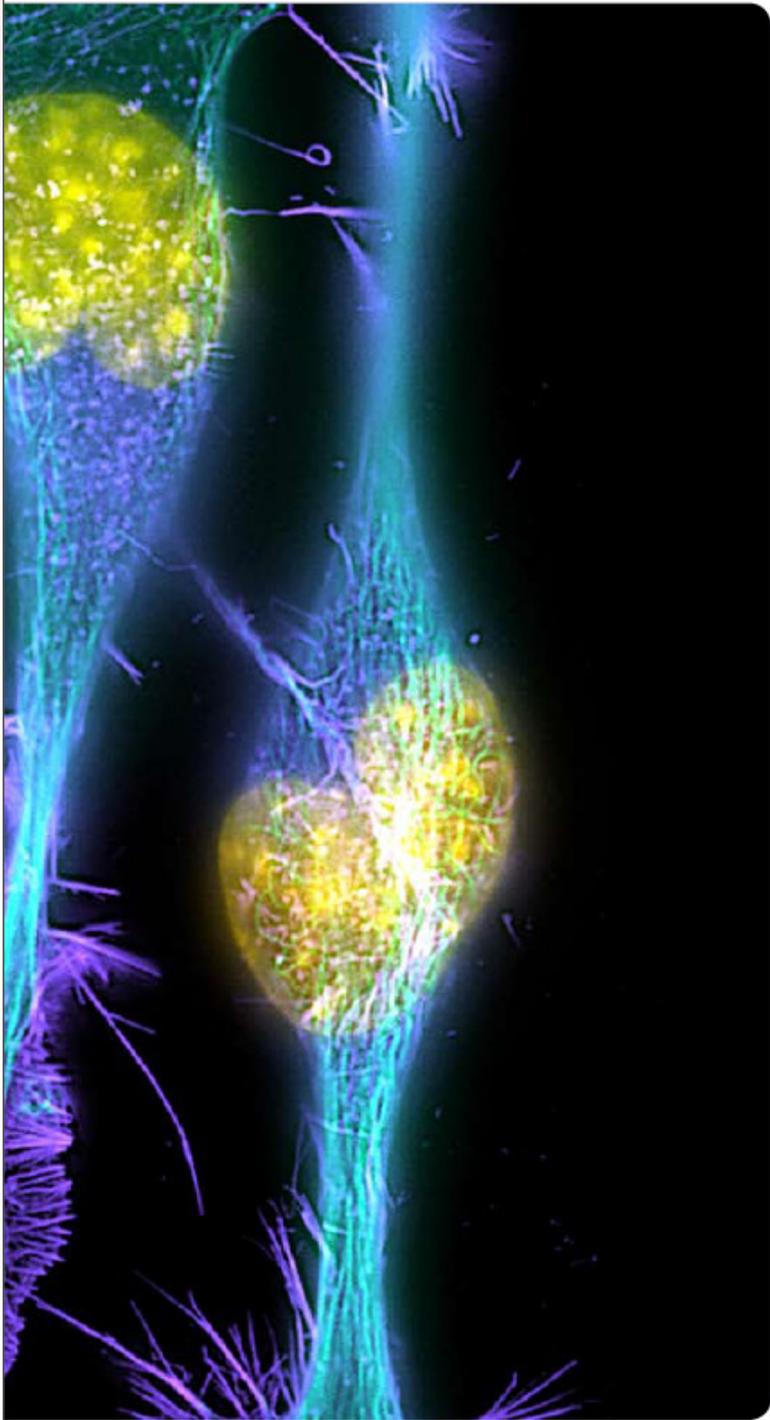
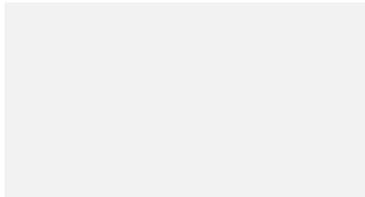
Peptide Therapeutics Update

Michael K. Dunn, Ph.D.

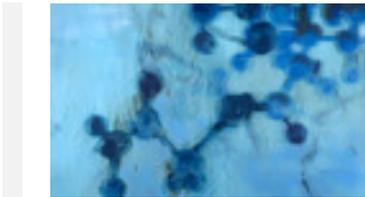


2018 Peptide Therapeutics Symposium





2008 Report



development trends for peptide therapeutics

THE FIRST COMPREHENSIVE QUANTITATIVE ANALYSIS OF PEPTIDE THERAPEUTICS IN CLINICAL DEVELOPMENT



PEPTIDE THERAPEUTICS FOUNDATION

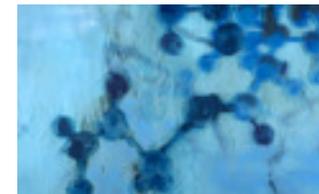




THE FIRST COMPREHENSIVE QUANTITATIVE ANALYSIS OF PEPTIDE THERAPEUTICS IN CLINICAL DEVELOPMENT

Compile everything known about every peptide that has ever been tested in a human, then analyze and develop compelling insights.

Peptide Database



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

Data collected

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

Inclusion

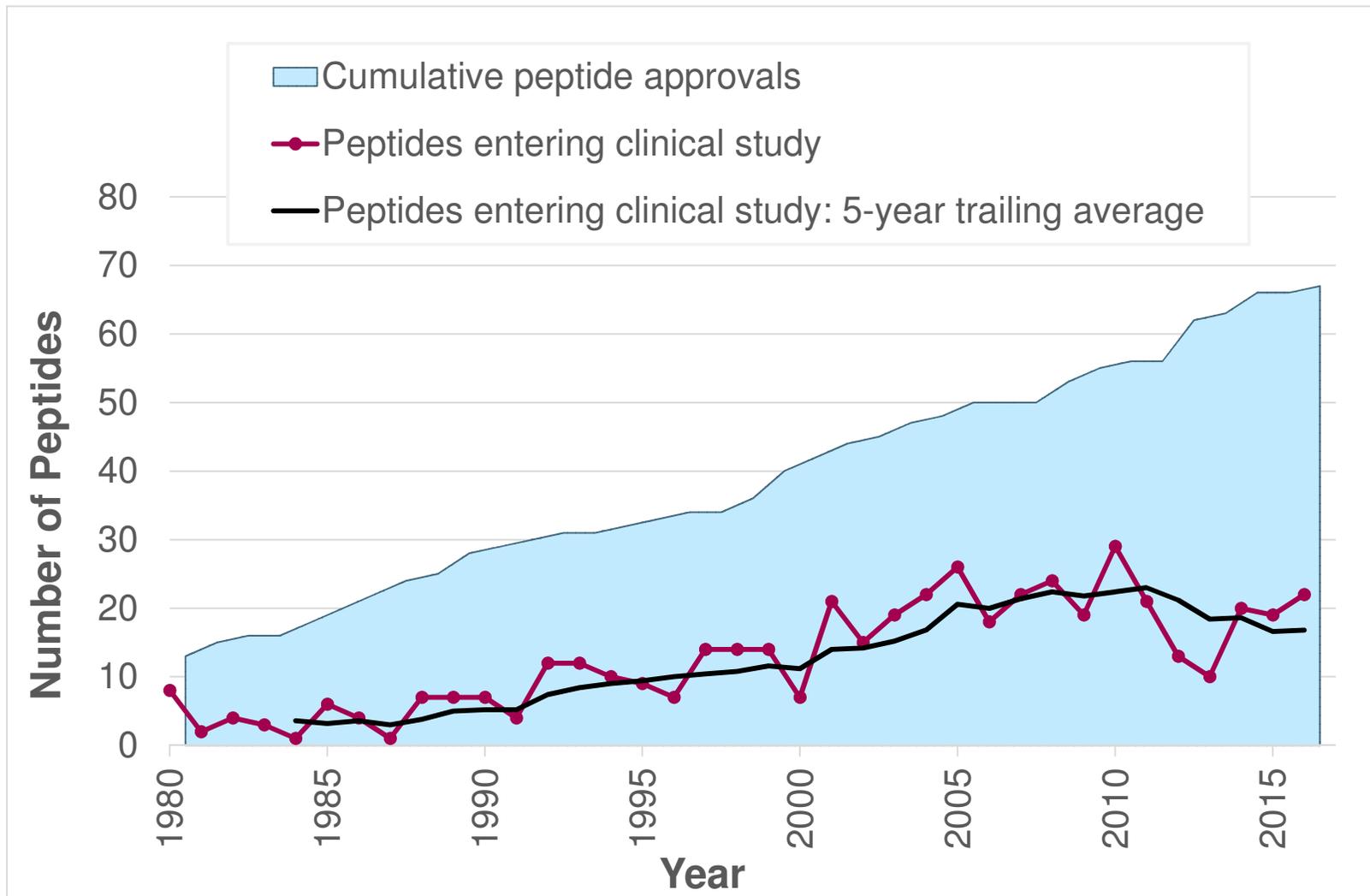
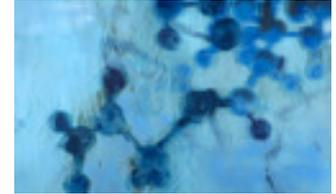
- ▶ Synthetic peptide of any length
- ▶ Recombinant peptide <50aa
- ▶ Hybrid molecule/conjugate with discrete peptide domain

Exclusion

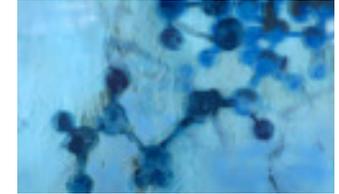
- ▶ Epitope-specific vaccines
- ▶ Bacterial fermentation products
- ▶ New formulations/uses of an already-included peptide

Insulin is excluded

Therapeutic Peptide Timeline



Peptide Therapeutics



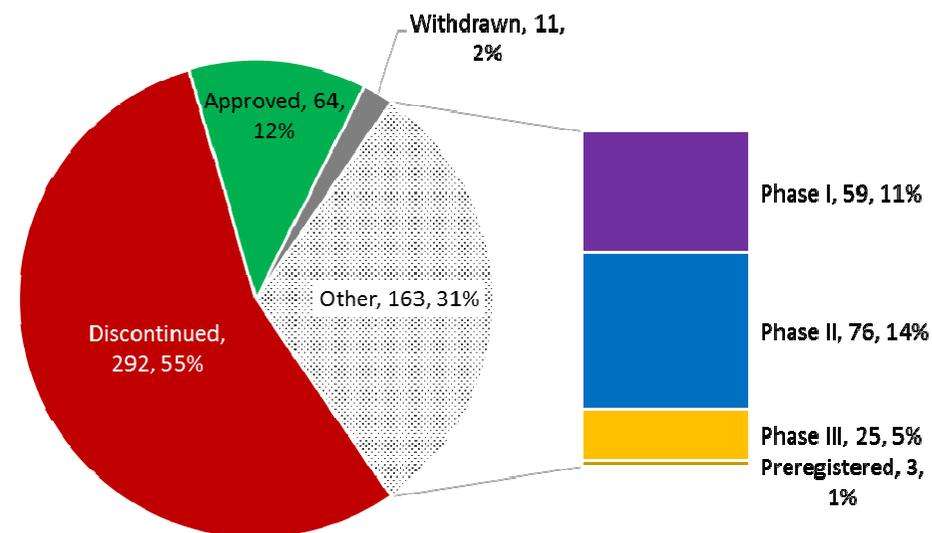
64 Therapeutic Peptides approved in US and/or Europe

- ▶ Most recent peptide drug approvals:

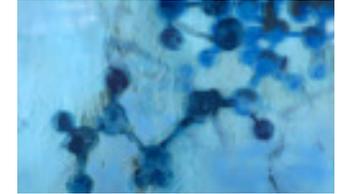
ONCE-WEEKLY
OZEMPIC[®]
semaglutide injection 0.5mg/1mg

GIAPREZA[™]
(angiotensin II)
injection for intravenous infusion

163 Peptides in Active Development



Peptide Diversity

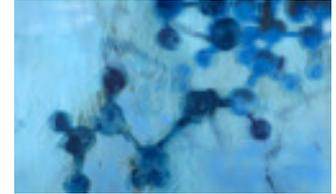


ONCE-WEEKLY
OZEMPIC[®]
 semaglutide injection 0.5mg | 1mg

GIAPREZA[™]
 (angiotensin II)
 injection for intravenous infusion

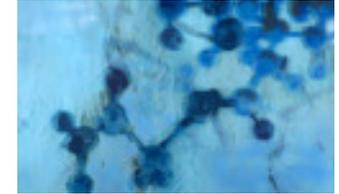
Type	Analog	Native
Size	31aa / 4114 M.W.	8aa / 1046 M.W.
Conjugated?	Yes - lipid	No
Target	GLP1R	AT1R
Target Class	GPCR-B	GPCR-A
MoA	Agonist	Agonist
Therapeutic Area	Metabolic	Critical care
RoA	s.c. weekly	Continuous i.v.
IND → Approval	~ 10.5 years	~3.5 years

Properties of Development Peptides

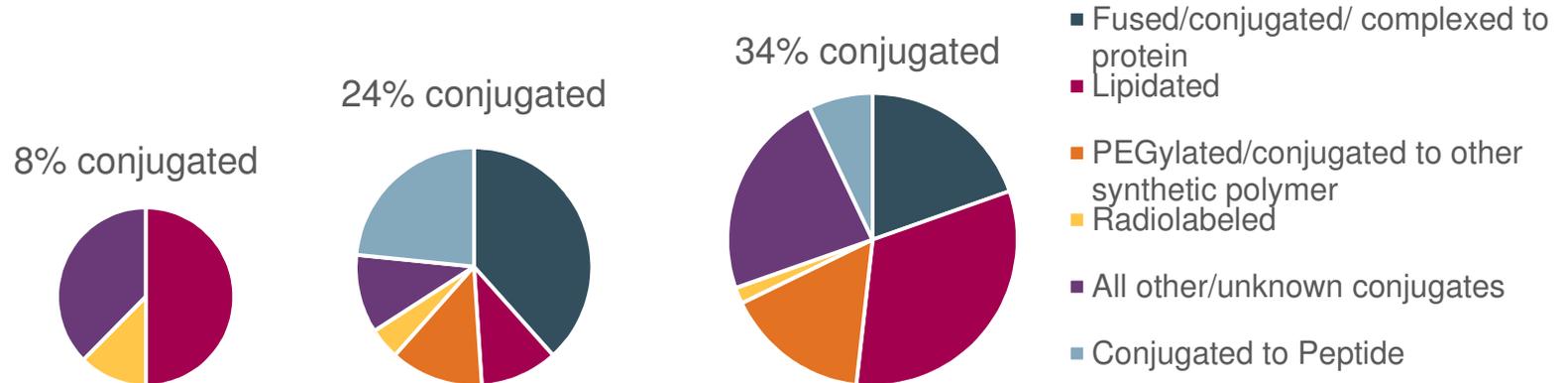


- ▶ Number of amino acids
- ▶ Conjugated vs. Non-conjugated
- ▶ Molecular Targets
- ▶ Duration of Development
- ▶ Likelihood of Phase Progression
- ▶ Top-Selling Peptide Drugs

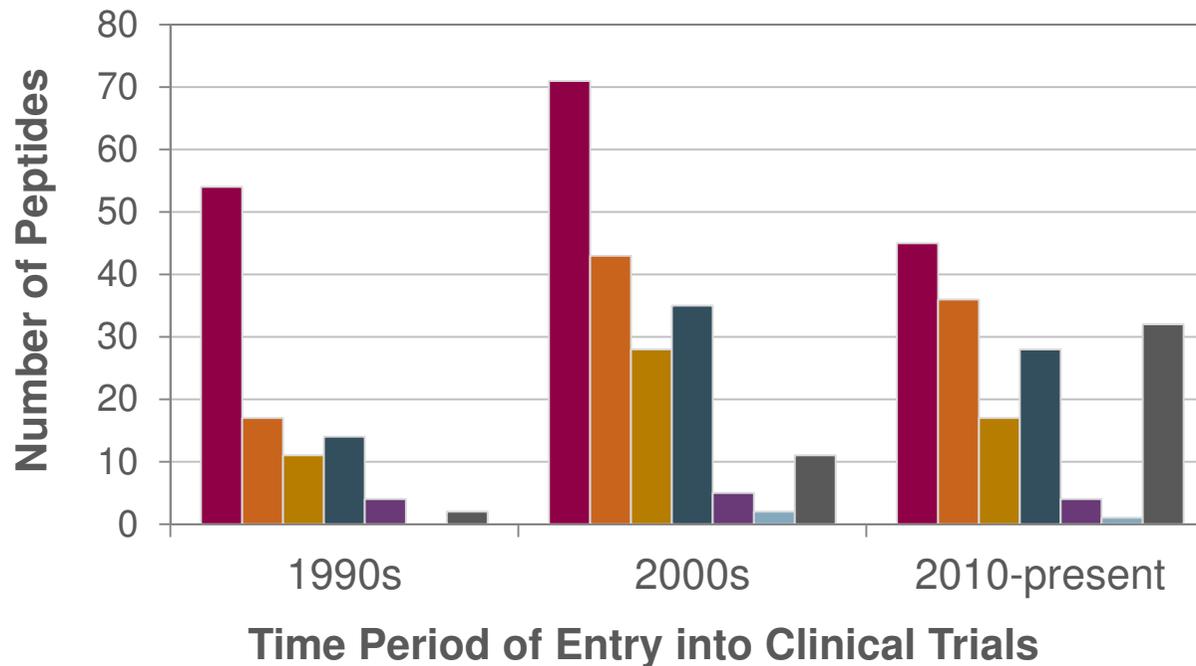
Size and Conjugation



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



Length of Peptides Entering Clinical Trials

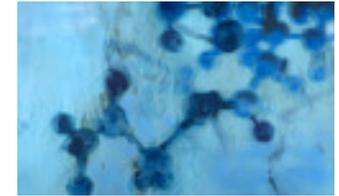


Amino Acids

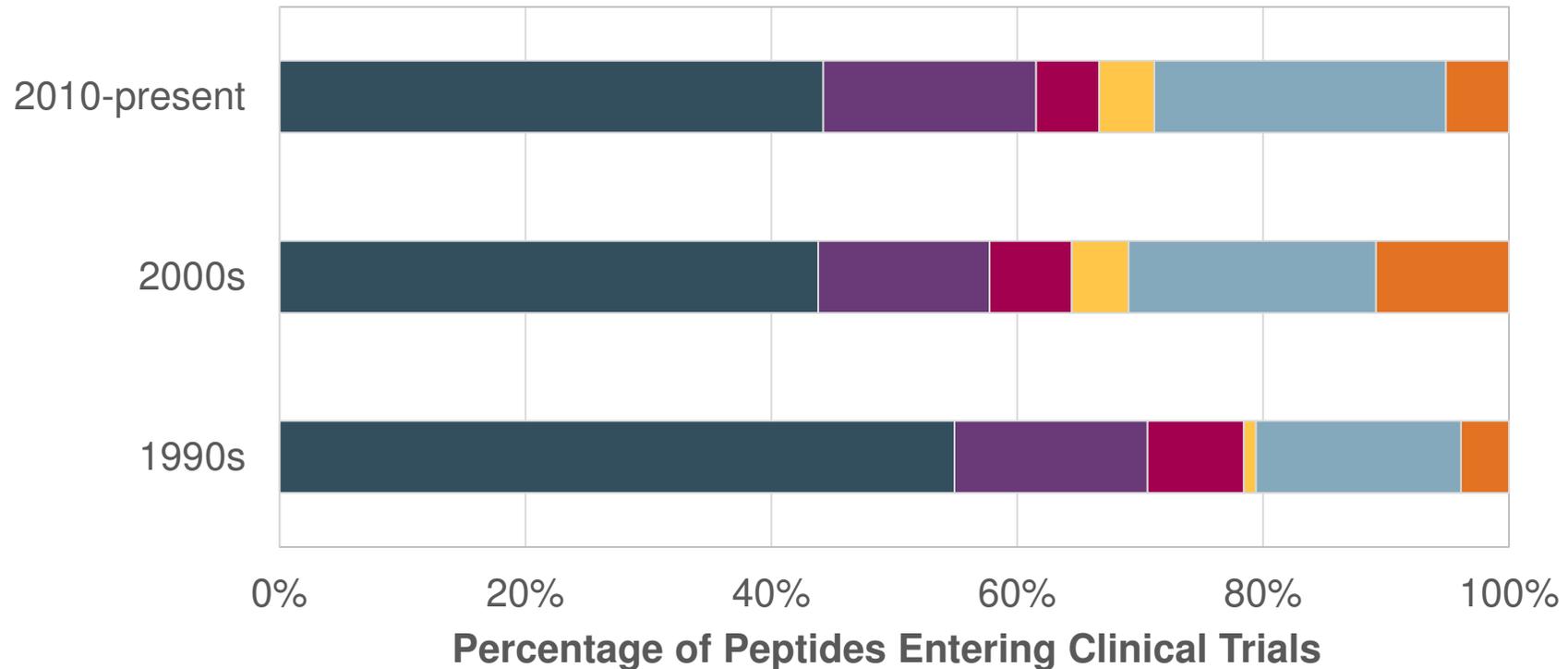
- 2 to 10
- 11 to 20
- 21 to 30
- 31 to 40
- 41 to 50
- >50
- Unknown



Molecular Target Classes



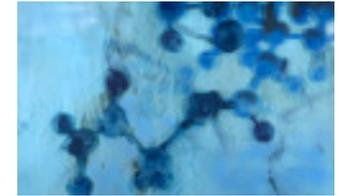
Target Classes of Peptides Entering Development



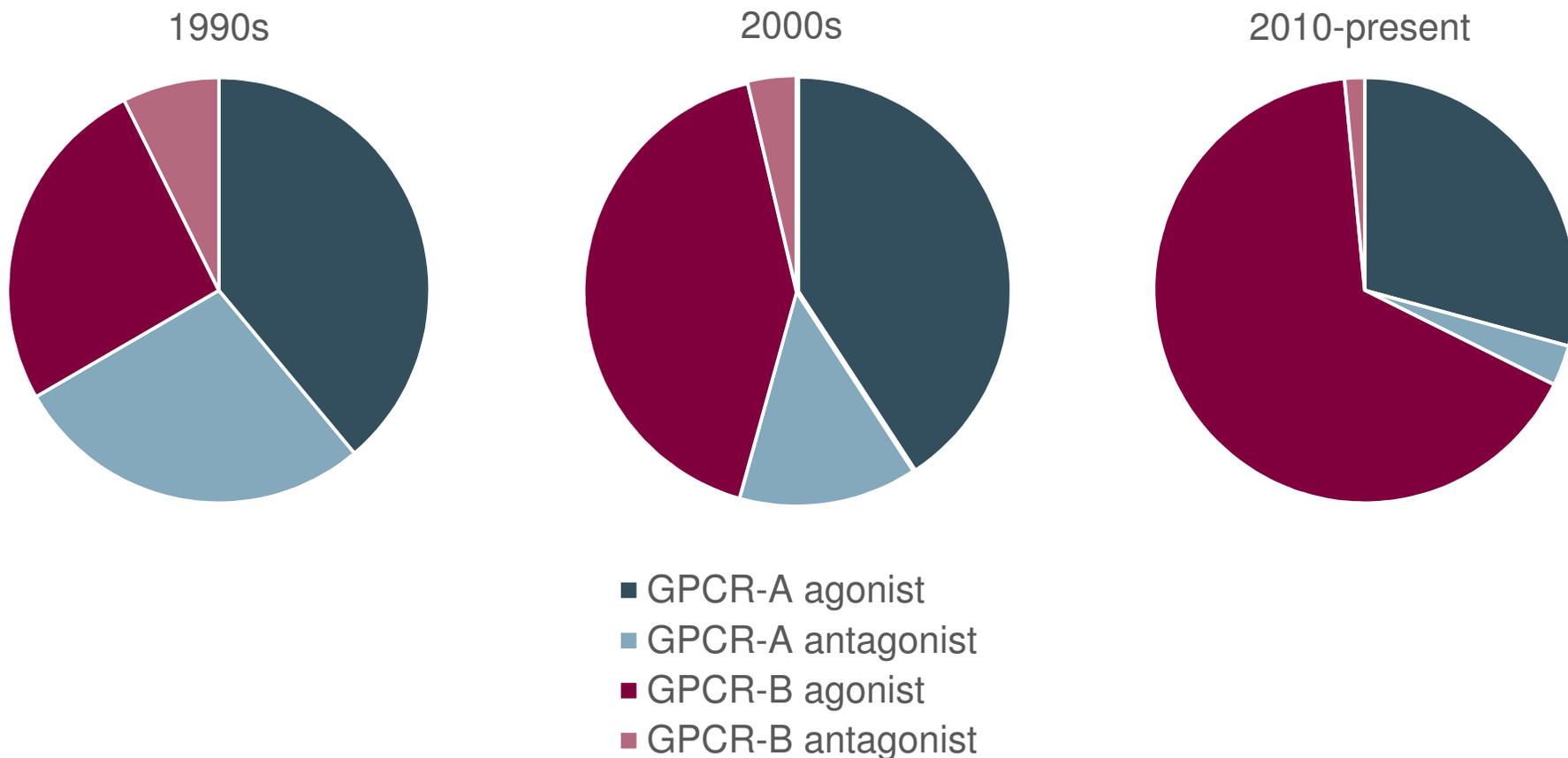
- GPCR
- Catalytic and other Ig-family receptors
- Anti-microbial targets
- Ion channels
- Other extracellular targets
- Intracellular targets/unknown



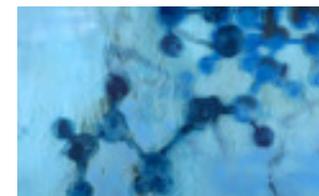
GPCR Modalities



GPCR Modalities for All Development Peptides



Molecular Targets



All-Time Top Targets for All Development Peptides

GLP-1 receptor	53
GnRH receptor	22
SST receptors	17
MC receptors	15
AMY receptors	12
NPR-A	11
Ghrelin receptor	10

By Decade

1990's

GnRH receptor	6
AMY receptors	4
TRH receptors	4
MC receptors	4

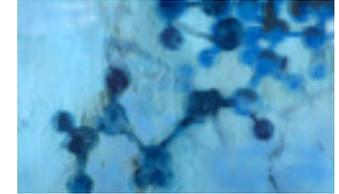
2000's

GLP-1 receptor	20
PTH1 receptor	6
MC receptors	6
SST receptors	6
GnRH receptor	5
CXCR4	5
Ghrelin receptor	5
CD36	5

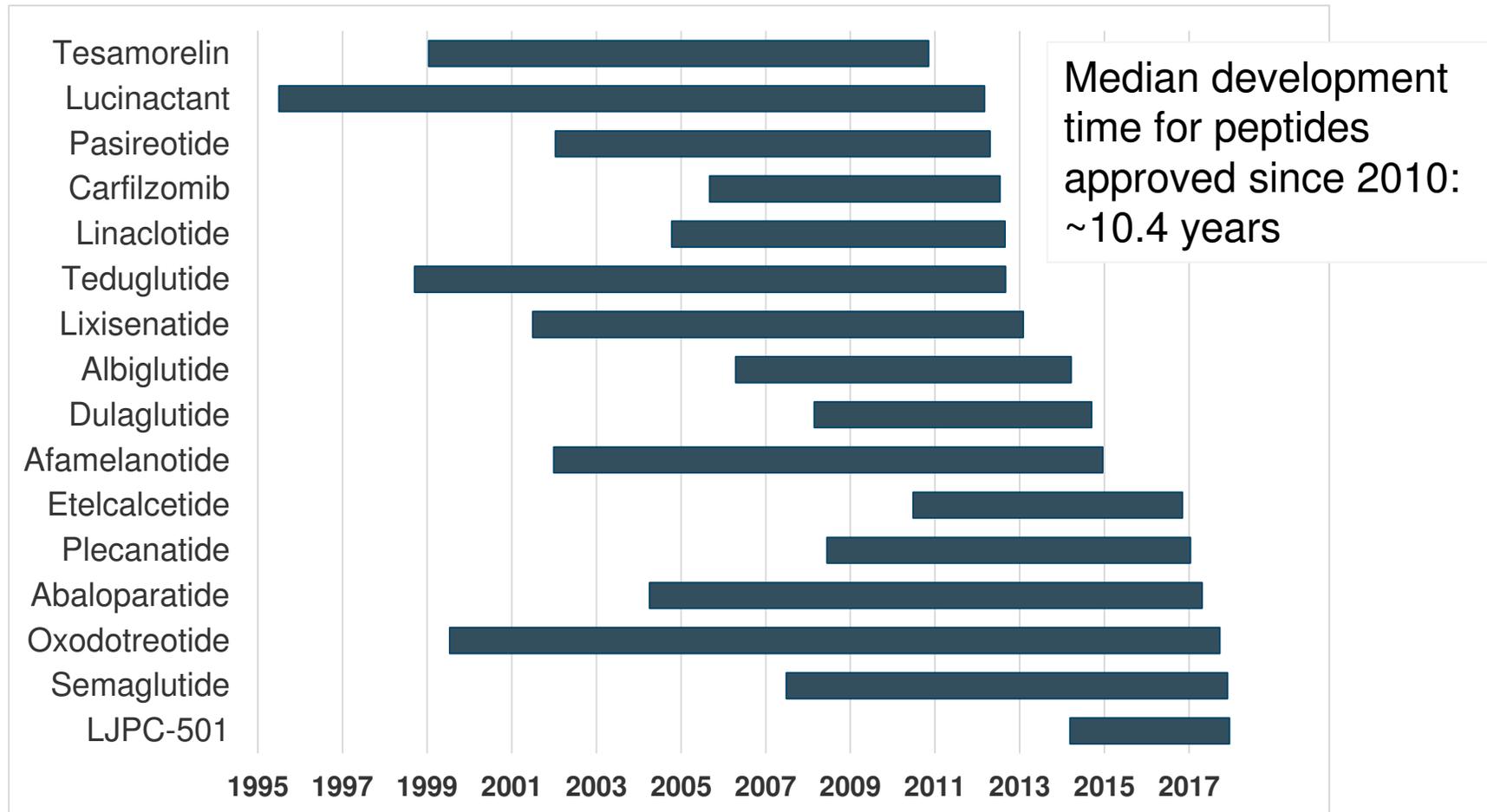
2010's

GLP-1 receptor	30
Glucagon receptor	5
AMY receptors	4
SST receptors	4
MC receptors	4

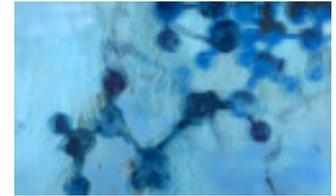
Clinical Development Time



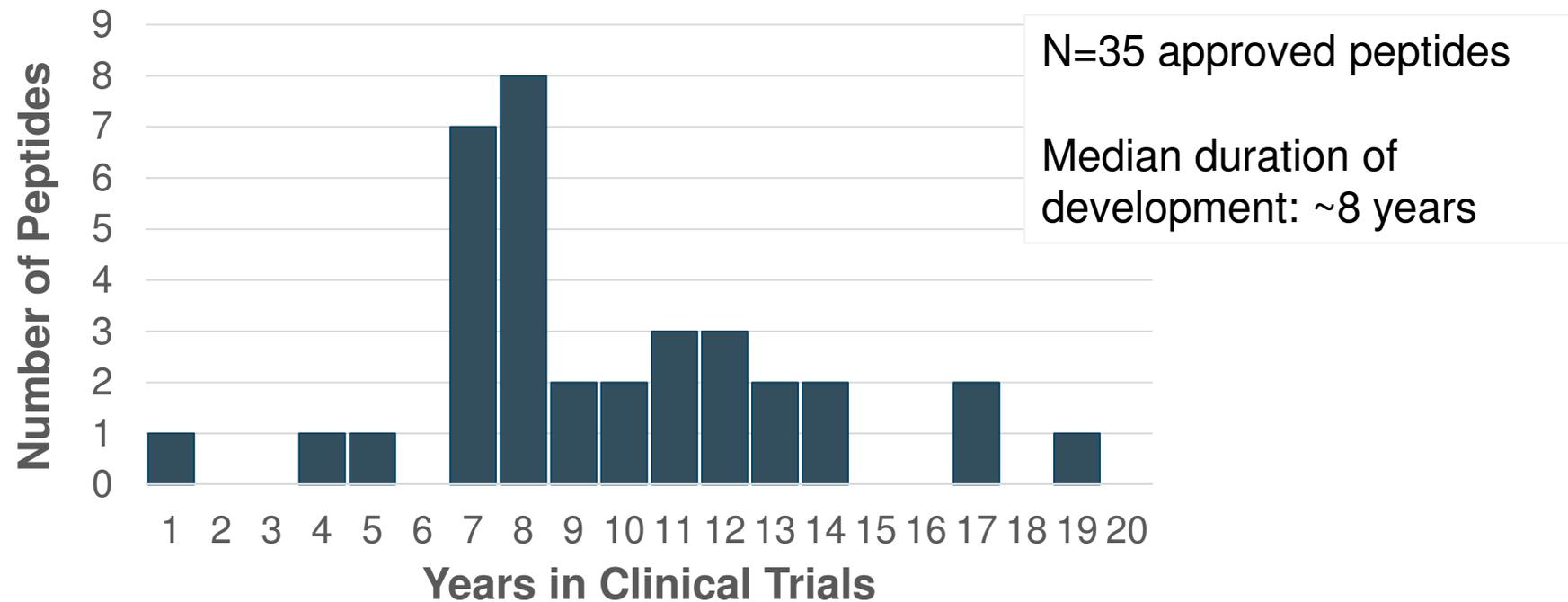
Peptides approved since 2010



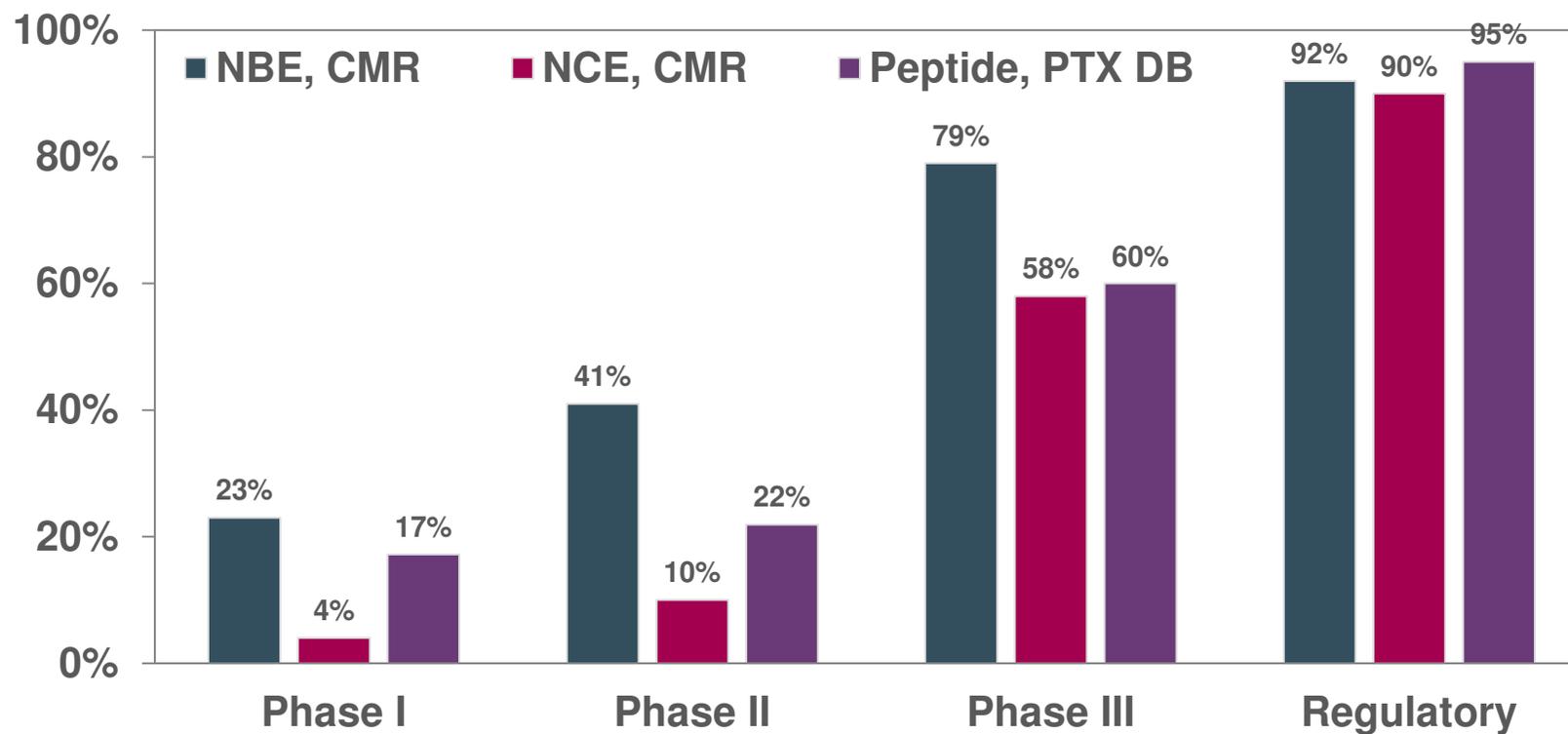
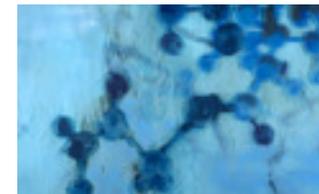
Clinical Development Time



Peptides that Entered the Clinic since 1990



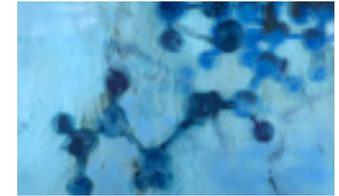
Likelihood of Approval



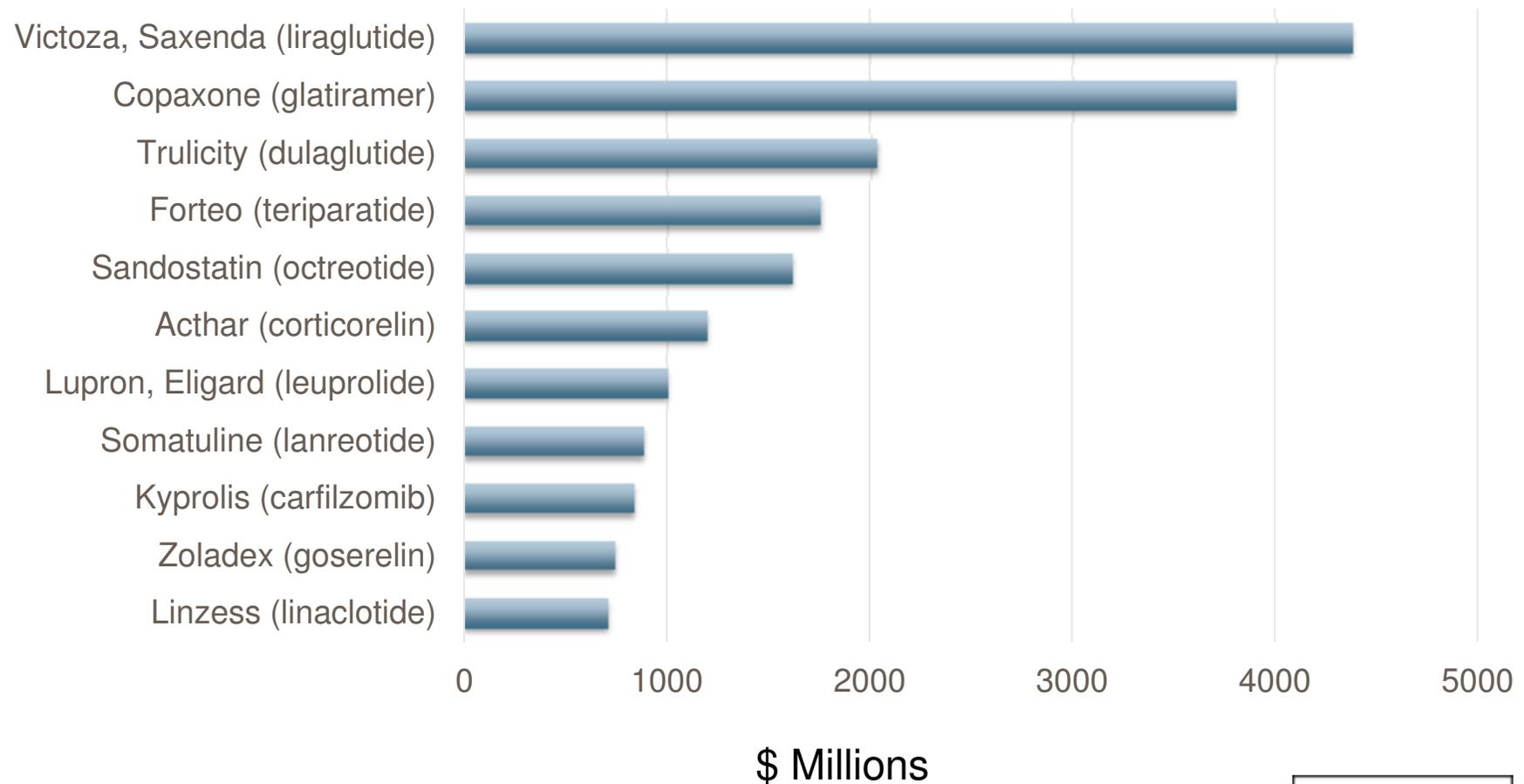
Sources: CMR 2016; FRI Peptide Database (PTX DB)
NBE: new biological entity; NCE: new chemical entity



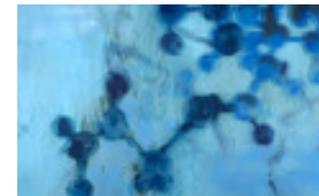
Top-Selling Peptide Drugs, 2017



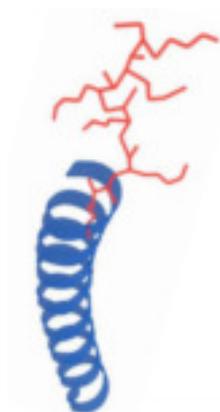
2017 Sales (\$M)



Current Phase 3 Peptides

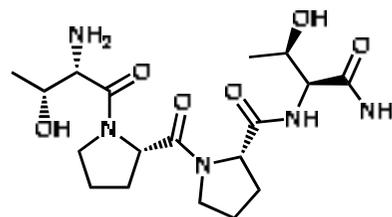


- Forigerimod
- Omiganan
- NGR-hTNF
- Timbetasin
- Difelikefalin
- Glepaglutide
- Dusquetide
- NA-1
- Vosoritide
- Setmelanotide
- Murepavadin
- Relamorelin
- Dasiglucagon
- Efpeglenatide
- APL-2
- Voclosporin
- PXL-01
- ACT-1
- Rapastinel
- Elamipretide
- Reltecimod
- BL-8040
- TDM-621
- B2A



Glepaglutide

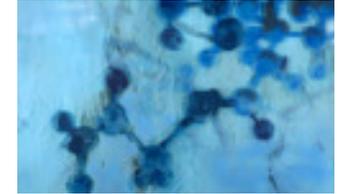
Source: Zealand Investor Slides



Rapastinel

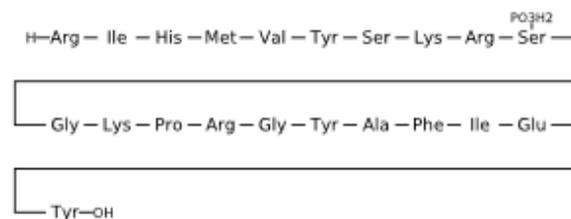


Current Phase 3 Peptides

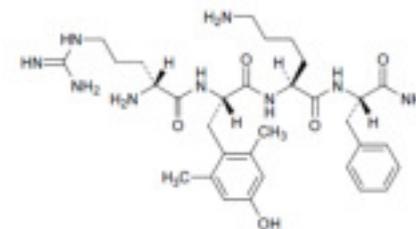


Presented at PTS, 2006-present

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



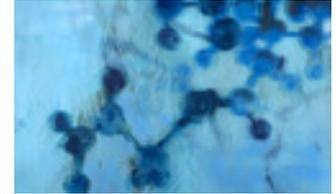
Forigerimod



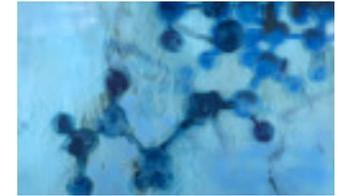
Elamipretide



What next?



#1: Technology-Driven Progress

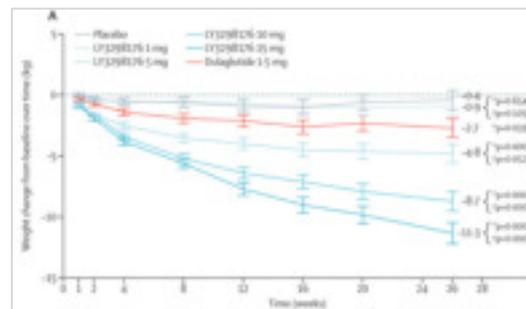


Continue to Develop and Apply Technology to Defy Conventional Wisdom

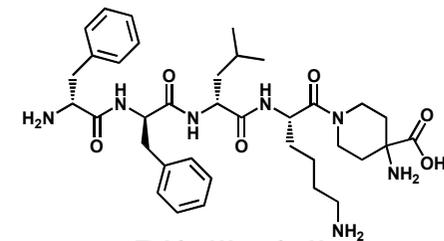
- ▶ Short half life → Innovative HLE strategies
- ▶ Parenteral administration → Oral delivery
- ▶ Peripheral restriction → Cell- and brain-penetrating peptides
- ▶ Polypharmacy



Dulaglutide



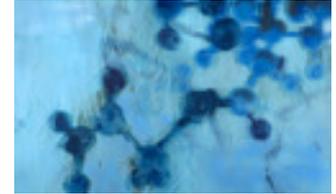
LY3298176



Difelikefalin



#2: New Target Discovery

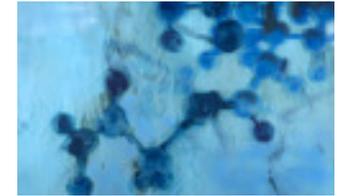


“ **I**t’s astonishing that to this day, we’re still discovering hormones that we didn’t know existed.

— *Brian J. Feldman, endocrinologist, Stanford University*

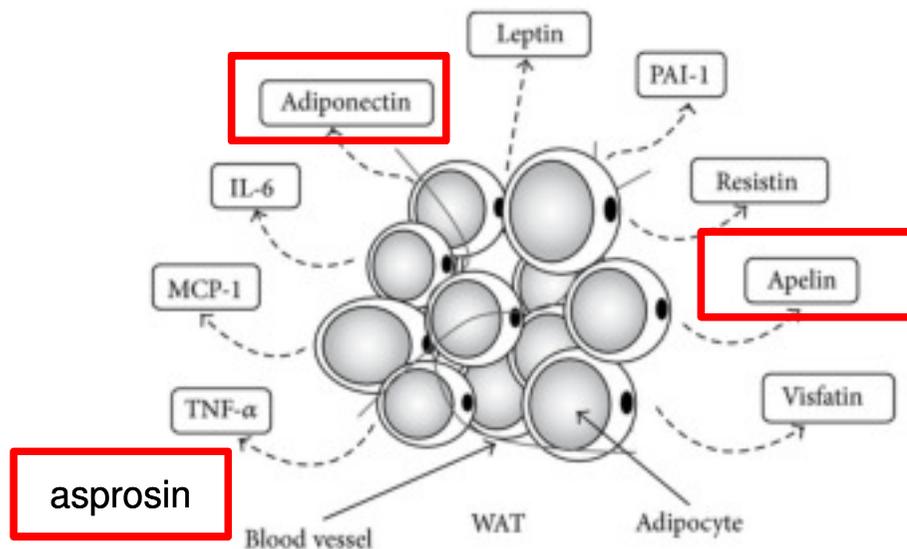
“Hormones reveal the secret life of fat cells”, C&EN 96, Oct 6, 2018

Opportunities for Discovery?



“New” Endocrine Organs

Adipokines



Sakarai and Kizaki, *Int. J. Endo*, 2013

Cardiokines

Heart Peptides

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]

Oxytocin [33, 34]

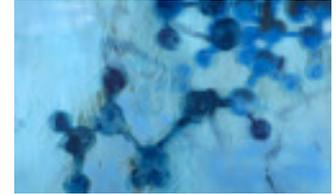
CCK [35, 36]

Angiotensins [38]



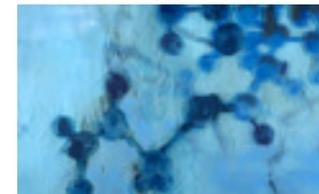
Takahashi and Herzig, *Peptides*, in press

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



Jolene Lau

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Contributors to Peptide Database

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University of Lille

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