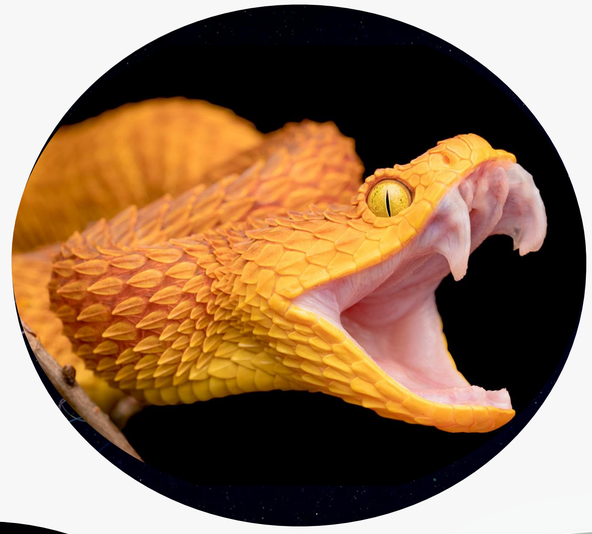
Conotoxins: therapeutic potentials & applications from the sea

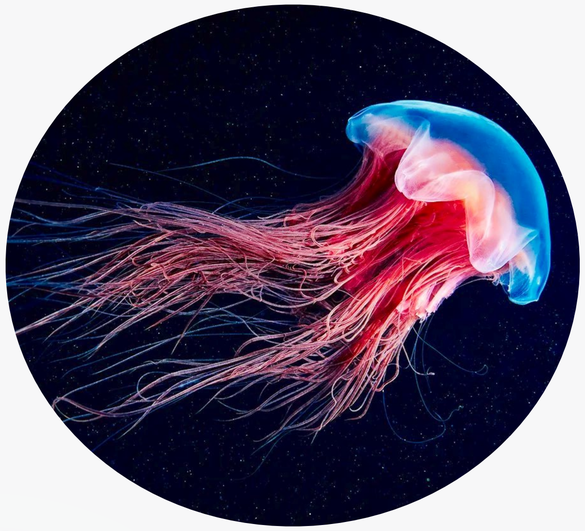
Danielle Morgan

Group Meeting Literature Talk

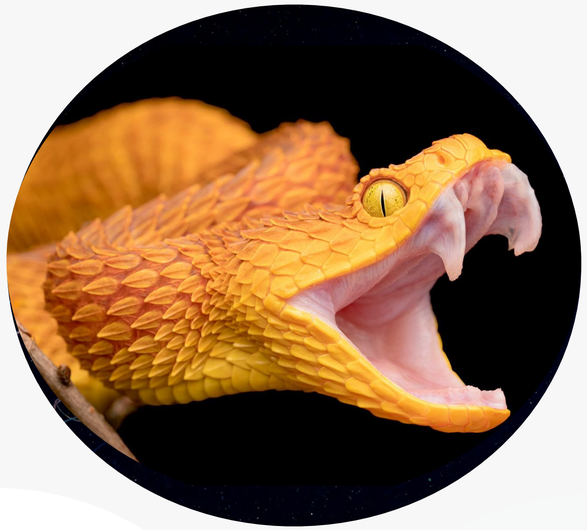
May 23rd, 2024

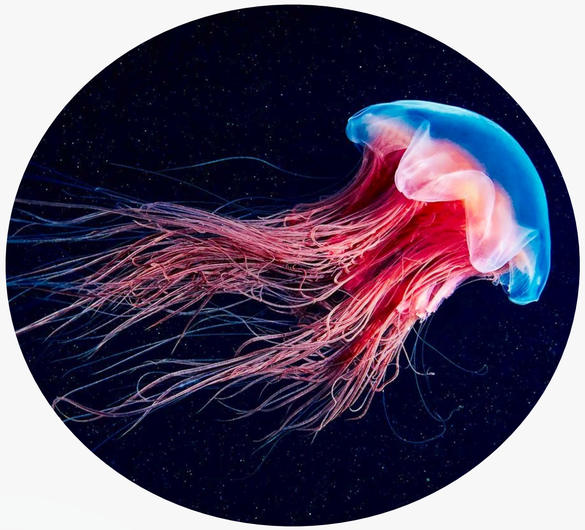
Venomous Species



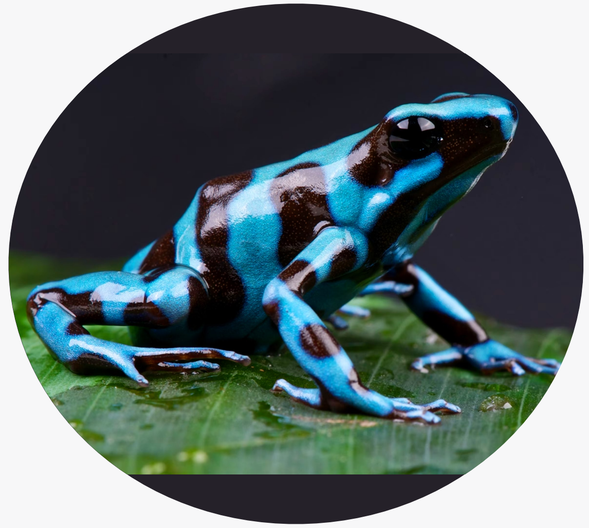


Venomous Species

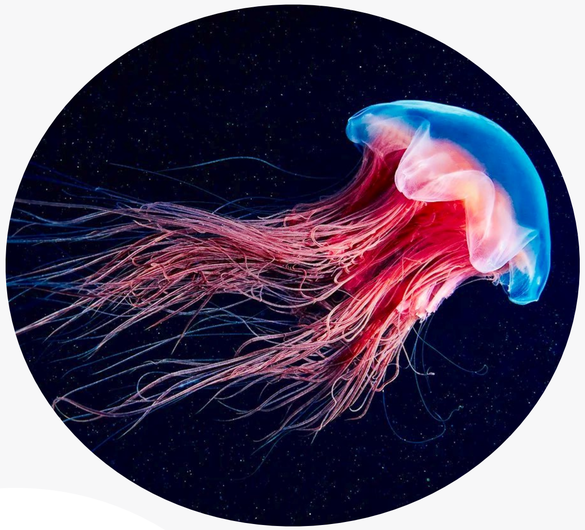




venoms contain
~100-500 **biologically active** compounds

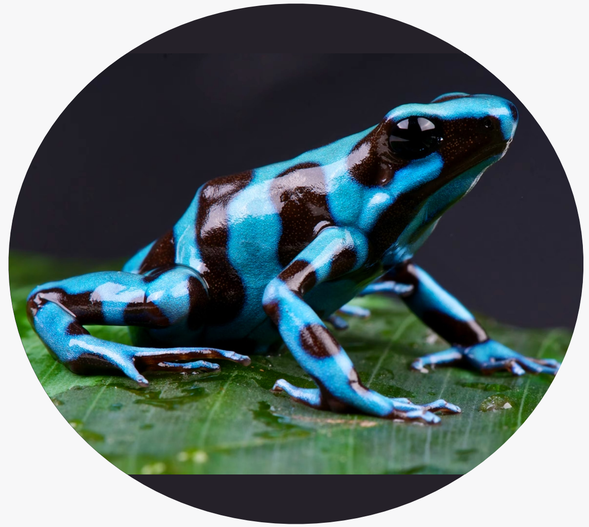


Venomous Species

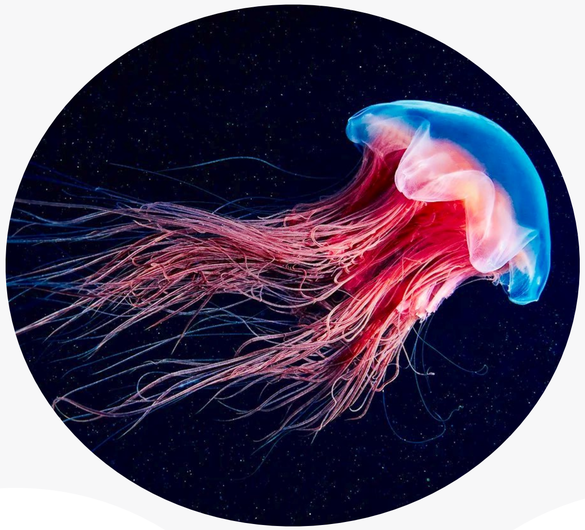


venoms contain ~100-500 **biologically active** compounds

~10-50 million natural compounds for **drug discovery**



Venomous Species



venoms contain ~100-500 **biologically active** compounds

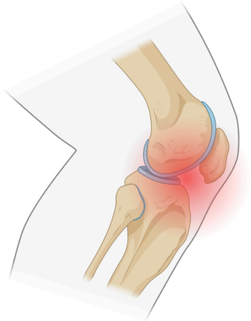
~10-50 million natural compounds for **drug discovery**

< 0.01% compounds identified and characterized

A Brief History of Medicinal Use of Venom…

20th Century

scorpion venom



arthritic joints

mumps

wounds

20th Century

John Vane

late 1960s - understanding the mechanism of action of **Aspirin**

Nobel prize in Physiology or Medicine in **1982**

John Vane

Sérgio Ferreira

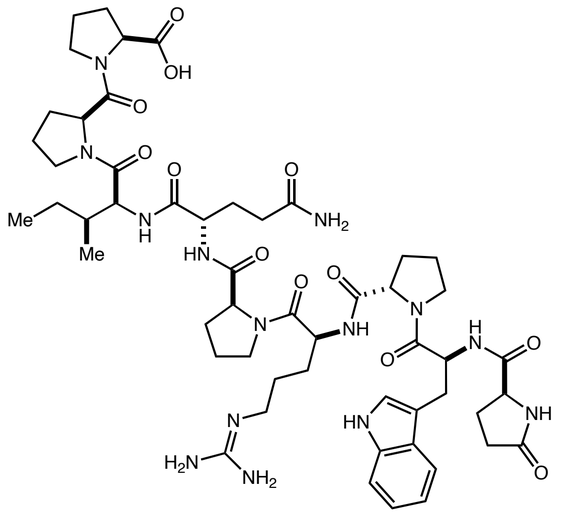
early 1970s - studied heart failure & high blood pressure at the Royal College of Surgeons, London

Brazilian snake, ***Bothrops Jararaca***

20th Century

John Vane

Sérgio Ferreira



Teprotide (ACE inhibitor)

lowers blood pressure

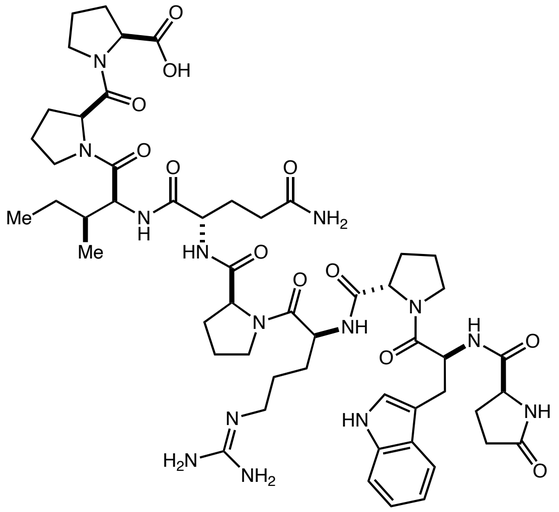
poor oral bioavailability

20th Century

John Vane

Sérgio Ferreira

ER Squibb and Sons



Teprotide (ACE inhibitor)

lowers blood pressure

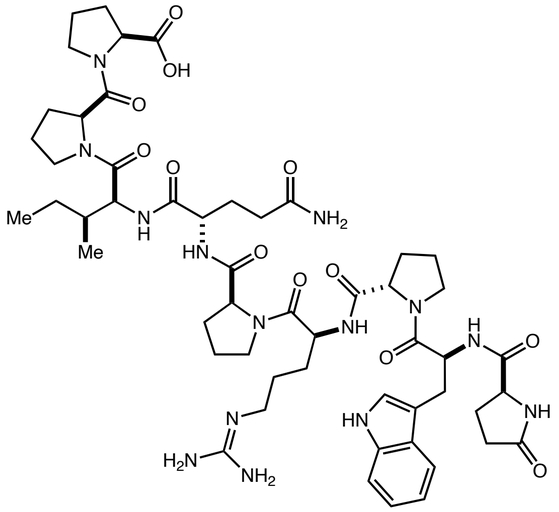
poor oral bioavailability

20th Century

John Vane

Sérgio Ferreira

Bristol Myers Squibb



Teprotide (ACE inhibitor)

lowers blood pressure

poor oral bioavailability

20th Century

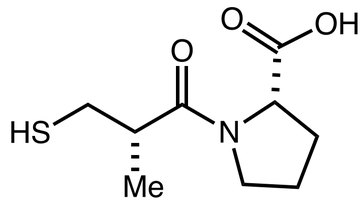
John Vane

Sérgio Ferreira

Bristol Myers Squibb

1970-1973 - studied structure/function of Teprotide

screened 2,000 fragments for ACE inhibitor activity



Captopril

1980 - first venom-derived FDA approved drug

20th Century

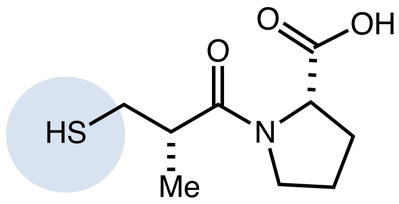
John Vane

Sérgio Ferreira

Bristol Myers Squibb

1970-1973 - studied structure/function of Teprotide

screened 2,000 fragments for ACE inhibitor activity



Captopril

1980 - first venom-derived FDA approved drug

bitter, metallic taste

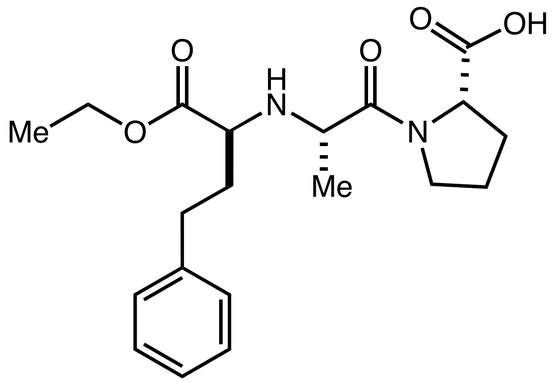
20th Century

John Vane

Sérgio Ferreira

Bristol Myers Squibb

MERCK

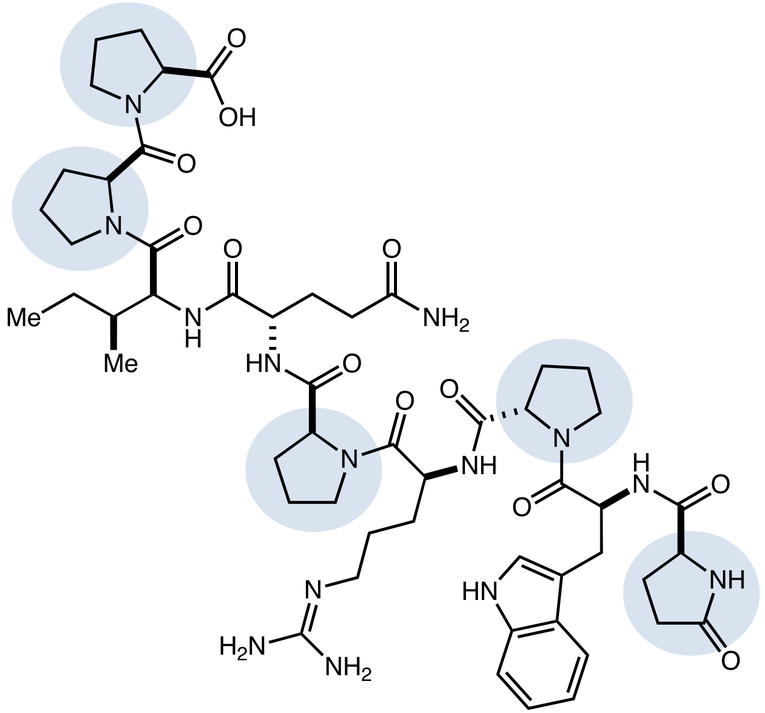


Enalapril

1981 - competitor drug FDA approved

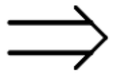
1988 - became Merck's first **billion dollar-selling** drug

20th Century

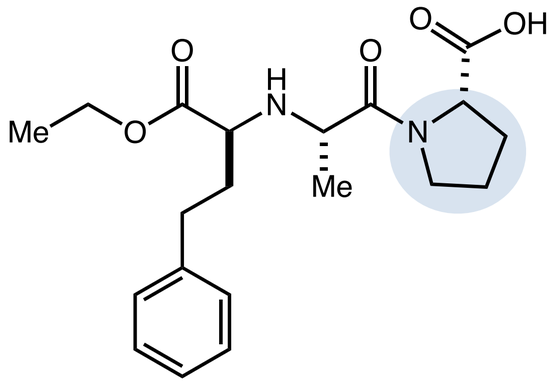


Teprotide (ACE inhibitor)

Brazilian snake, ***Bothrops Jararaca***



MERCK

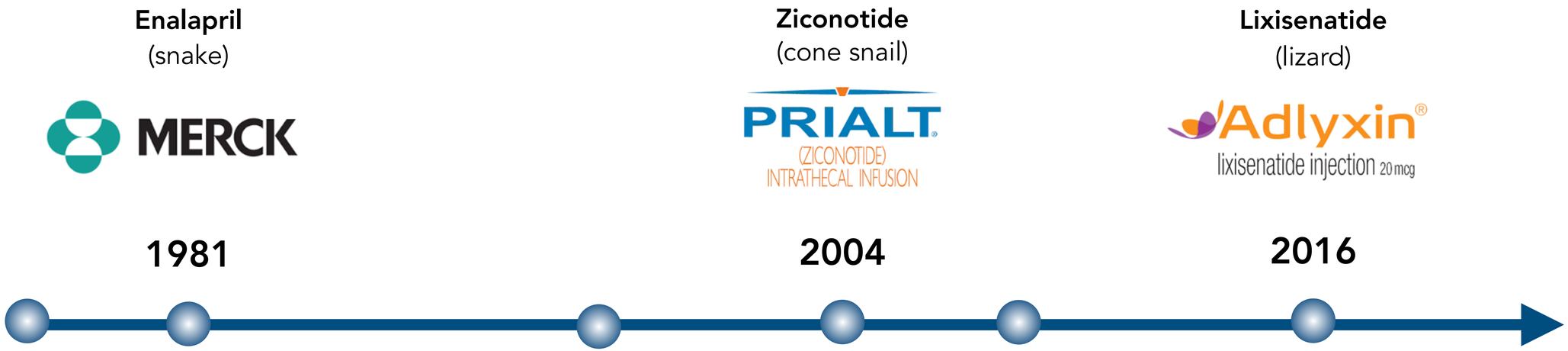


Enalapril

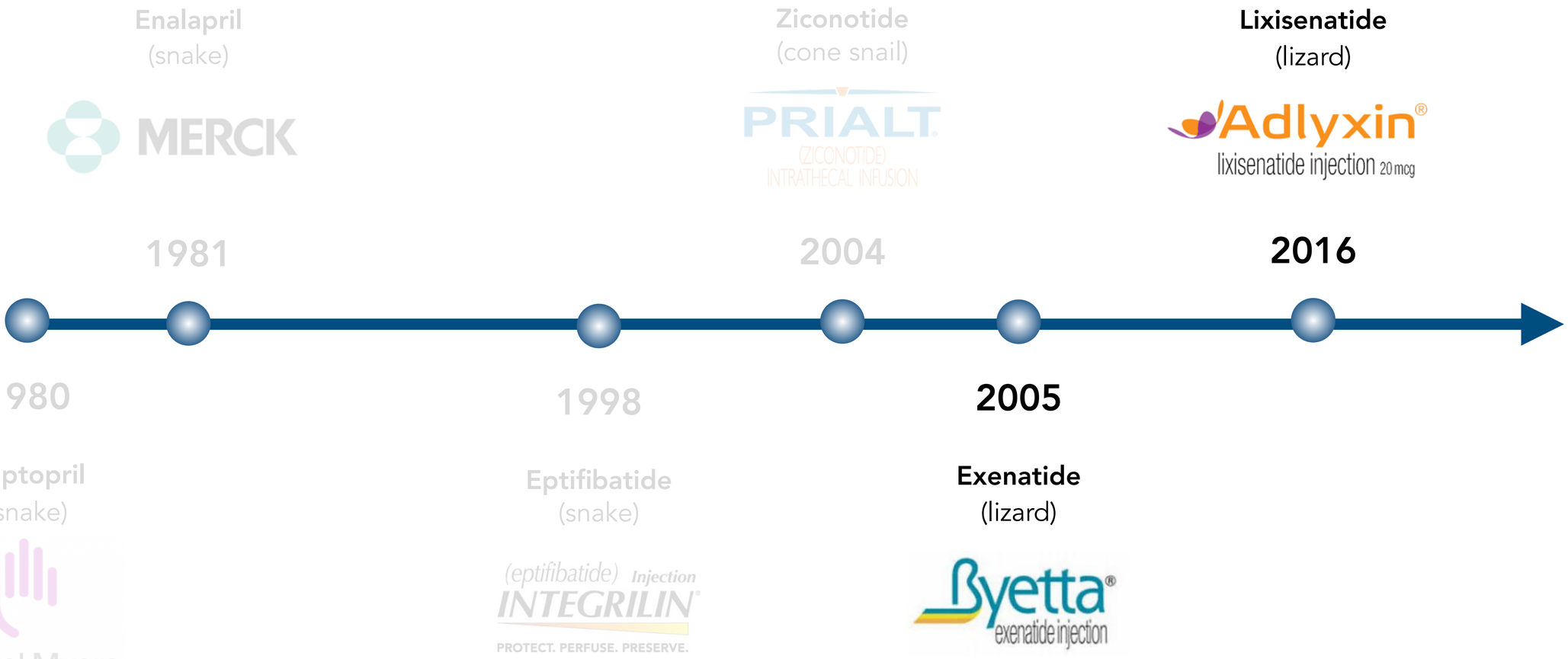
1981 - competitor drug FDA approved

1988 - became Merck's first **billion dollar-selling** drug

FDA Approved Medicines Inspired by Venoms



FDA Approved Medicines Inspired by Venoms



FDA Approved Medicines Inspired by Venoms

1980

Captopril
(snake)

Bristol Myers Squibb™

1981

Enalapril
(snake)

MERCK

1998

Eptifibatide
(snake)

(eptifibatide) Injection
INTEGRILIN®
PROTECT. PERFUSE. PRESERVE.

2004

Ziconotide
(cone snail)

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

2005

Exenatide
(lizard)

Byetta®
exenatide injection

GLP-1 agonist

2016

GLP-1 agonist

Lixisenatide
(lizard)

Adlyxin®
lixisenatide injection 20 mcg

2017

Semaglutide

OZEMPIC®
semaglutide injection 0.5mg, 1mg, 2mg

novo nordisk®

GLP-1 agonist

FDA Approved Medicines Inspired by Venoms

2024

***$16.1 billion** total sales*

(66% in U.S.)

1980

Captopril
(snake)

Bristol Myers Squibb™

1981

Enalapril
(snake)

MERCK

1998

Eptifibatide
(snake)

(eptifibatide) Injection
INTEGRILIN®
PROTECT. PERFUSE. PRESERVE.

2004

Ziconotide
(cone snail)

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

2005

Exenatide
(lizard)

Byetta®
exenatide injection

GLP-1 agonist

2017

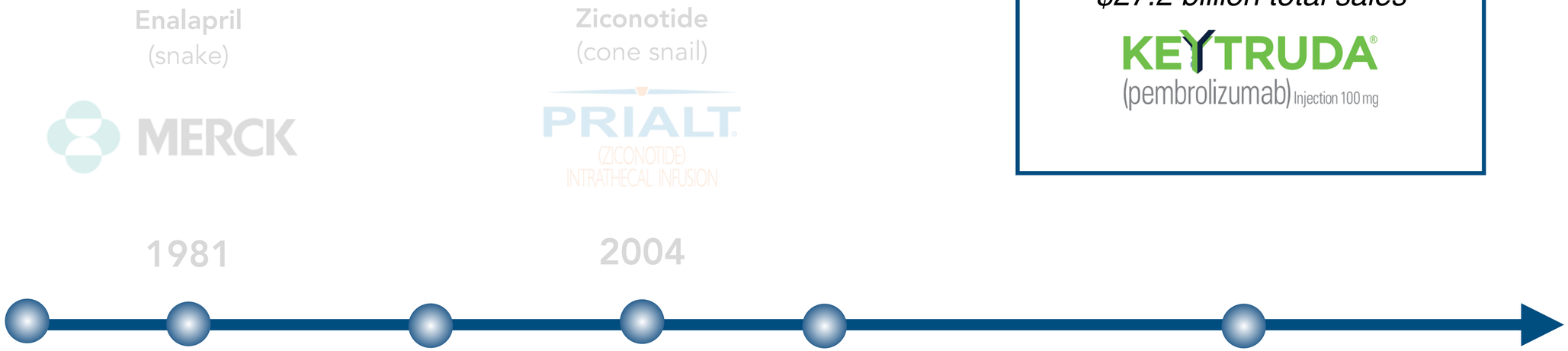
Semaglutide

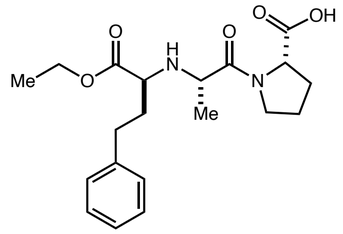
OZEMPIC®
semaglutide injection 0.5mg, 1mg, 2mg

novo nordisk®

GLP-1 agonist

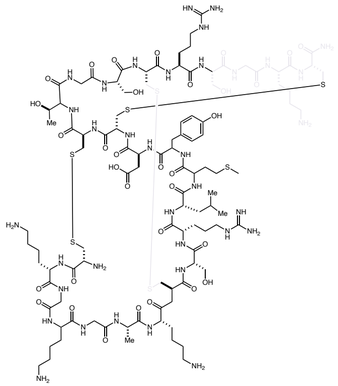
FDA Approved Medicines Inspired by Venoms





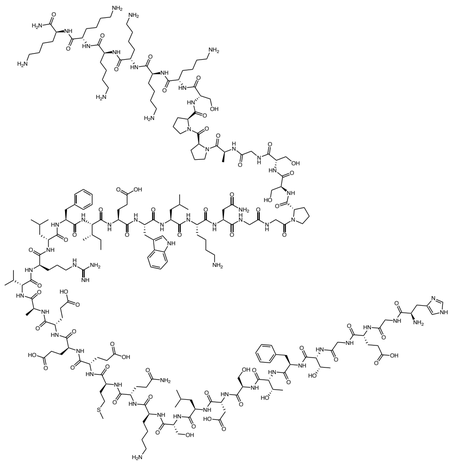
Enalapril
(snake)

1981



Ziconot**ide**
(cone snail)

2004

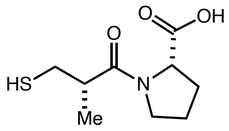


Lixisena**tide**
(lizard)

2016

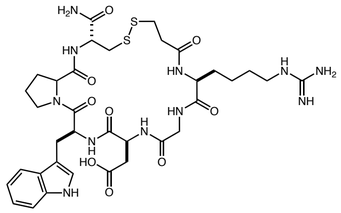
1980

Captopril
(snake)



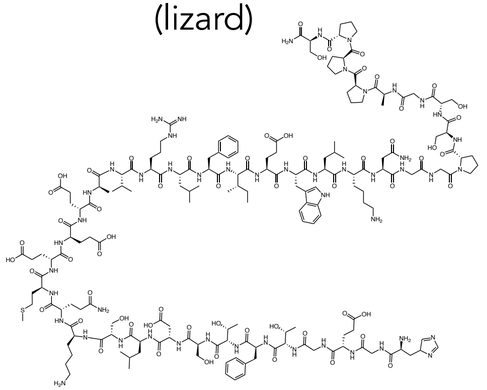
1998

Eptifiba**tide**
(snake)



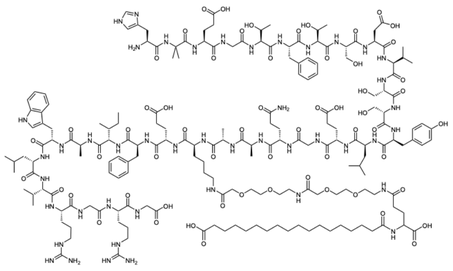
2005

Exena**tide**
(lizard)



2017

Semaglu**tide**
(lizard)



Enalapril

Lixisenatide

key takeaways

1. compounds found in venoms have huge potential in ***drug discovery***

2. ***peptides*** *within venoms inform drug development*

1980

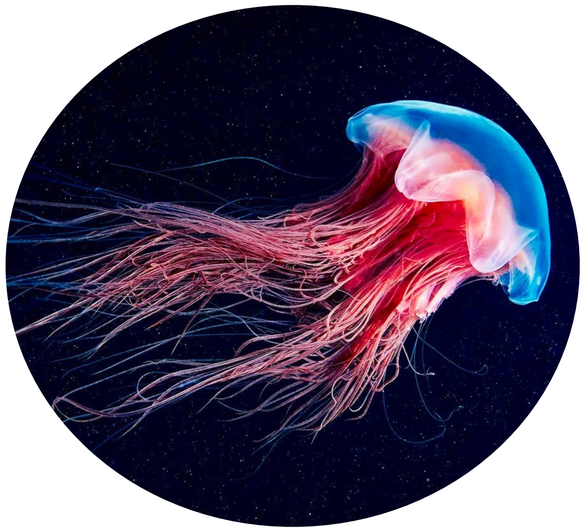
Captopril
(snake)

(snake)

(lizard)

7

utide
(lizard)



cone snail

cone snail

Part I

Introduction

cone snail venom & hunting strategies

venom diversity & nomenclature

Part II

Case study: *Ziconotide*

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

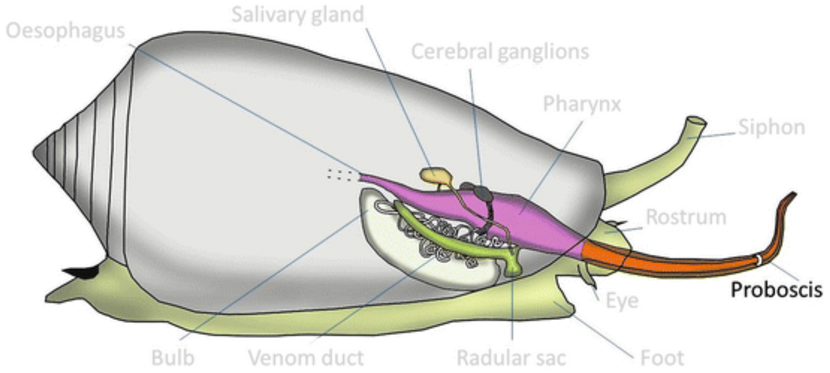
chronic pain (FDA approved)

Part III

Outlook & Future Directions

Cone Snails

Cone Snails



beautiful shells (camoflage)

proboscis (harpoon)

Cone Snails

Conus marmoreus

Conus textile

Conus magus

Conus geographus

Conus pergrandis

Conus ermineus

Conus kinoshitai

Conus pulicarius

Conus mustelinus

Cone Snails

Conus marmoreus

aphus

Conus pergrandis

*cone snails all have their own **unique venoms**.…*

Conus ermineus

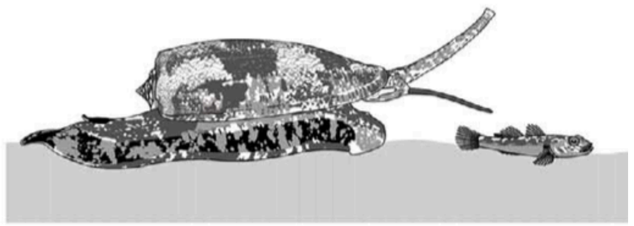
Conus kinoshitai

Conus pulicarius

Conus mustelinus

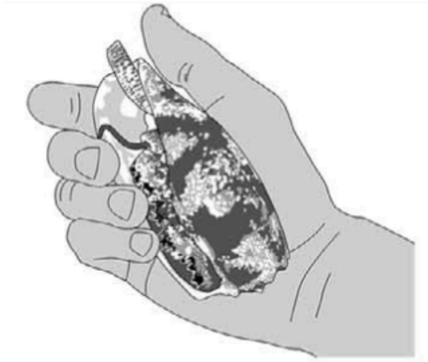
Cone Snail Venoms

predatory venom



Conus geographus
(fish)

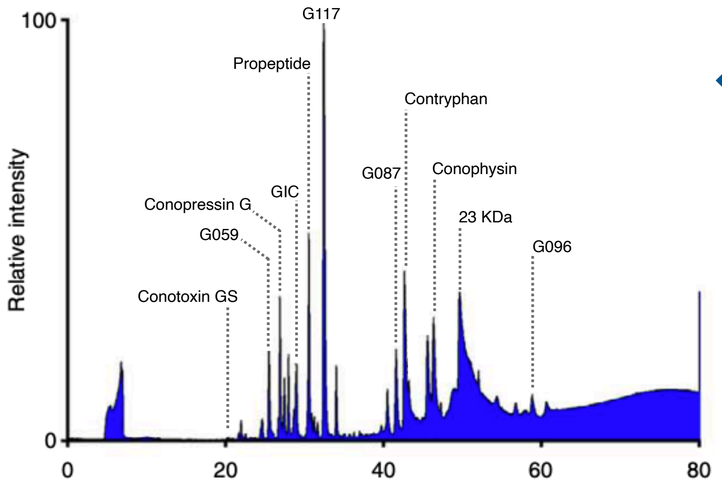
defense venom



S. Dutertre, A.-H. Jin, I. Vetter, B. Hamilton, K. Sunagar, V. Lavergne, V. Dutertre, B. G. Fry, A. Antunes, D. J. Venter, P. F. Alewood and R. J. Lewis, *Nature Comms.* **2014**, 5.

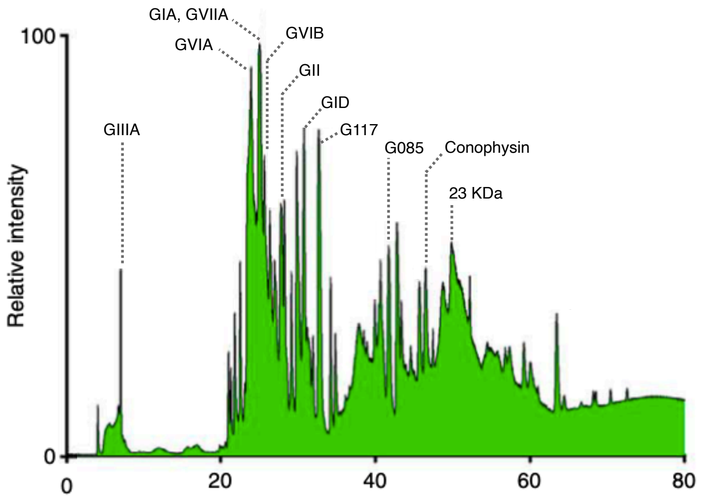
Cone Snail Venoms

predatory venom



Conus geographus
(fish)

defense venom



S. Dutertre, A.-H. Jin, I. Vetter, B. Hamilton, K. Sunagar, V. Lavergne, V. Dutertre, B. G. Fry, A. Antunes, D. J. Venter, P. F. Alewood and R. J. Lewis, *Nature Comms.* **2014**, 5.

Famously Lethal Venoms

Conus geographus
(fish)

Nickname *- “cigarette snail”*

victims only enough time to smoke a cigarette before dying

reality *- one to five hours to kill a healthy human*

Conotoxins: from Fact to Fiction

Hawaii 5-O

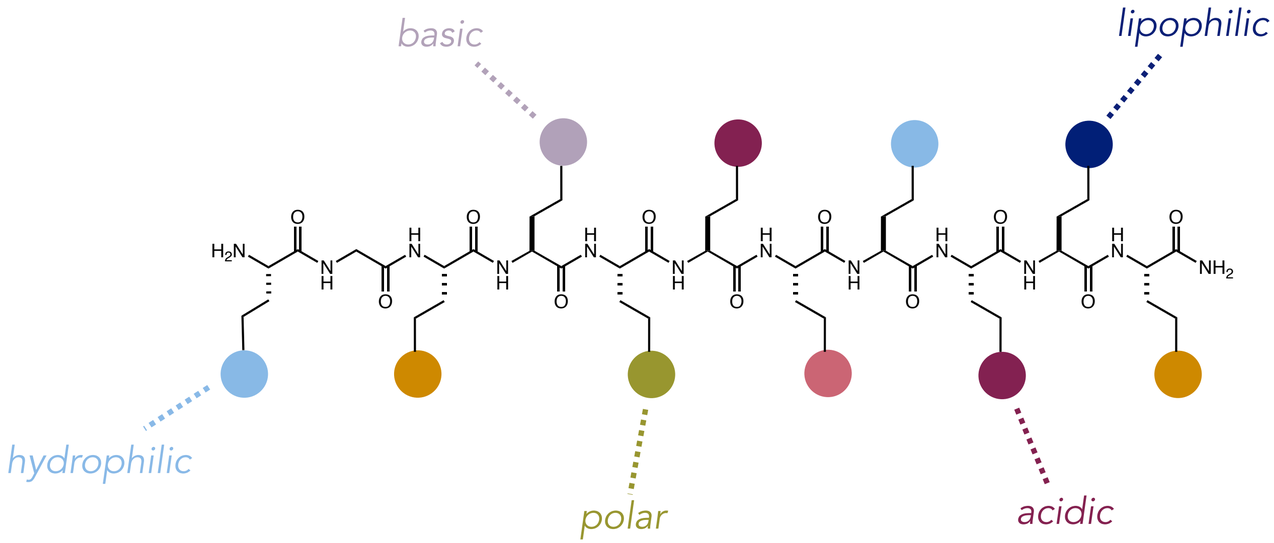
murder weapon in the 1970s television show

Jurassic Park 2

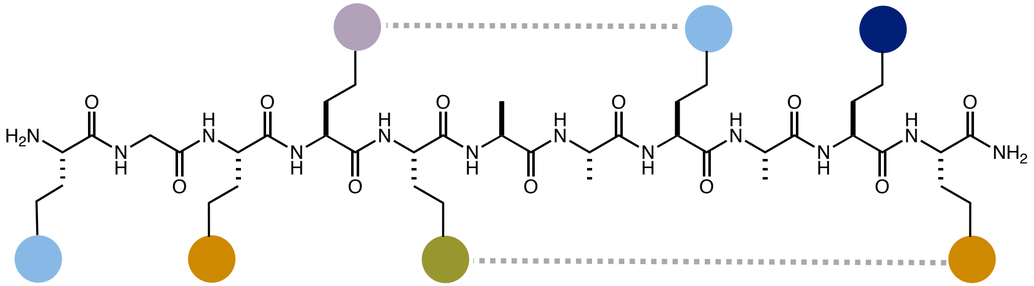
only cone snail venom was powerful enough to take down the T-rex

“most powerful neurotoxin in the world”

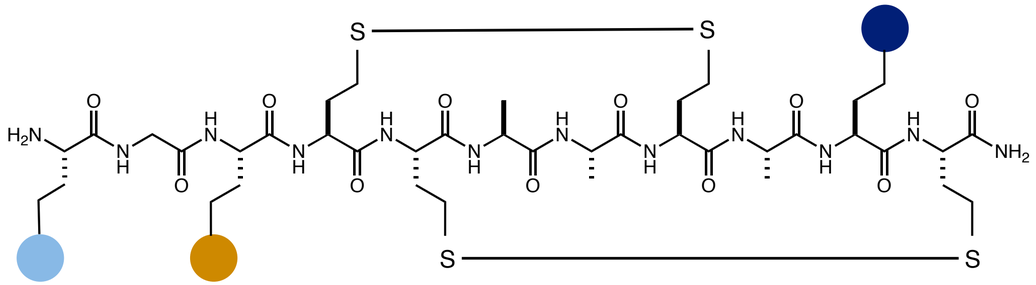
*why are cone snail venoms **medicinally interesting**?*


basic
lipophilic
hydrophilic
polar
acidic

Bioactive Component of Cone Snail Venom

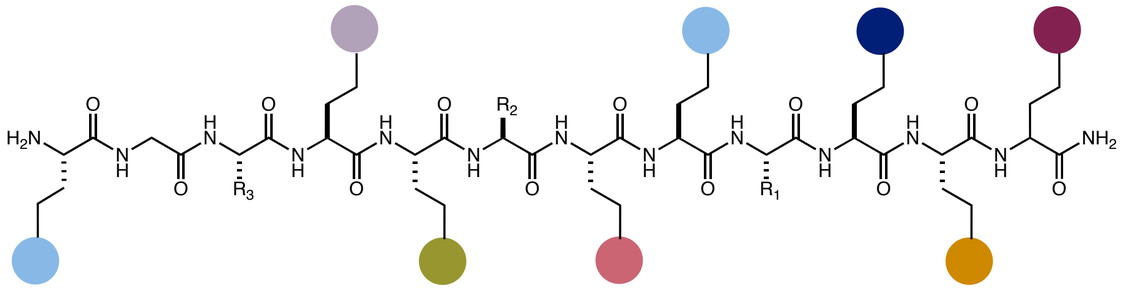


Bioactive Component of Cone Snail Venom

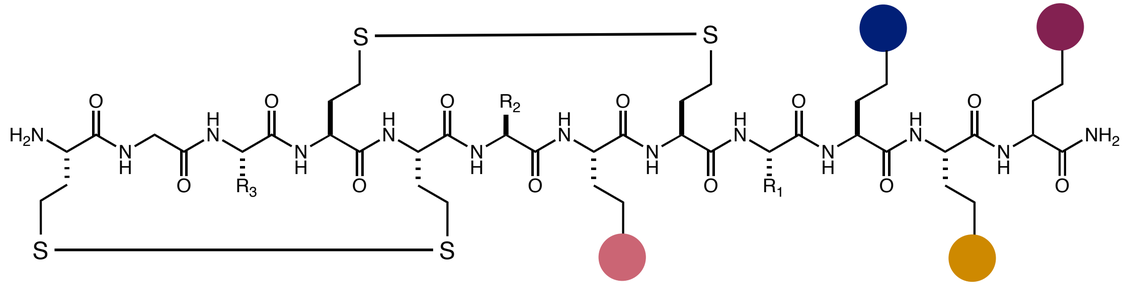


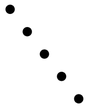
conotoxins

Cysteine Frameworks in Conotoxins



Cysteine Frameworks in Conotoxins



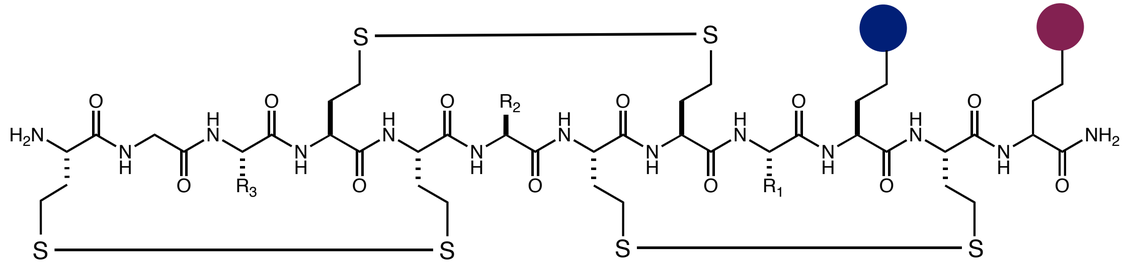


“2-loop” frameworks

1 **2**

CC - - - C - - - C

Cysteine Frameworks in Conotoxins



“3-loop” frameworks

1 2 3

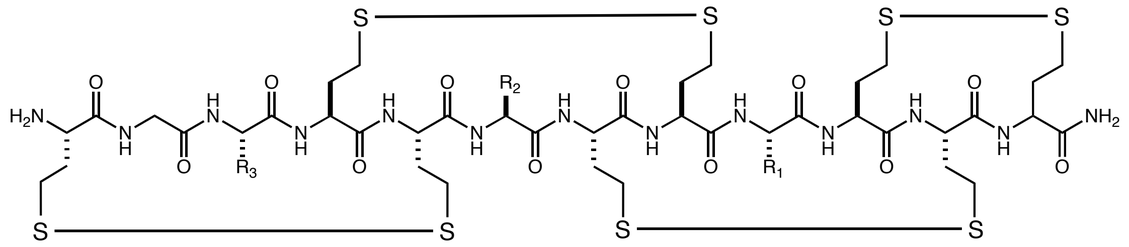
CC - - - C - - - C - - - C

“2-loop” frameworks

1 2

CC - - - C - - - C

Cysteine Frameworks in Conotoxins



“4-loop” frameworks

1 2 3 4

C - - - C - - - CC - - - C - - - C

“3-loop” frameworks

1 2 3

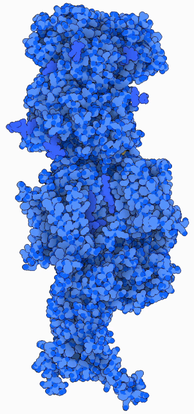
CC - - - C - - - C - - - C

“2-loop” frameworks

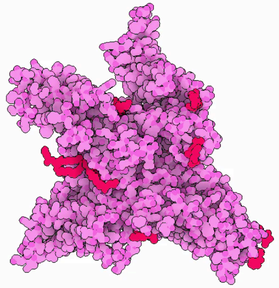
1 2

CC - - - C - - - C

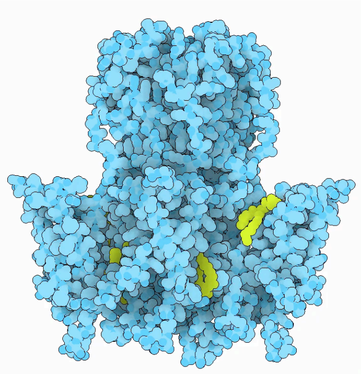
Cysteine Frameworks in Conotoxins



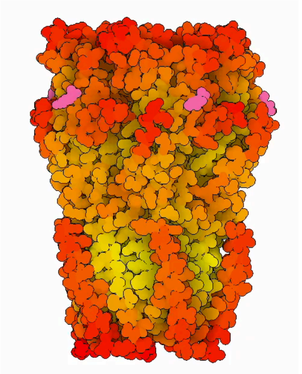
Ca channels



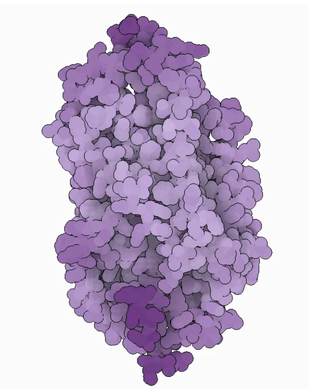
Na channels



K channels



nicotinic acetylcholine receptor (nAChR)



Norepinephrine Transporter (NE)

“4-loop” frameworks

```
 1     2       3     4
C - - - C - - - CC - - - C - - - C
```

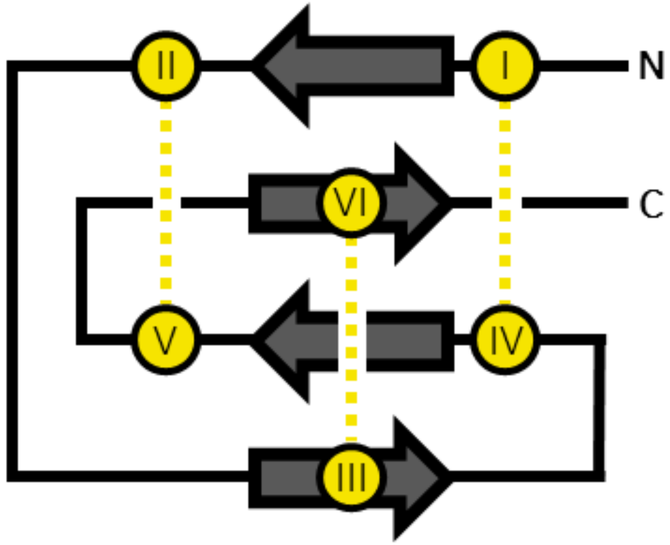
“3-loop” frameworks

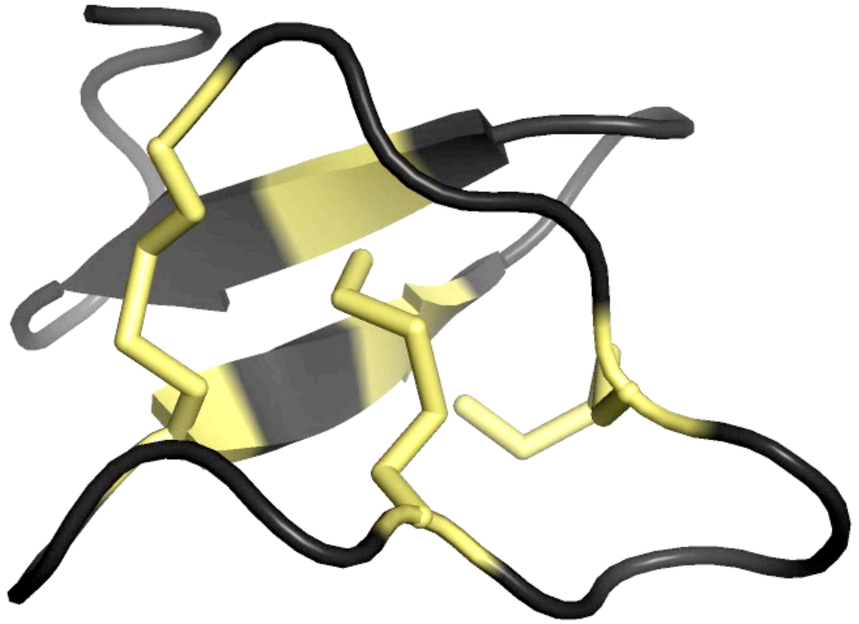
```
 1     2       3
CC - - - C - - - C - - - C
```

“2-loop” frameworks

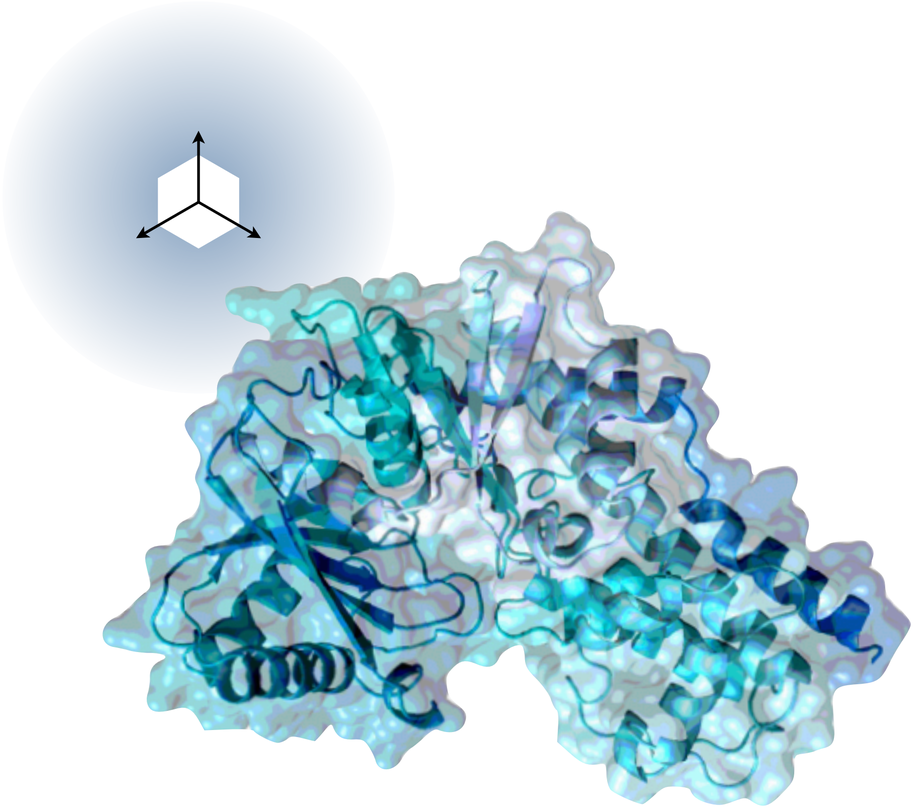
```
 1     2
CC - - - C - - - C
```

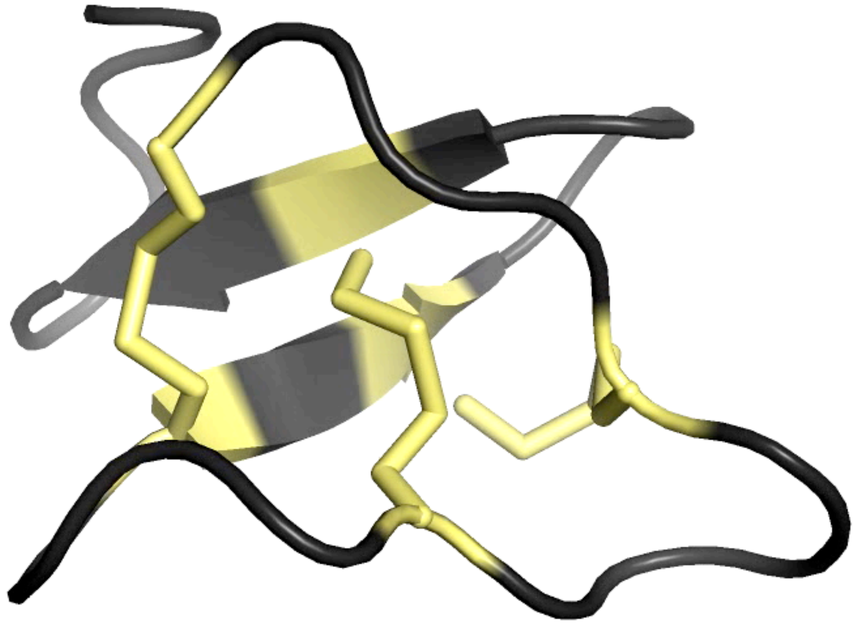
Selectivity from Structural Rigidity





Selectivity from Structural Rigidity





escaped “flatland”…..

allows specific receptor binding

Cone Snail & Conotoxin Diversity

Cone Snail & Conotoxin Diversity

over 700 different cone snails

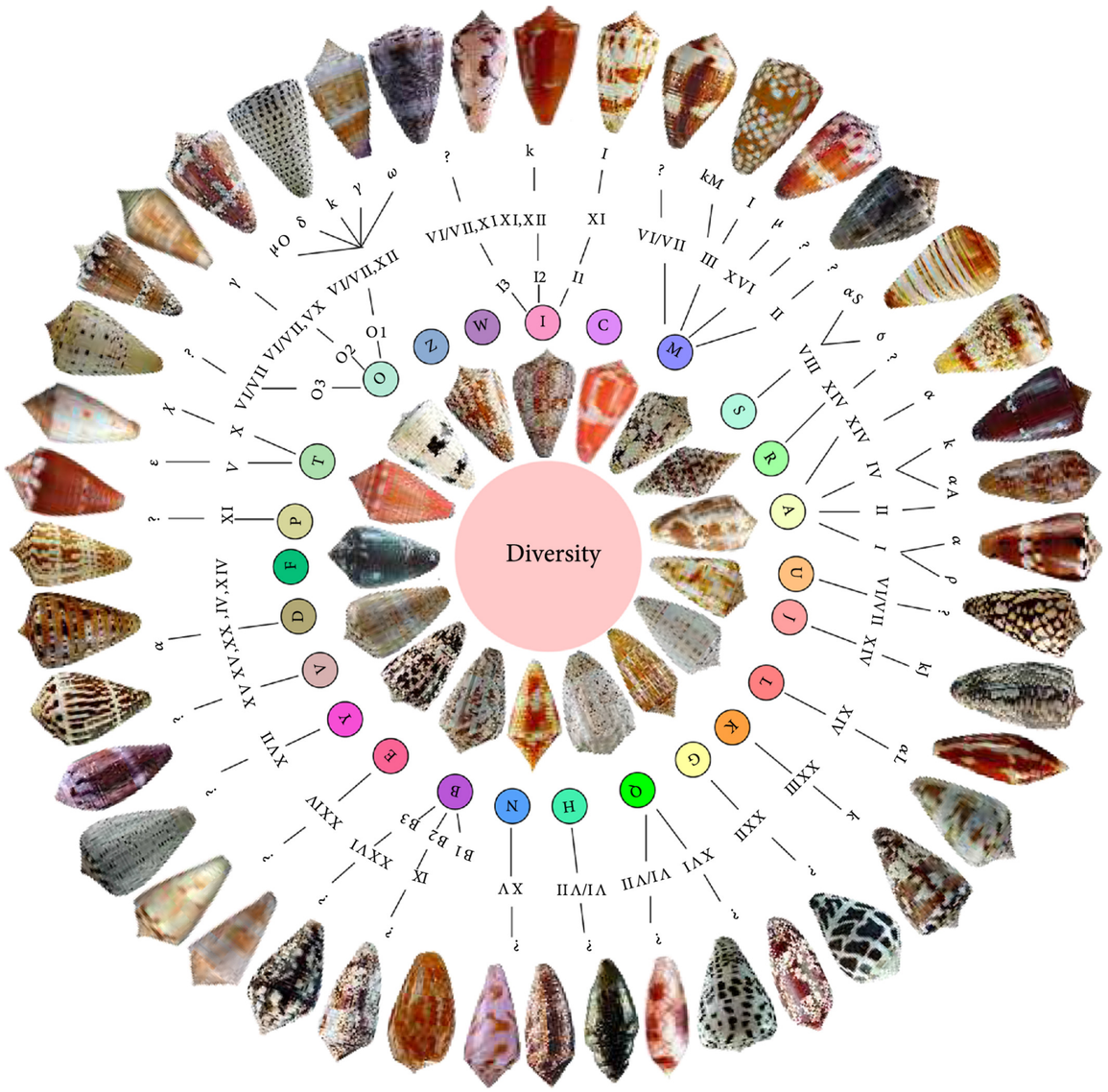
each venom contains around 100 peptides

over 100,000 pharmacologically active peptides

↓

rich source of peptide-based therapeutics

Cone Snail & Conotoxin Diversity



over 700 different cone snails

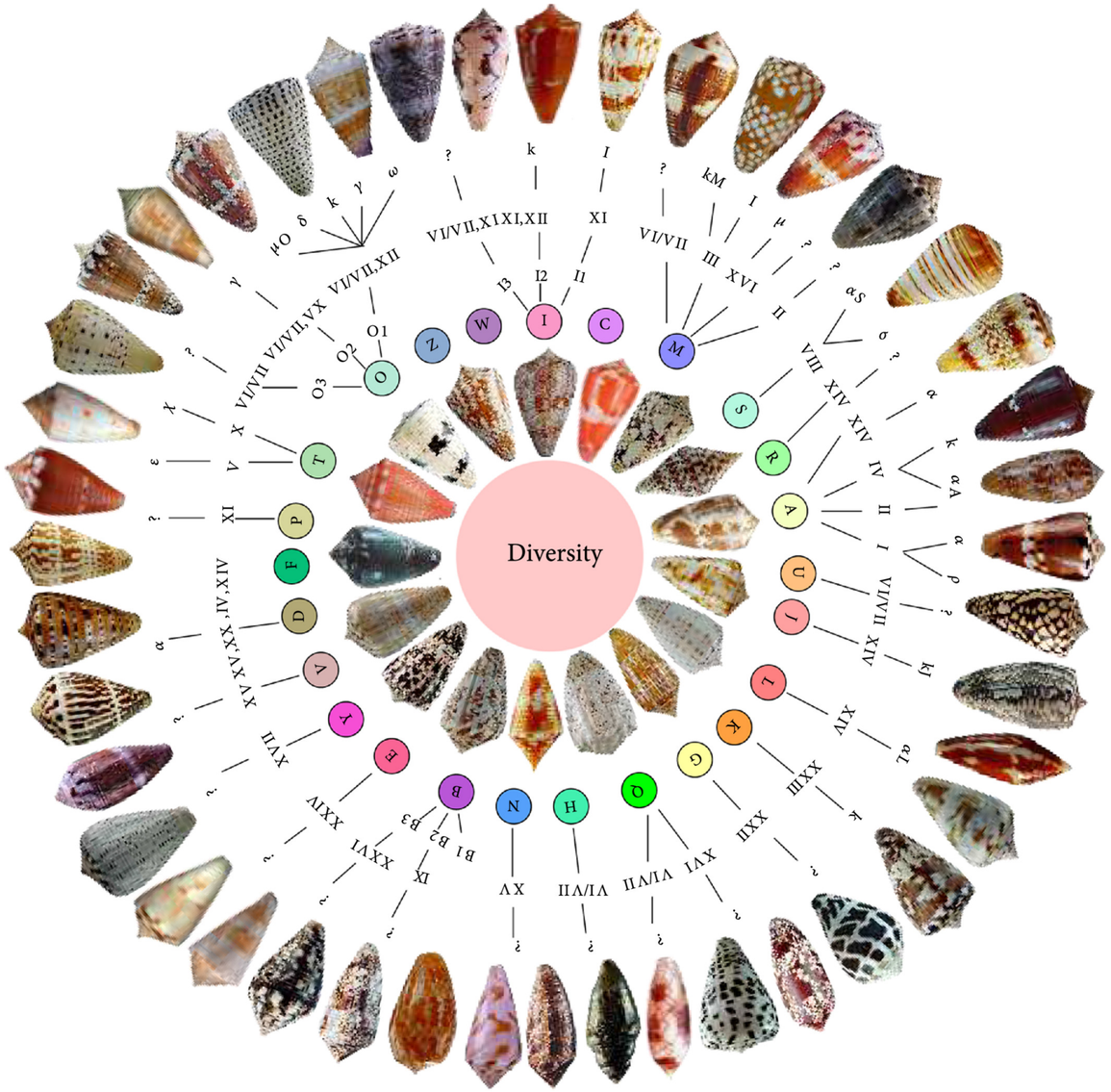
each venom contains around 100 peptides

over 100,000 pharmacologically active peptides

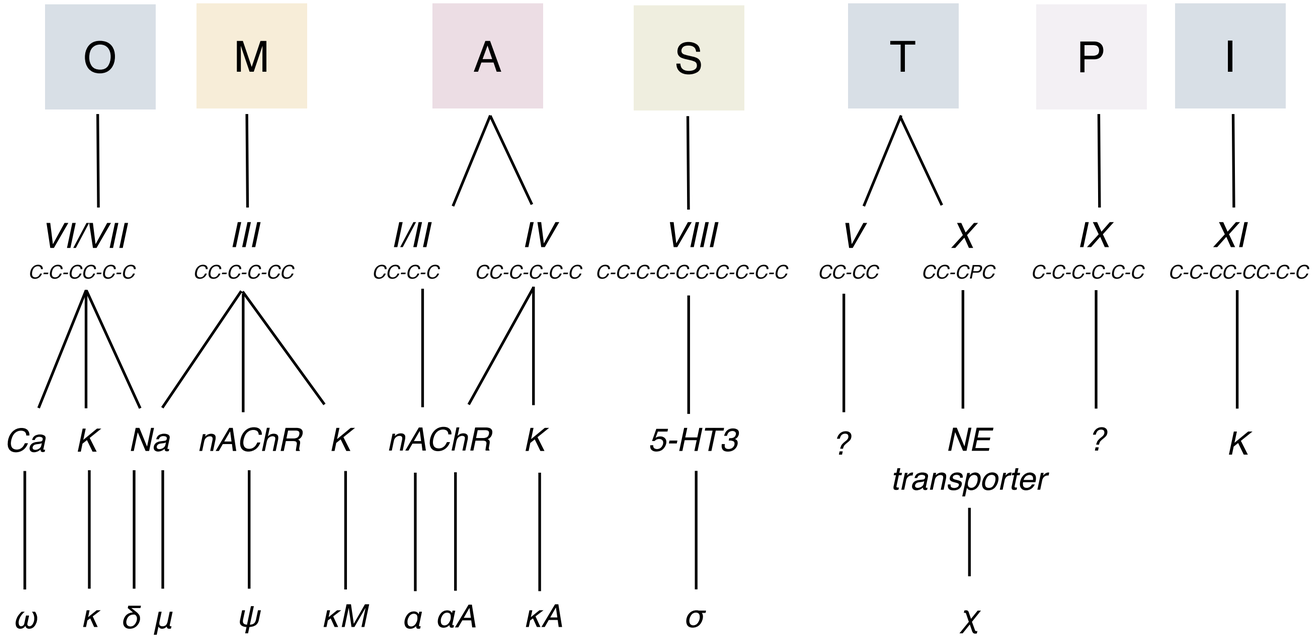
↓

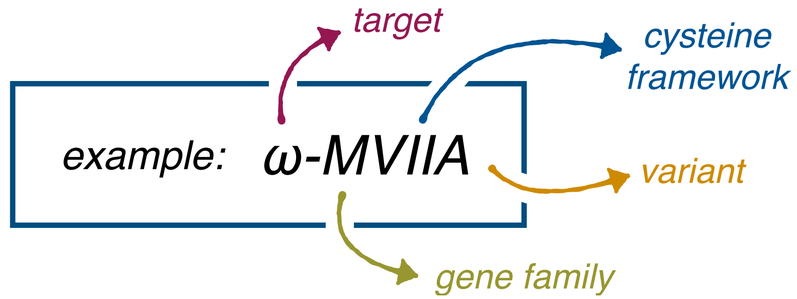
rich source of peptide-based therapeutics

Conotoxin Nomenclature



Conotoxins - disulfide rich



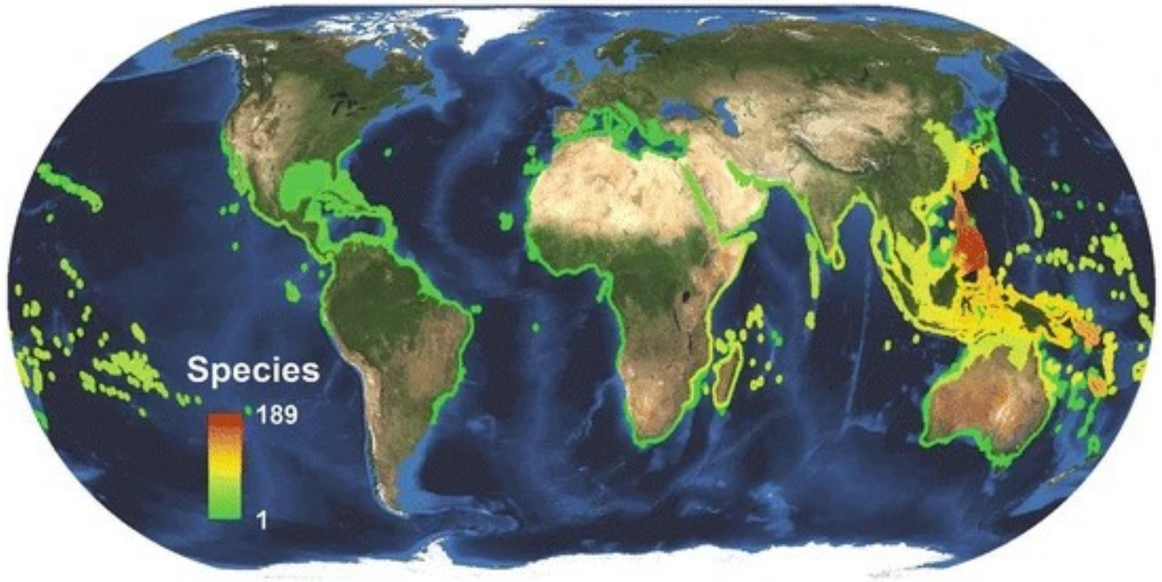


Founding Father of Conotoxins

Prof. Baldomero Olivera

***born 1941** - Philippines*

"hot spots" for cone snails

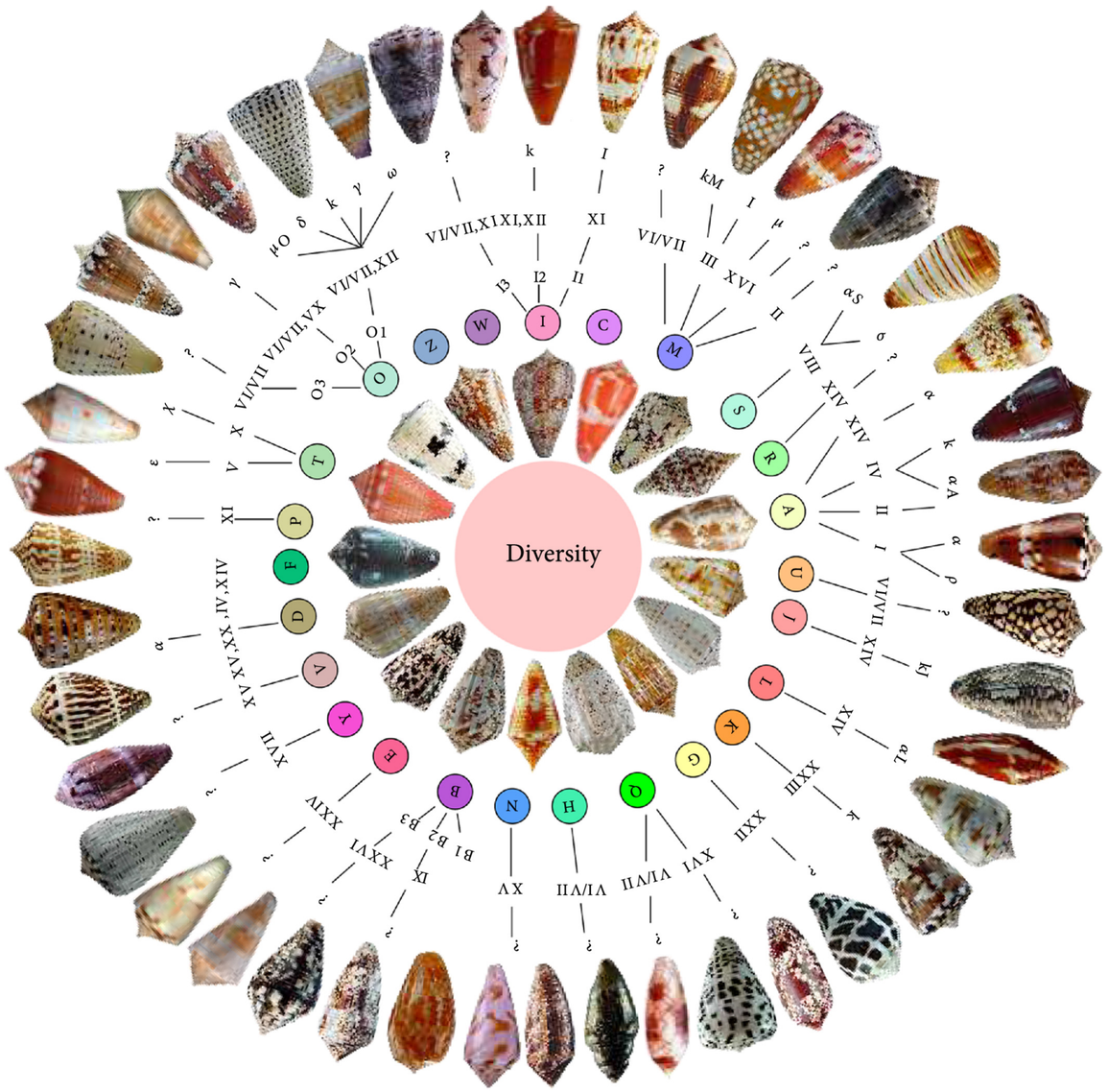


PhD at Caltech
1966

PDRA at Stanford
1966-1968

Professor at Utah
1970-present

Founding Father of Conotoxins



Oliviera group

over 2,000 conotoxin publications

1977 - 2024

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

co-founder of ***Ziconotide***

cone snail

Part I

Introduction

cone snail venom & hunting strategies

venom diversity & nomenclature

Part II

Case study: *Ziconotide*

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

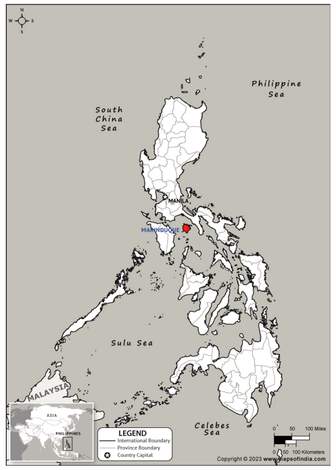
chronic pain (FDA approved)

Part III

Outlook & Future Directions

Medicinal Discovery of Conotoxins

Prof. Baldomero Olivera
“founding father of Conotoxins”



Marinduque, Philippines

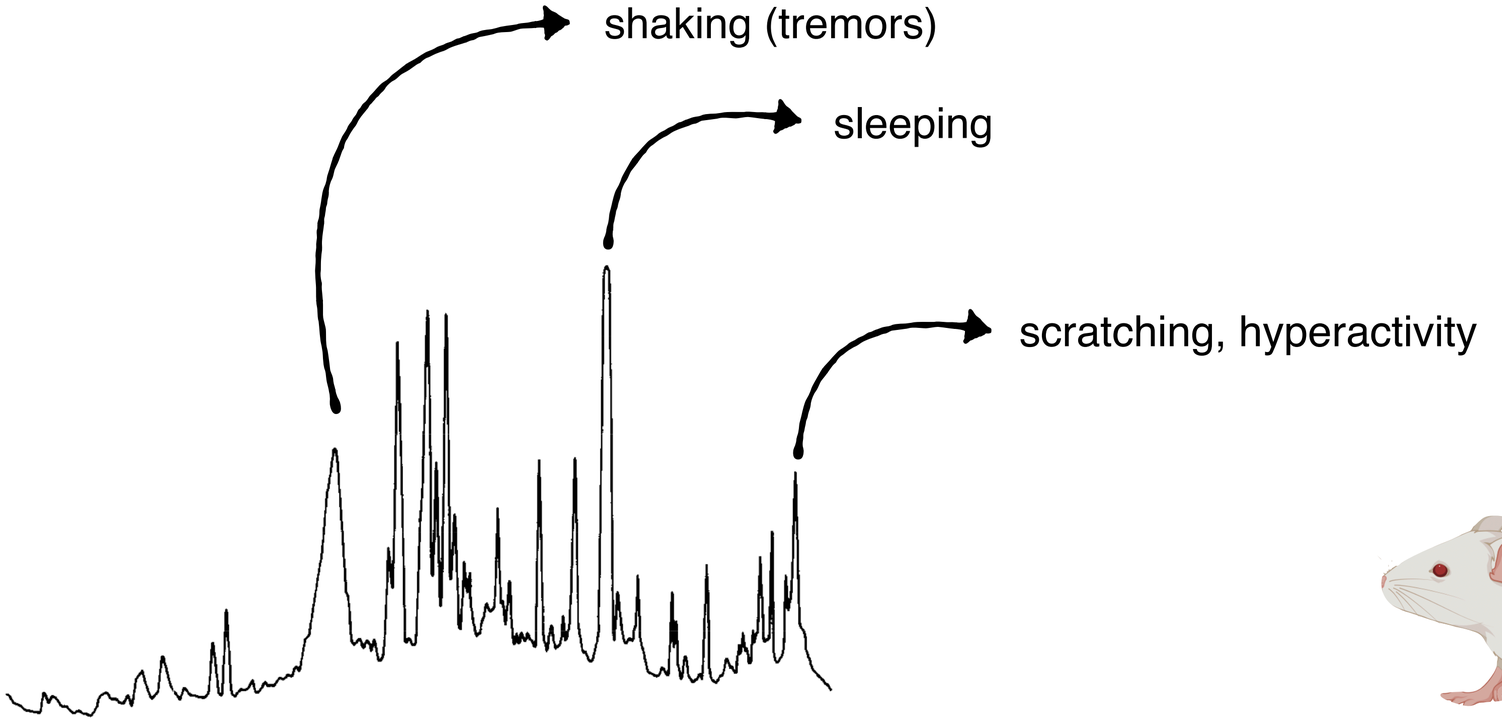
1977 - divers collect cone snails from around the island of Marinduque

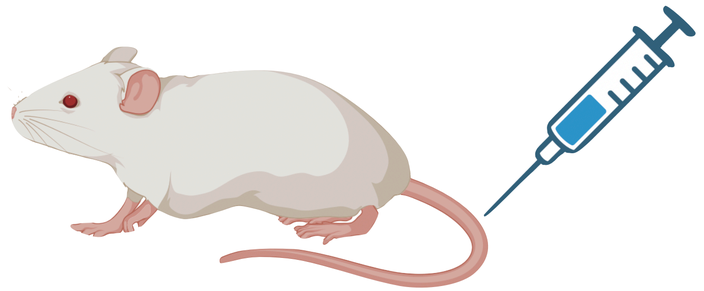
disect venom ducts & isolate proteins (294 mg from 200 snails)

Conus geographus
“cigarette snail”

Conus magnus

Profiling Cone Snail Venoms





observe effects in mice

Profiling Cone Snail Venoms

Conus geographus

1978 - 1985 - 8 publications

L. J. Cruz, W. R. Gray, **B. M. Olivera**, *Arch. Biochem. Biophys.* **1978** *190*, 539.

W. R. Gray, A. Luque, **B. M. Olivera**, J. Barrett, L. J. Cruz, *J. Biol. Chem.* **1981**, *256*, 4734

C. Clark, **B. M. Olivera**, L. J. Cruz, *Toxicon.* **1981,** *19*, 691.

W. R. Gray et al., *Biochemistry* **1984,** *23*, 2796.

B. M. Olivera, J. M. McIntosh, L. J. Cruz, F. A. Luque, W. R. Gray *Biochemistry* **1984**, *23*, 5087.

B. M. Olivera *et al.*, *Toxicon.* **1985**, *23*, 277.

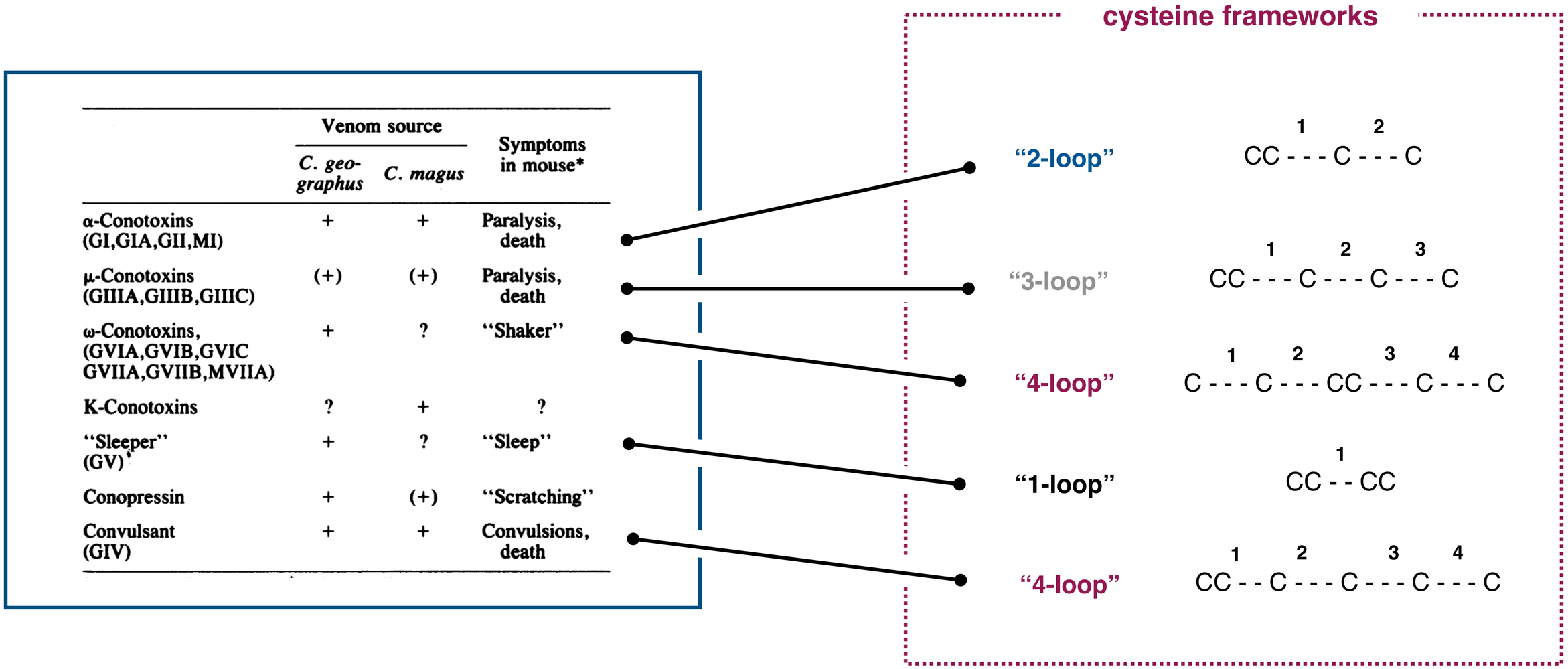
J. M. McIntosh, **B. M. Olivera**, L. J. Cruz, W. R. Gray, *J. Biol. Chem.* **1985,** *259*, 14343.

L. J. Cruz *et al.*, *J. Biol. Chem.* **1985**, *260*, 9280.

Conus magnus

Profiling Cone Snail Venoms

	Venom source		Symptoms in mouse*
	C. geographus	*C. magus*	
α-Conotoxins (GI,GIA,GII,MI)	+	+	Paralysis, death
μ-Conotoxins (GIIIA,GIIIB,GIIIC)	(+)	(+)	Paralysis, death
ω-Conotoxins, (GVIA,GVIB,GVIC GVIIA,GVIIB,MVIIA)	+	?	"Shaker"
K-Conotoxins	?	+	?
"Sleeper" (GV)	+	?	"Sleep"
Conopressin	+	(+)	"Scratching"
Convulsant (GIV)	+	+	Convulsions, death



B. M. Olivera, W. R. Gray, R. Zeikus, J. M. McIntosh, J. Varga, V. De Santos and L. J. Cruz, *Science* **1985**, *230*, 1338-1343.

Profiling Cone Snail Venoms

	Venom source		Symptoms in mouse*
	C. geographus	*C. magus*	
α-Conotoxins (GI,GIA,GII,MI)	+	+	Paralysis, death
μ-Conotoxins (GIIIA,GIIIB,GIIIC)	(+)	(+)	Paralysis, death
ω-Conotoxins, (GVIA,GVIB,GVIC GVIIA,GVIIB,MVIIA)	**+**	**?**	**"Shaker"**
K-Conotoxins	?	+	?
"Sleeper" (GV)	+	?	"Sleep"
Conopressin	+	(+)	"Scratching"
Convulsant (GIV)	+	+	Convulsions, death

cysteine frameworks

"2-loop"	1 2 CC - - - C - - - C
"3-loop"	1 2 3 CC - - - C - - - C - - - C
"4-loop"	**1 2 3 4** **C - - - C - - - CC - - - C - - - C**
"1-loop"	1 CC - - CC
"4-loop"	1 2 3 4 CC - - C - - - C - - - C - - - C

B. M. Olivera, W. R. Gray, R. Zeikus, J. M. McIntosh, J. Varga, V. De Santos and L. J. Cruz, *Science* **1985**, *230*, 1338-1343.

Profiling Cone Snail Venoms

	Venom source		Symptoms in mouse*
	C. geographus	*C. magus*	
α-Conotoxins (GI,GIA,GII,MI)	+	+	Paralysis, death
μ-Conotoxins (GIIIA,GIIIB,GIIIC)	(+)	(+)	Paralysis, death
ω-Conotoxins, (GVIA,GVIB,GVIC GVIIA,GVIIB,MVIIA)	**+**	**?**	**"Shaker"**
K-Conotoxins	?	+	?
"Sleeper" (GV)	+	?	"Sleep"
Conopressin	+	(+)	"Scratching"
Convulsant (GIV)	+	+	Convulsions, death

Conus geographus

CKSHyGSS**C**SHyTSYN**CC**RGS**C**NHyYTKR**C**

GVIC

Conus magnus

CKGKGAK**C**SRLMYD**CC**TGS**C**RSGK**C**

MVIIA

B. M. Olivera, W. R. Gray, R. Zeikus, J. M. McIntosh, J. Varga, V. De Santos and L. J. Cruz, *Science* **1985**, *230*, 1338-1343.

Profiling Cone Snail Venoms

	Venom source		Symptoms in mouse*
	C. geographus	*C. magus*	
α-Conotoxins (GI,GIA,GII,MI)	+	+	Paralysis, death
μ-Conotoxins (GIIIA,GIIIB,GIIIC)	(+)	(+)	Paralysis, death
ω-Conotoxins, (GVIA,GVIB,GVIC GVIIA,GVIIB,MVIIA)	**+**	**?**	**"Shaker"**
K-Conotoxins	?	+	?
"Sleeper" (GV)	+	?	"Sleep"
Conopressin	+	(+)	"Scratching"
Convulsant (GIV)	+	+	Convulsions, death

Conus geographus

CKSHyGSS**C**SHyTSYN**CC**RGS**C**NHyYTKR**C**

GVIC

Conus magnus

CKGKGAK**C**SRLMYD**CC**TGS**C**RSGK**C**

MVIIA

***same** cysteine framework, **difference** in sequence*

B. M. Olivera, W. R. Gray, R. Zeikus, J. M. McIntosh, J. Varga, V. De Santos and L. J. Cruz, *Science* **1985**, *230*, 1338-1343.

Profiling Cone Snail Venoms

	Venom source		Symptoms in mouse*
	C. geographus	*C. magus*	
α-Conotoxins (GI,GIA,GII,MI)	+	+	Paralysis, death
μ-Conotoxins (GIIIA,GIIIB,GIIIC)	(+)	(+)	Paralysis, death
ω-Conotoxins, (GVIA,GVIB,GVIC GVIIA,GVIIB,MVIIA)	**+**	**?**	**"Shaker"**
K-Conotoxins	?	+	?
"Sleeper" (GV)	+	?	"Sleep"
Conopressin	+	(+)	"Scratching"
Convulsant (GIV)	+	+	Convulsions, death

Conus geographus

CKSHyGSSCSHyTSYNCCRGSCNHyYTKRC

GVIC

Conus magnus

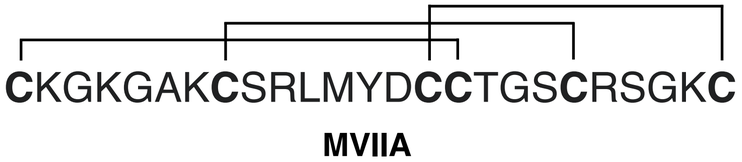
CKGKGAKCSRLMYDCCTGSCRSGKC

MVIIA

2-3 fold more potent

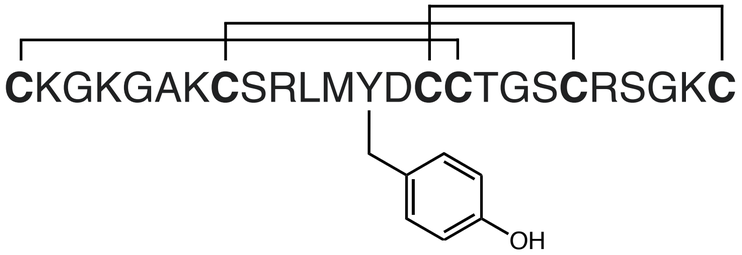
B. M. Olivera, W. R. Gray, R. Zeikus, J. M. McIntosh, J. Varga, V. De Santos and L. J. Cruz, *Science* **1985**, *230*, 1338-1343.

Understanding the Mechanism of “shaker peptides” - MVIIA



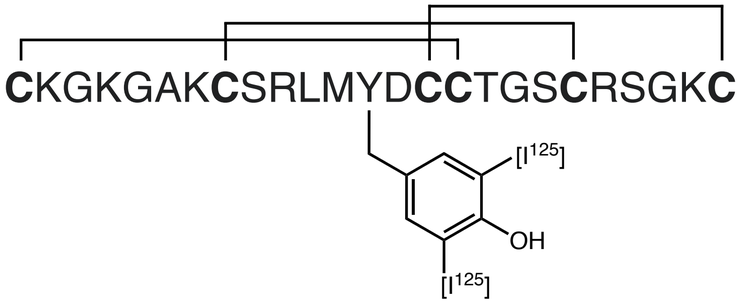
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

Understanding the Mechanism of “shaker peptides” - MVIIA



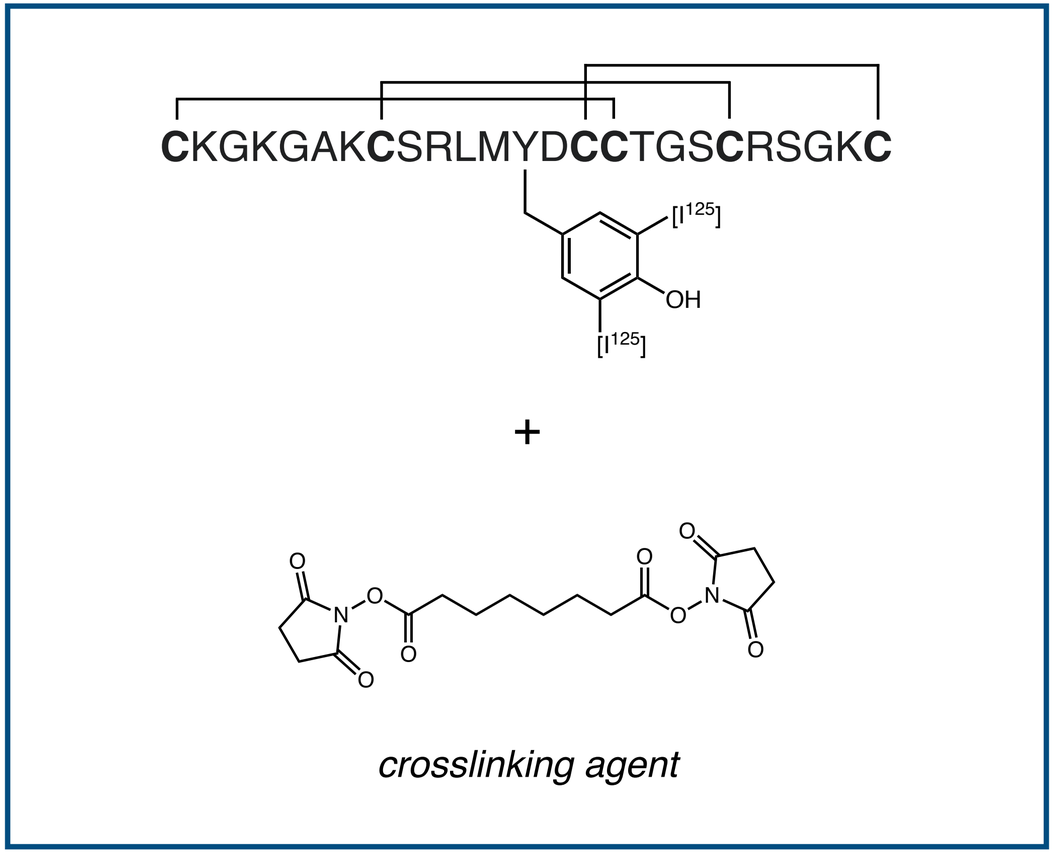
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

Understanding the Mechanism of “shaker peptides” - MVIIA



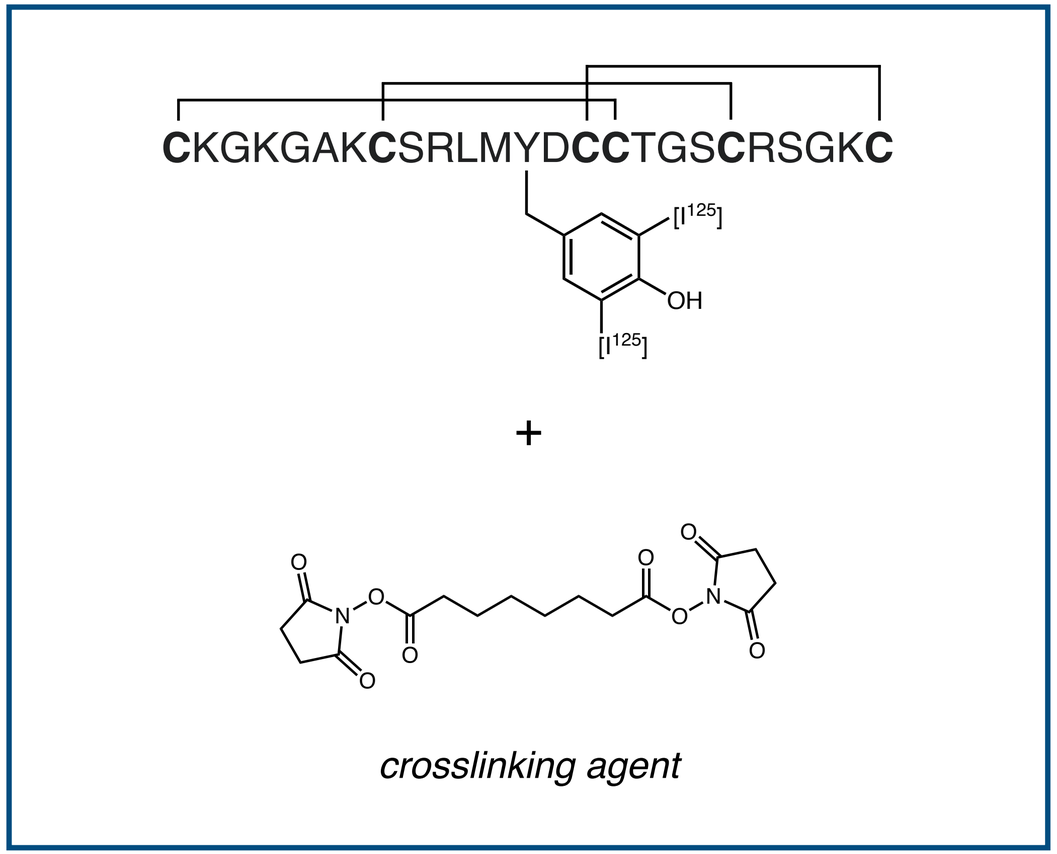
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

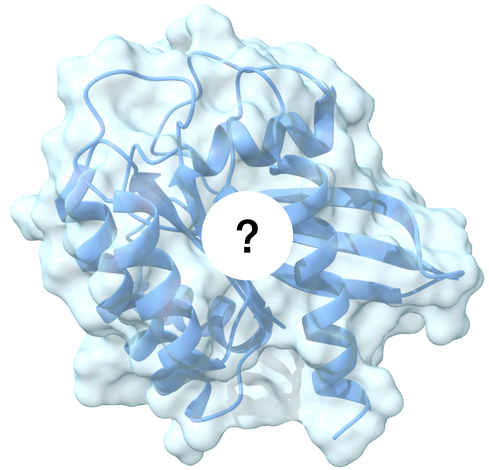
Understanding the Mechanism of “shaker peptides” - MVIIA



L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

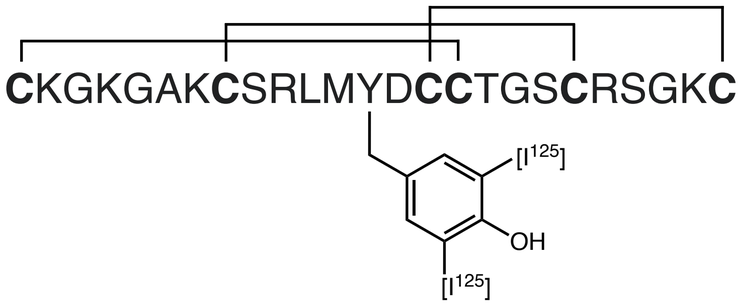
Understanding the Mechanism of “shaker peptides” - MVIIA



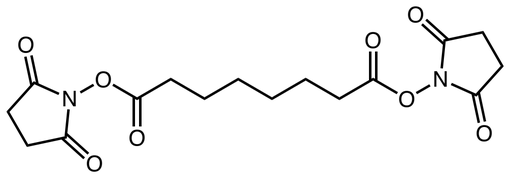


L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

Understanding the Mechanism of “shaker peptides” - MVIIA



+



crosslinking agent

. . . . . .

synaptic plasma membranes (SPM) from rat brain

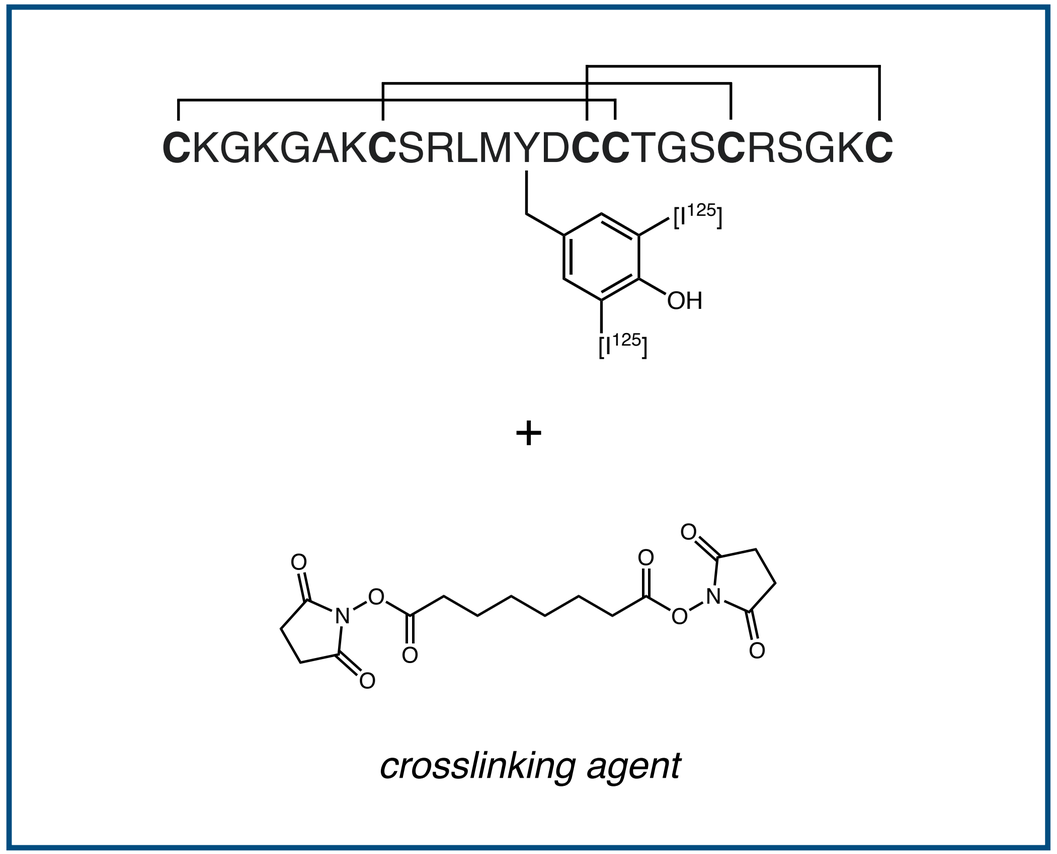
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.

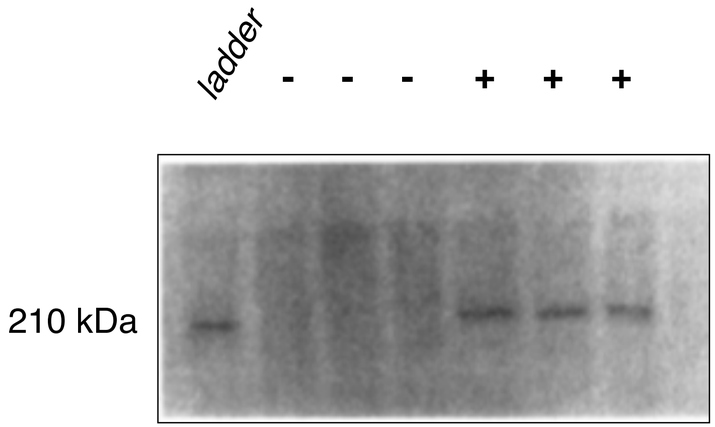
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.

L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.

B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

Understanding the Mechanism of "shaker peptides" - MVIIA





selectivity for one target

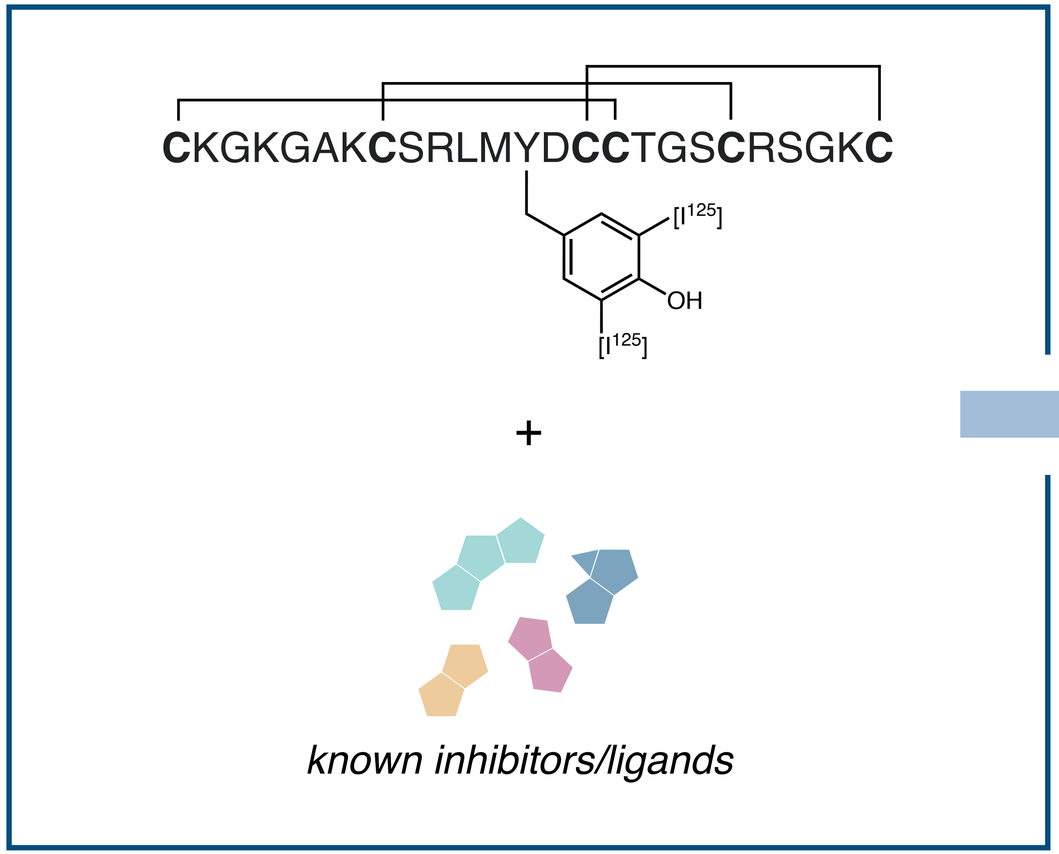
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.

T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.

L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.

B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

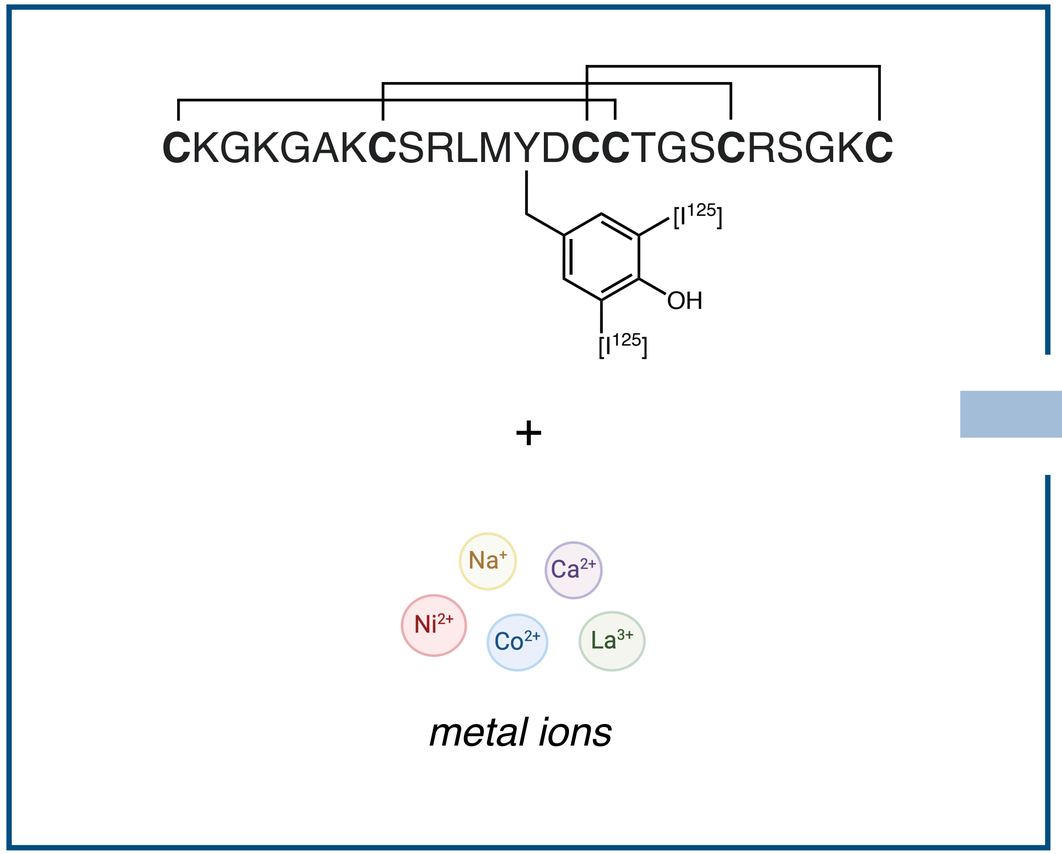
Understanding the Mechanism of “shaker peptides” - MVIIA



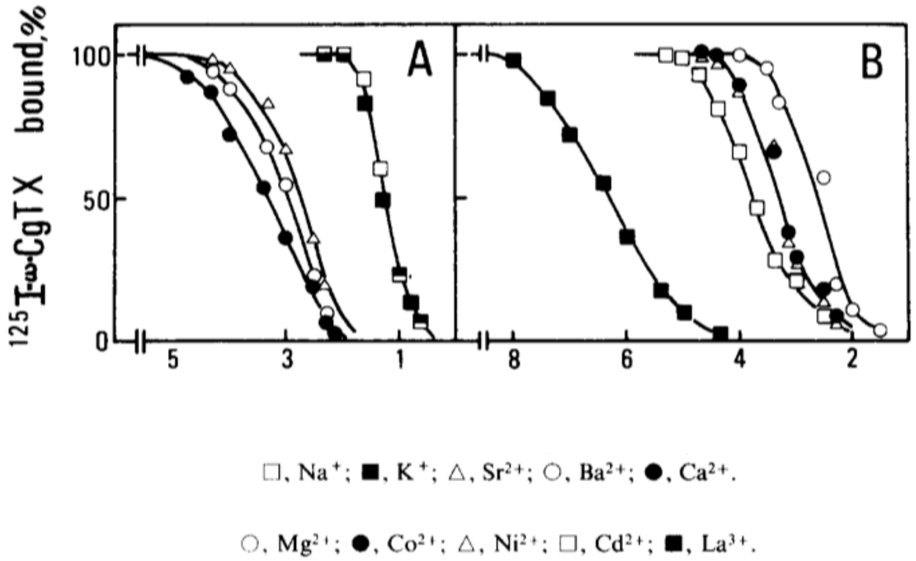
no change in binding

L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.
T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.
L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.
B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

Understanding the Mechanism of “shaker peptides” - MVIIA



change in binding



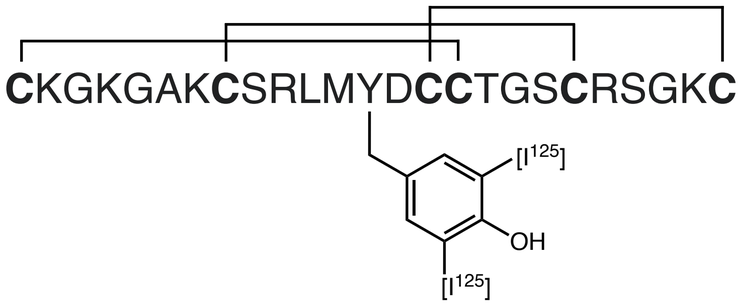
L. J. Cruz and B. M. Olivera *J. Biol. Chem.* **1986**, *261*, 6230-6233.

T. Abe, K. Kogano, H. Saisu, Y. Nishiuchi and S. Sakakibara *Neurosci. Lett.* **1986**, *71*, 203-208.

L. J. Cruz, D. S. Johnson and B. M. Olivera *Biochemistry* **1987**, *26*, 820–824.

B. M. Olivera, L. J. Cruz, et al. *Biochemistry* **1987**, *26*, 2086-2090.

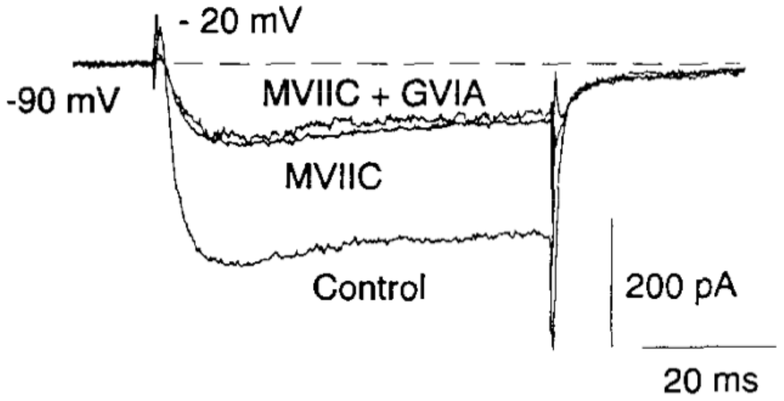
Understanding the Mechanism of “shaker peptides” - MVIIA



Ca2+

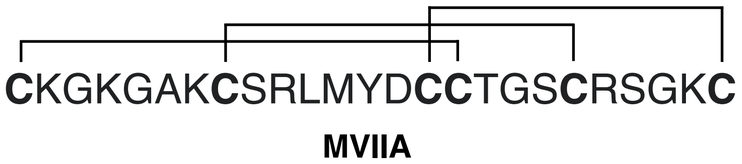
calcium binding assay

change in calcium current

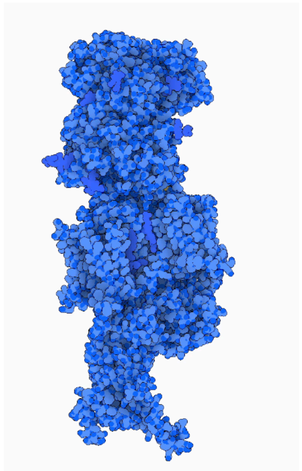


D. R. Hillyard, V. D. Monje, I. M. Mintz,* B. P. Bean,* L. Nadasdi, J. Ramachandran, G. Miljanich, A. Azimi-Zoonooz, J. M. McIntosh, L. J. Cruz, Julita S. Imperial and B. M. Oliviera *Neuron Vol.* **1992**, 69-77.

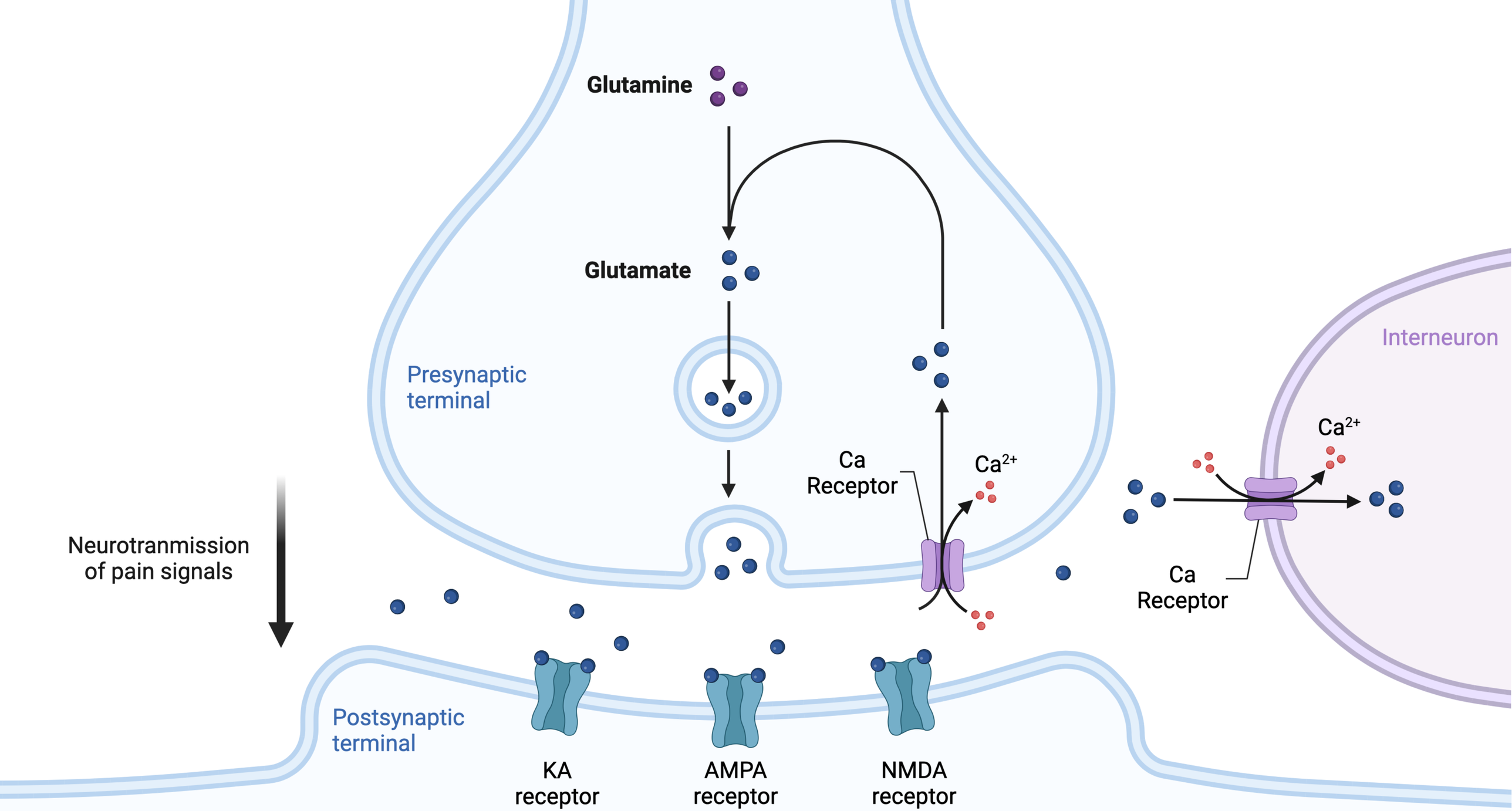
Understanding the Mechanism of “shaker peptides” - MVIIA

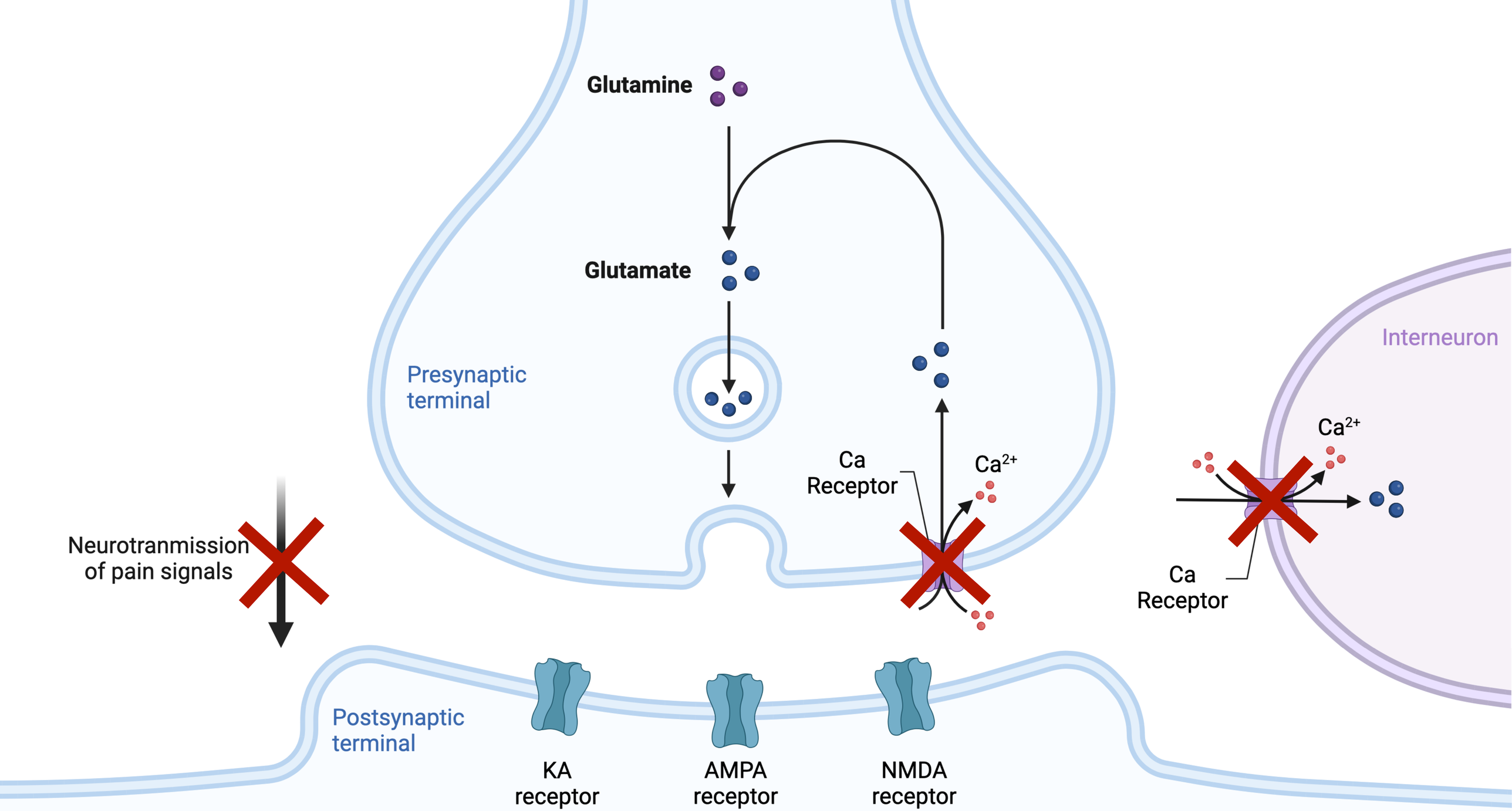


MVIIA



calcium ion channels

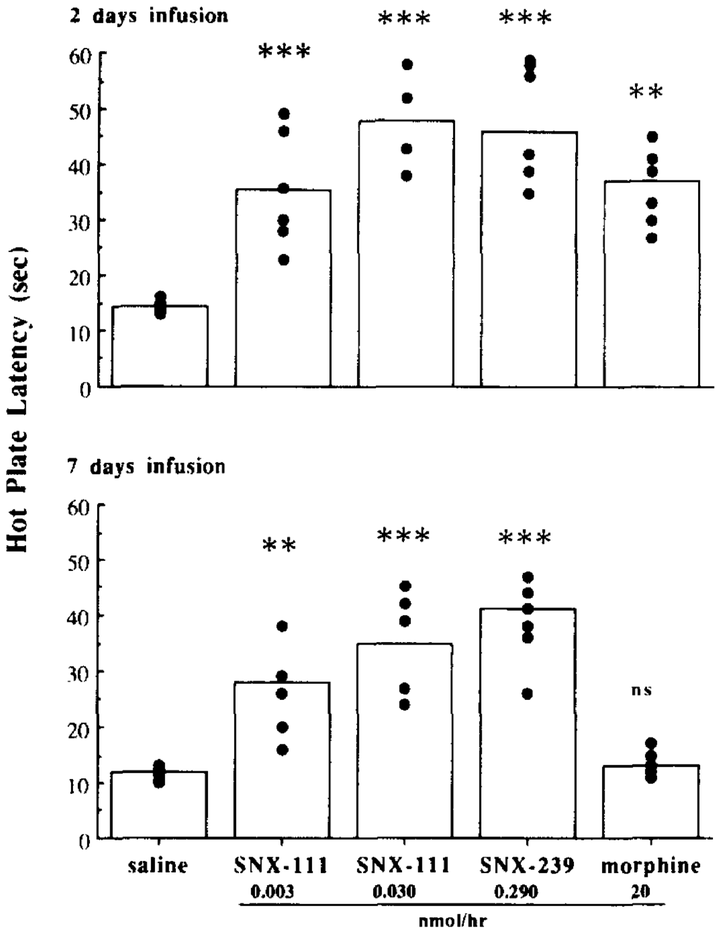

Glutamine
Glutamate
Presynaptic terminal
Ca Receptor
Ca^{2+}
Interneuron
Ca^{2+}
Ca Receptor
Neurotranmission of pain signals
Postsynaptic terminal
KA receptor
AMPA receptor
NMDA receptor


Glutamine
Glutamate
Presynaptic terminal
Ca Receptor
Ca^{2+}
Neurotranmission of pain signals
Interneuron
Ca^{2+}
Ca Receptor
Postsynaptic terminal
KA receptor
AMPA receptor
NMDA receptor

Preliminary Research for Pain Medication

hot plate test

readout: *time for mouse to flick paws/jump from the hot plate*



A. B. Malmberg and T. L. Yaksh *Pain* **1995**, *60*, 83-90.

Ziconotide Clinical Trials

Elan Pharmaceuticals

Phase I
1995

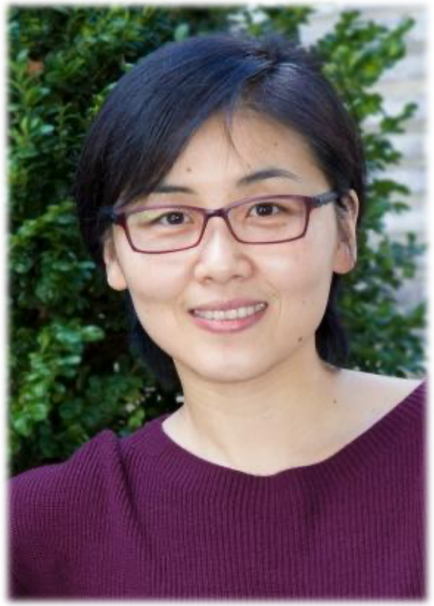
Phase II
2000

Phase III
2002-2004

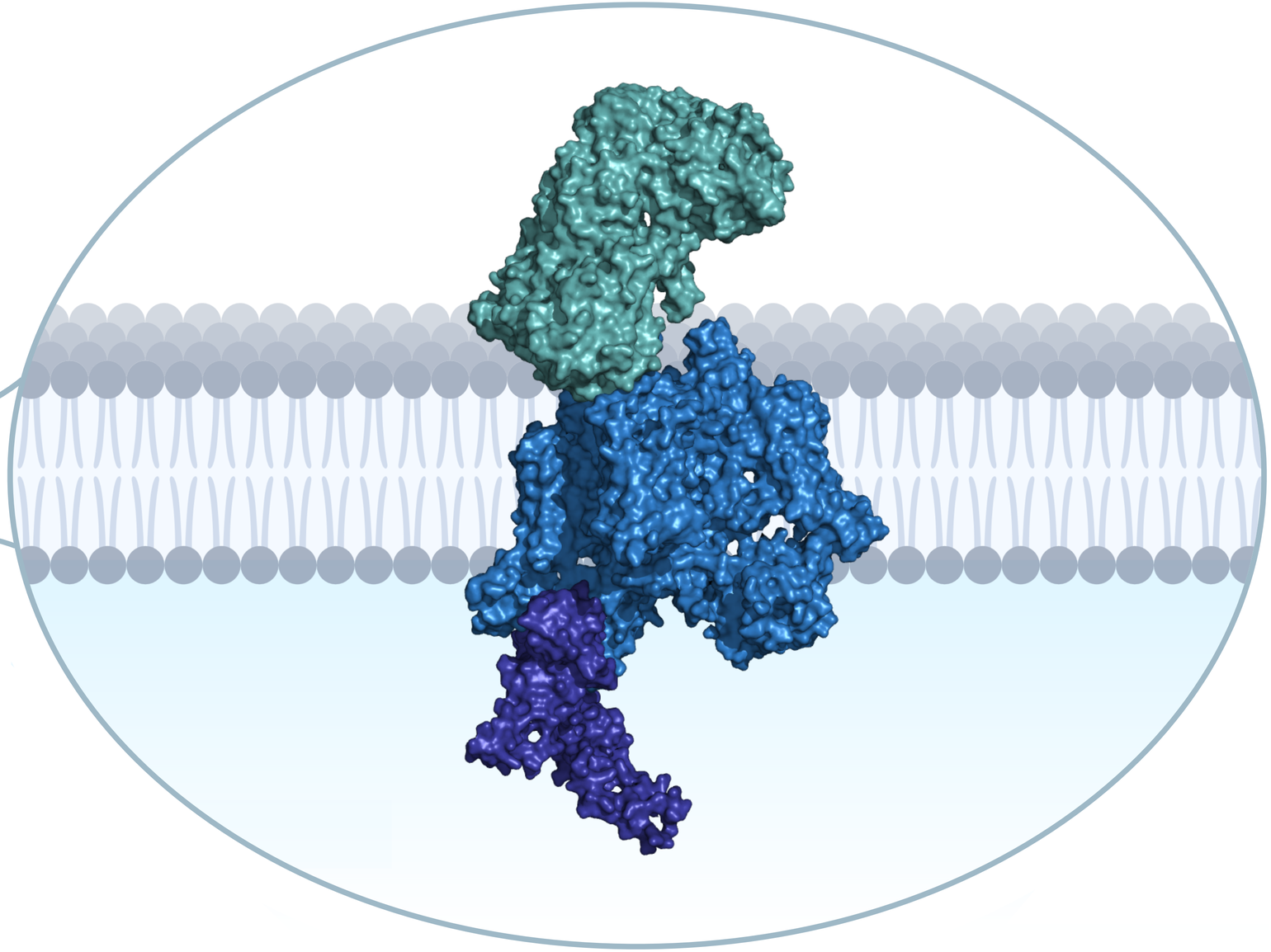
FDA approval
2004

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

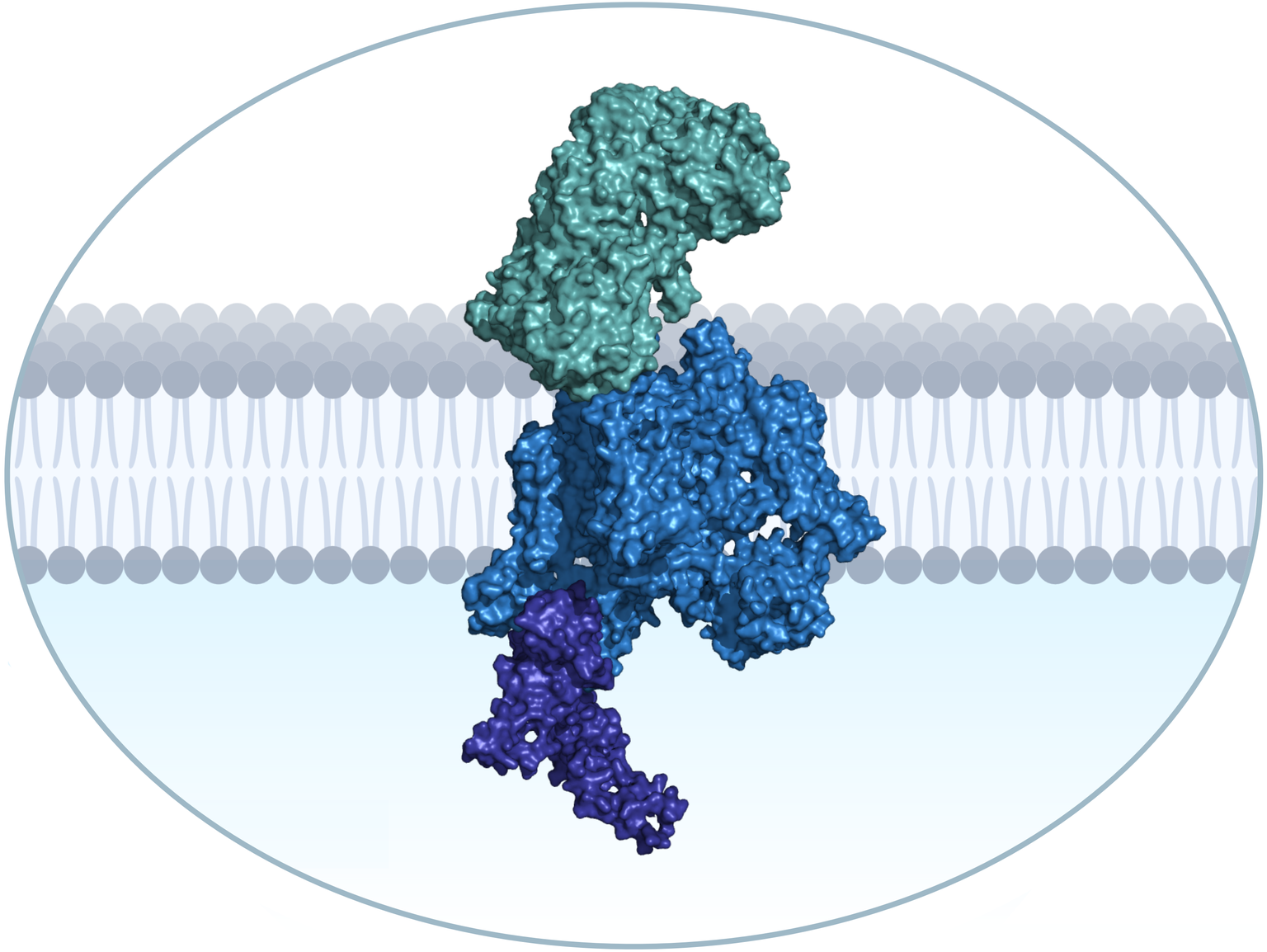
CryoEM Structure



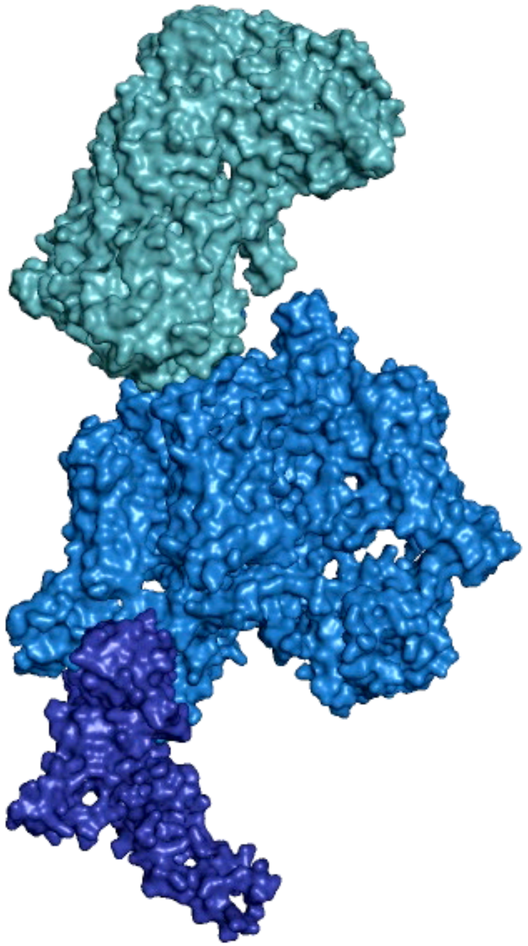
Prof. Nieng Yan, Princeton



CryoEM Structure

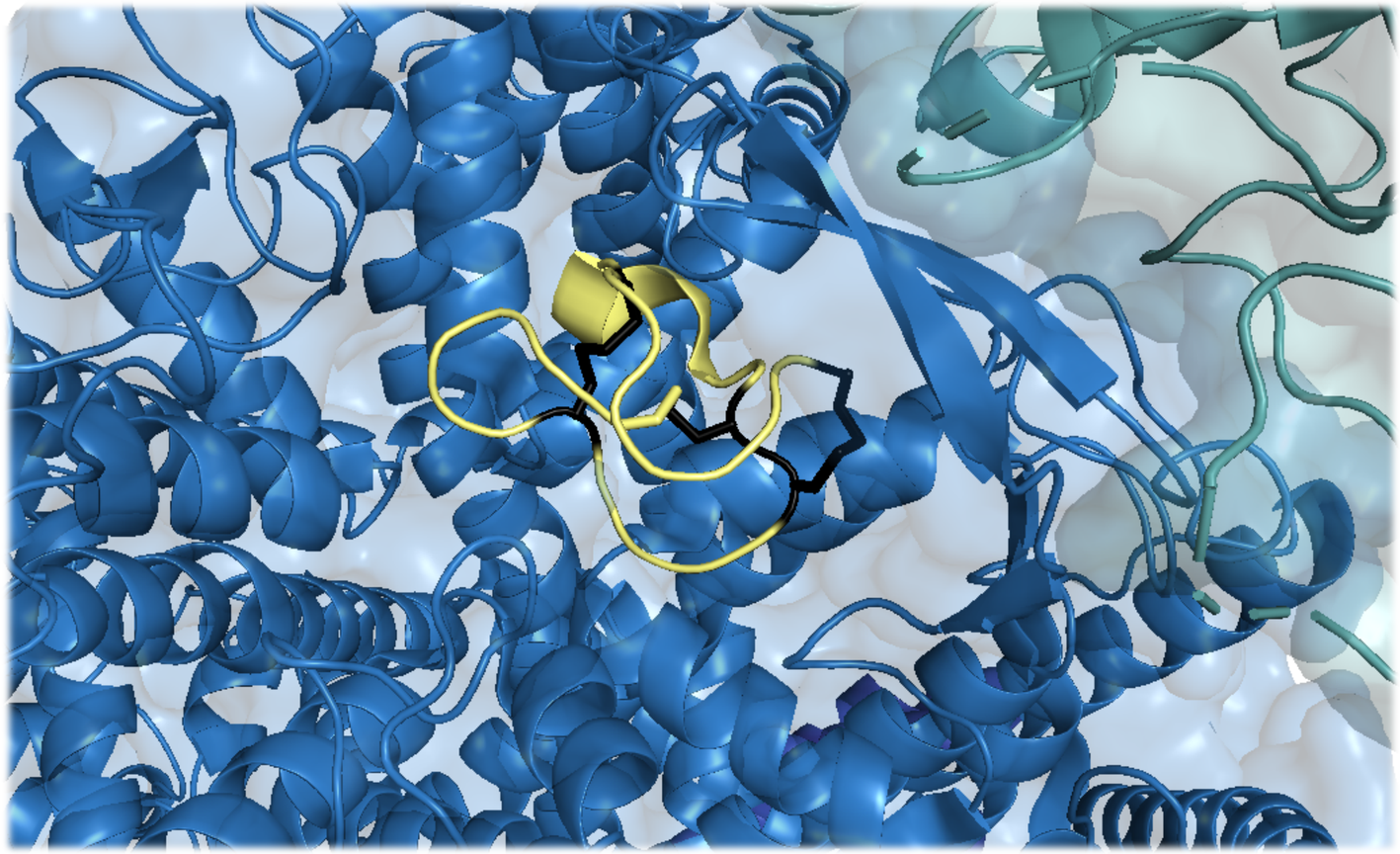


S. Gao, X. Shuai & N. Yan, *Nature* **2021**, *596*, 143–147.



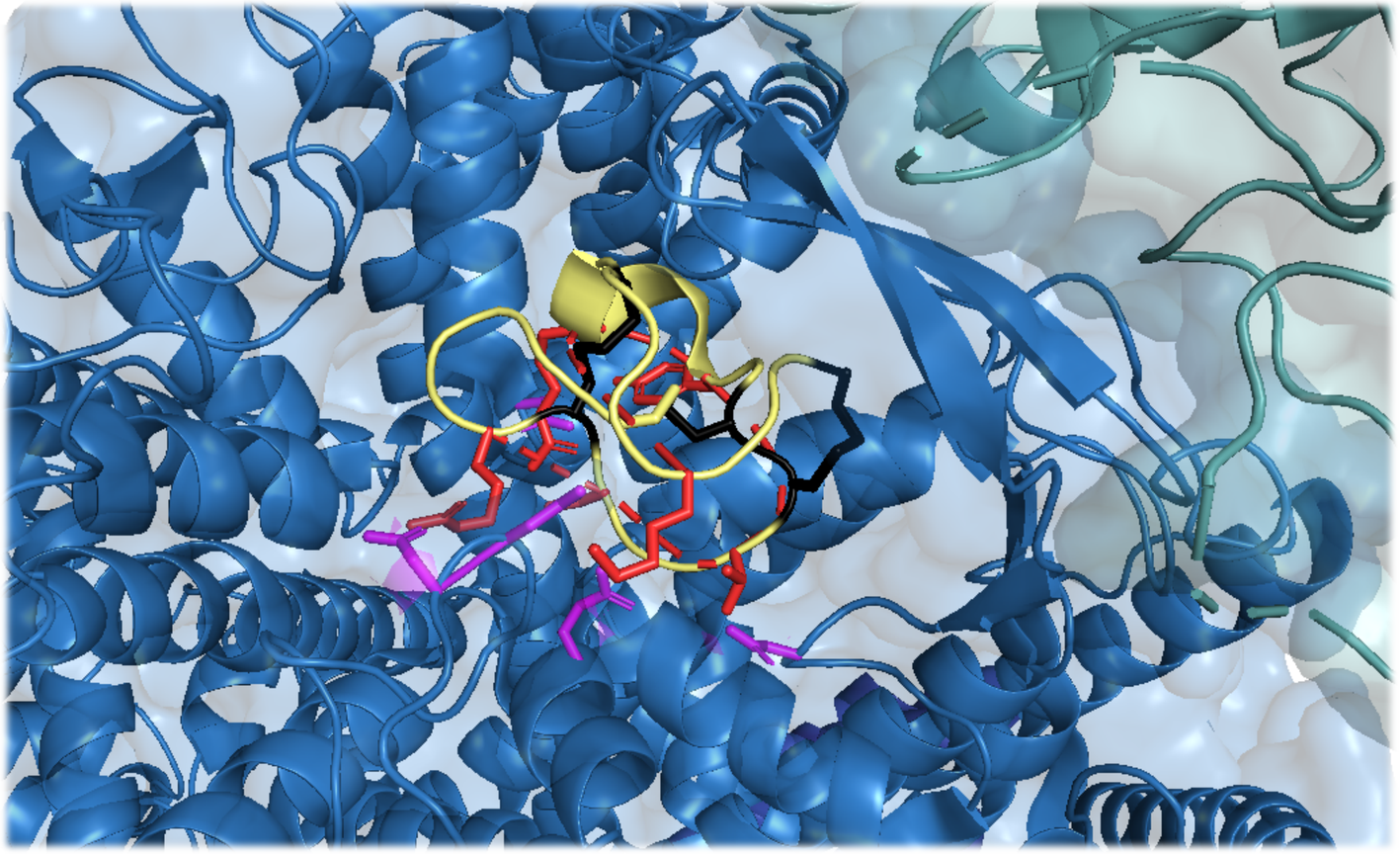
S. Gao, X. Shuai & N. Yan *Nature* **2021**, *596*, 143–147.

Ziconotide Binding Pocket



S. Gao, X. Shuai & N. Yan *Nature* **2021**, *596*, 143–147.

Ziconotide Binding Pocket

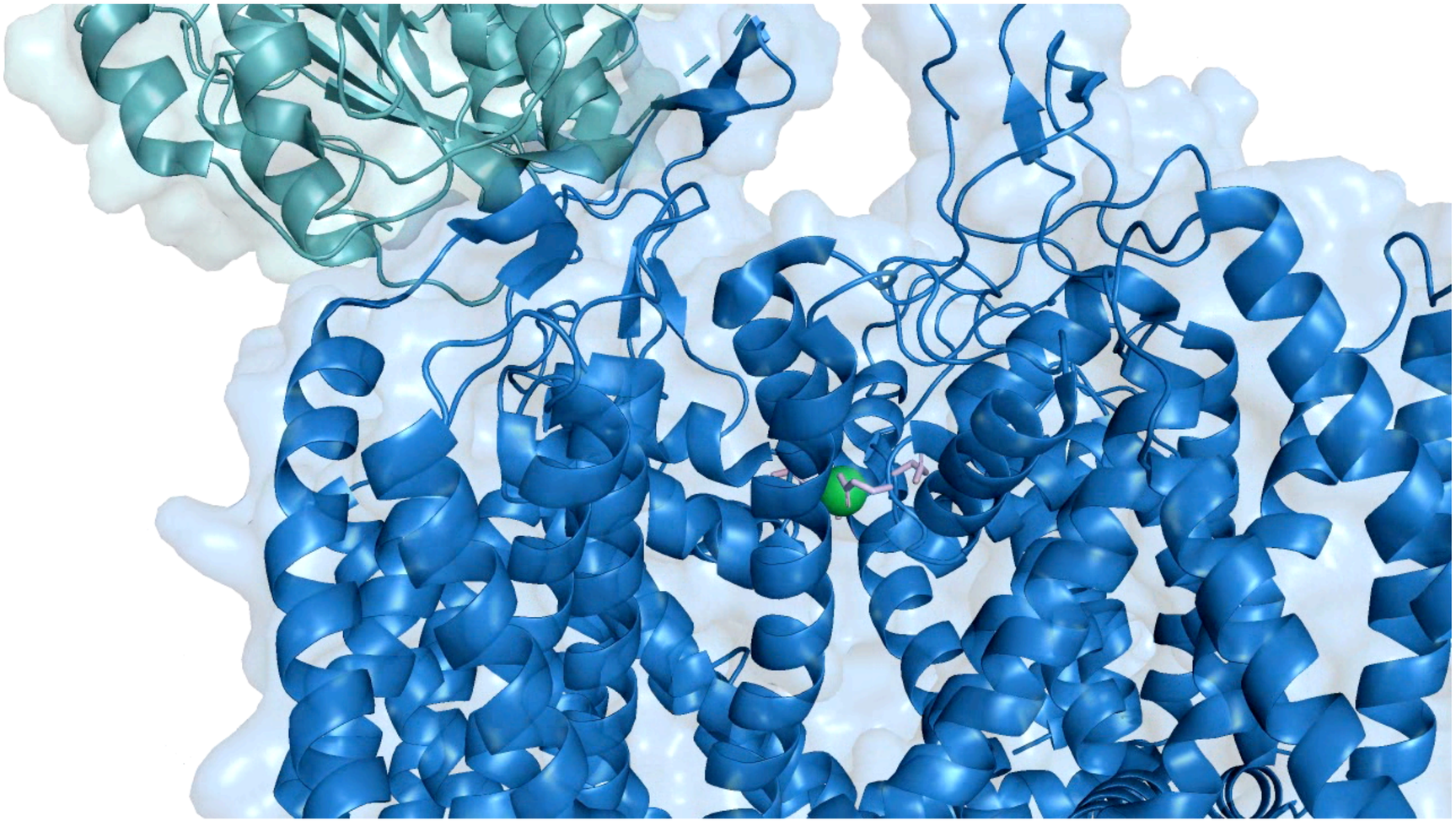


key interactions

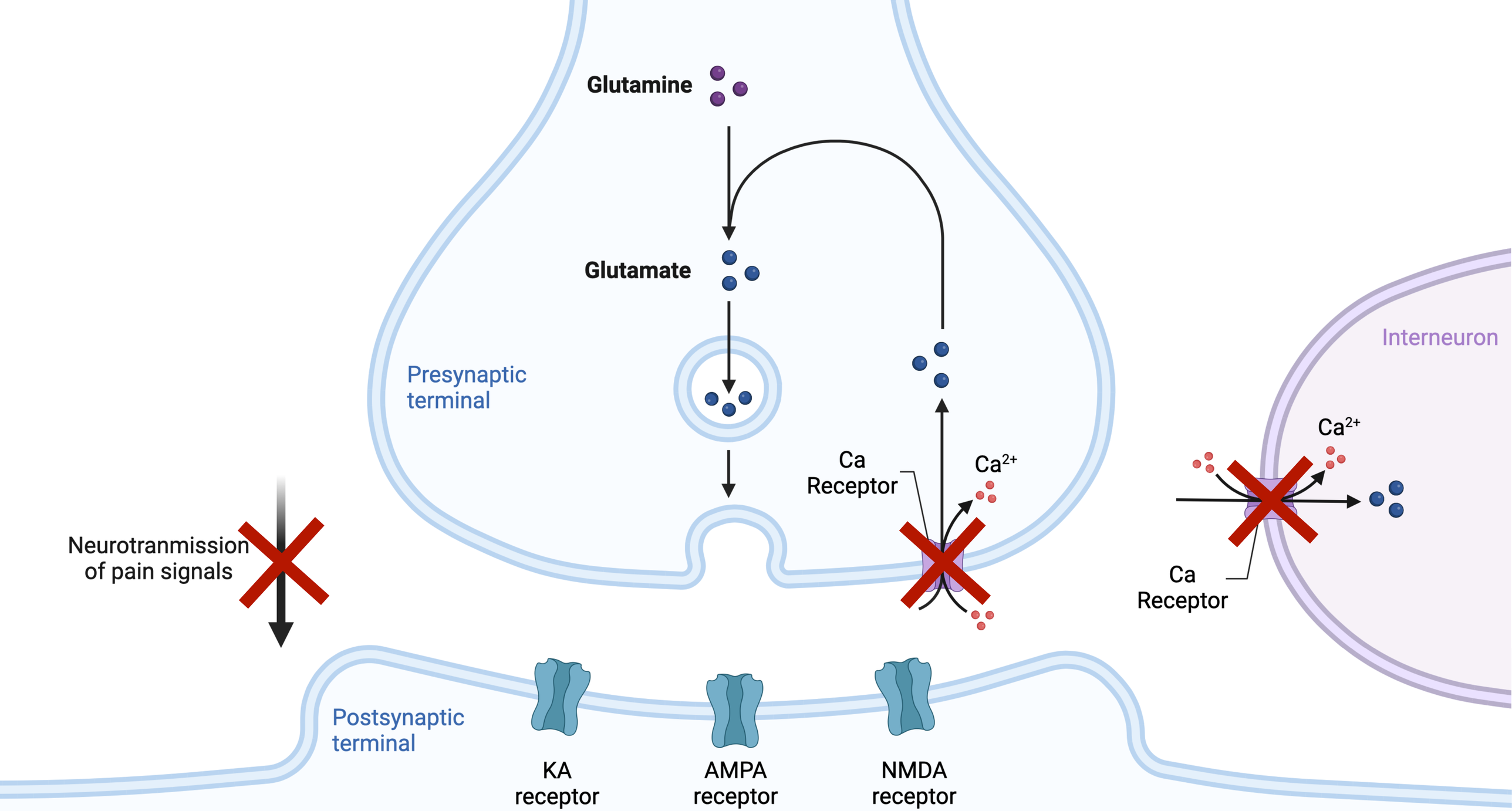
Ziconotide		*Ca Receptor*
Arg(10)	*Asp(664)*	
Tyr(13)	*Glu(1659)*	
Ser(19)	*Thr(1345)*	
Thr(17)	*Asp(1628)*	
Arg(21)	*Asp(1628)*	
Lys(4)		

S. Gao, X. Shuai & N. Yan *Nature* **2021**, *596*, 143–147.

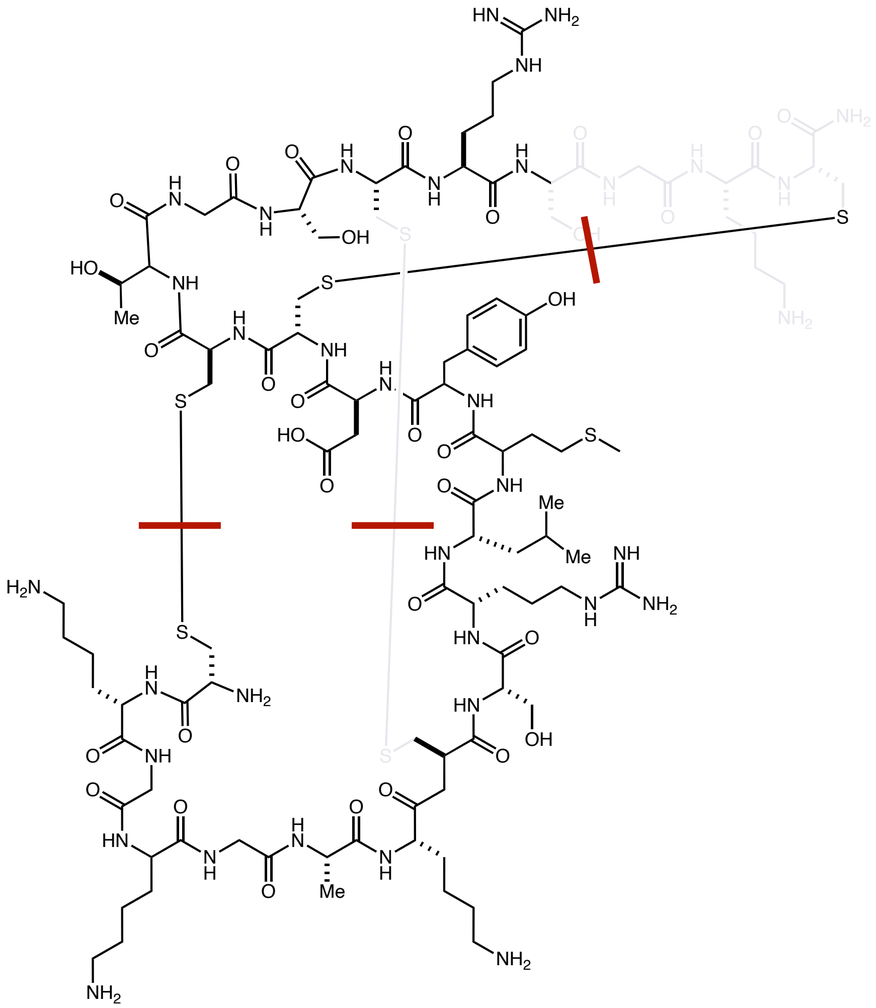
Pain Signaling - Calcium Blockade



S. Gao, X. Shuai & N. Yan *Nature* **2021**, *596*, 143–147.


Glutamine
Glutamate
Presynaptic terminal
Ca Receptor
Ca^{2+}
Neurotranmission of pain signals
Interneuron
Ca^{2+}
Ca Receptor
Postsynaptic terminal
KA receptor
AMPA receptor
NMDA receptor

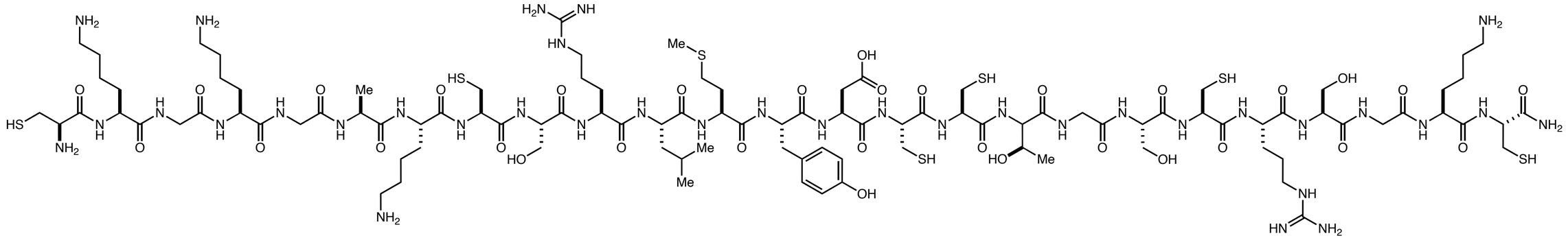
Synthesis of Ziconotide



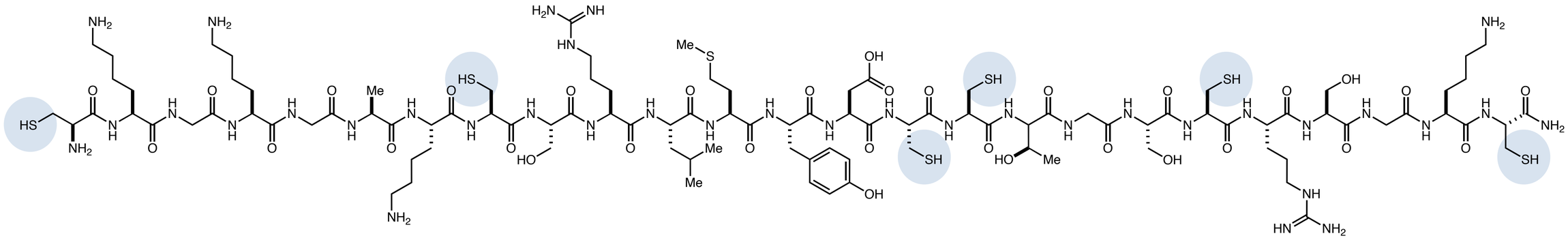
PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

3 disulfide bonds….

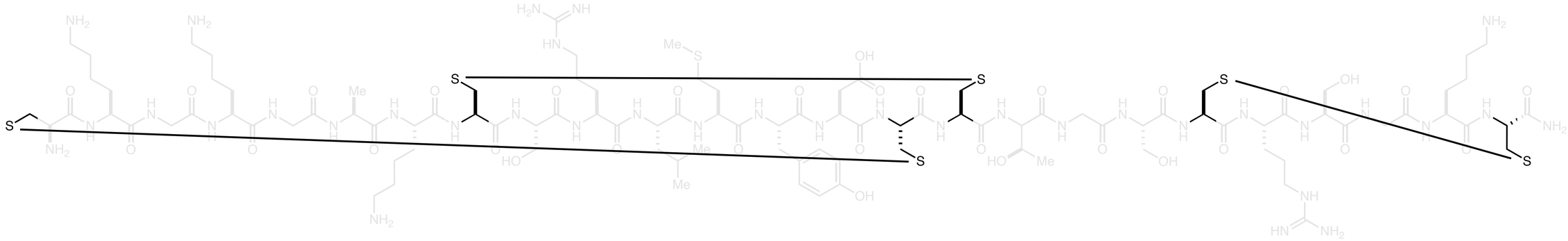
Synthesis of Ziconotide



Synthesis of Ziconotide

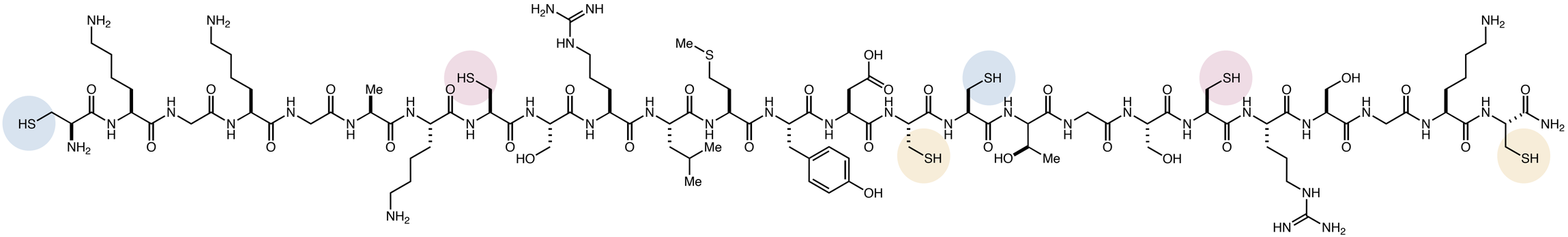


Synthesis of Ziconotide



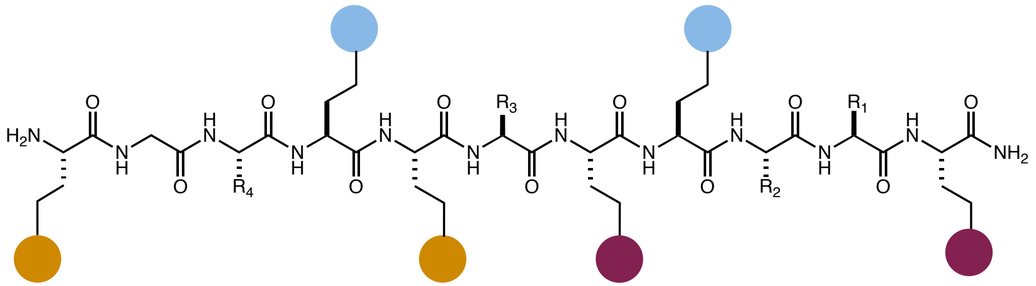
32 disulfide combinations possible…

Synthesis of Ziconotide



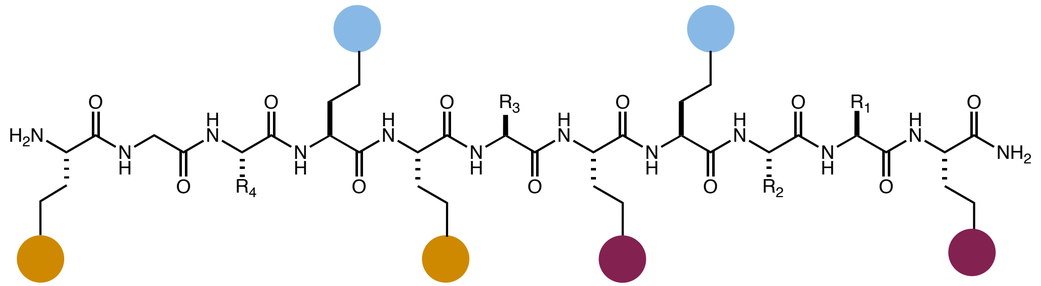
Ziconotide

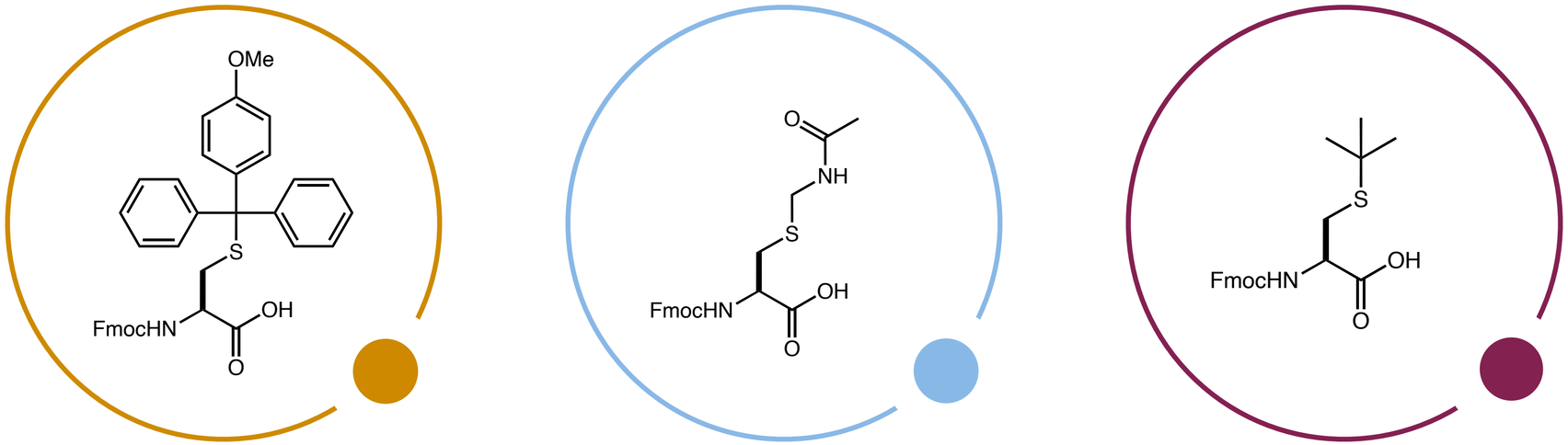
Orthogonal Cysteine Protecting Groups



Ziconotide

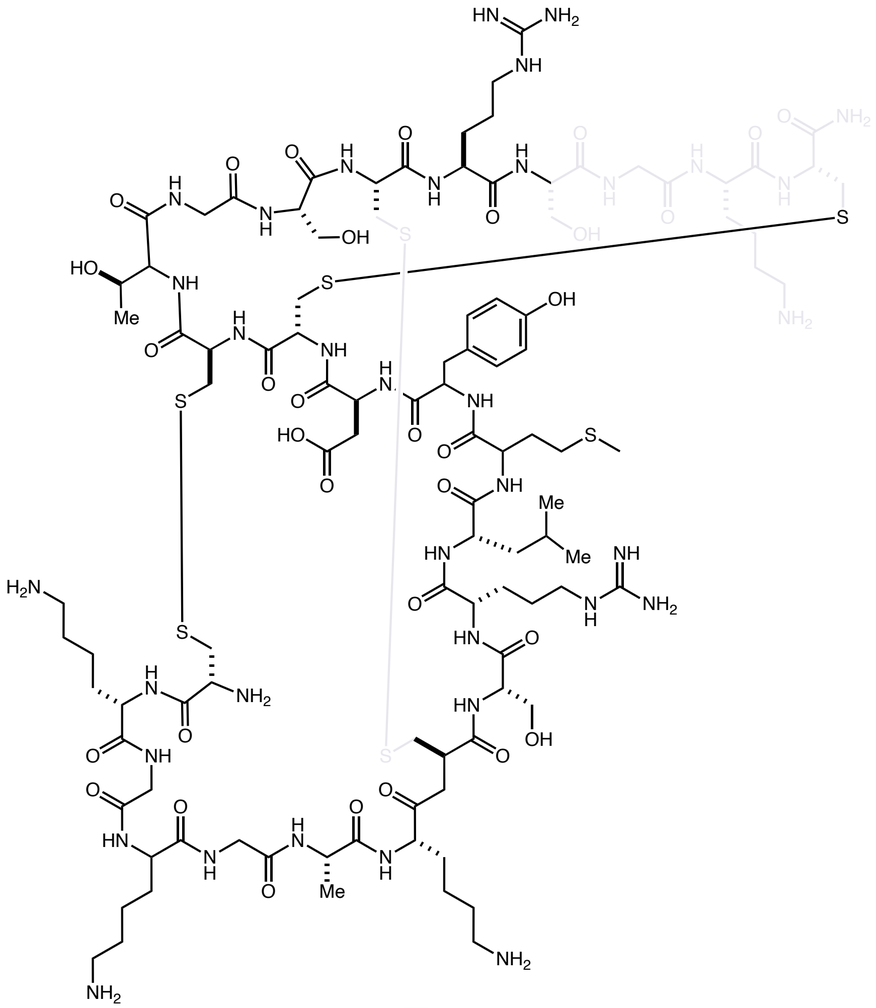
Orthogonal Cysteine Protecting Groups





examples of orthogonal protecting groups

Ziconotide (Prialt)



PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

FDA approval in 2004

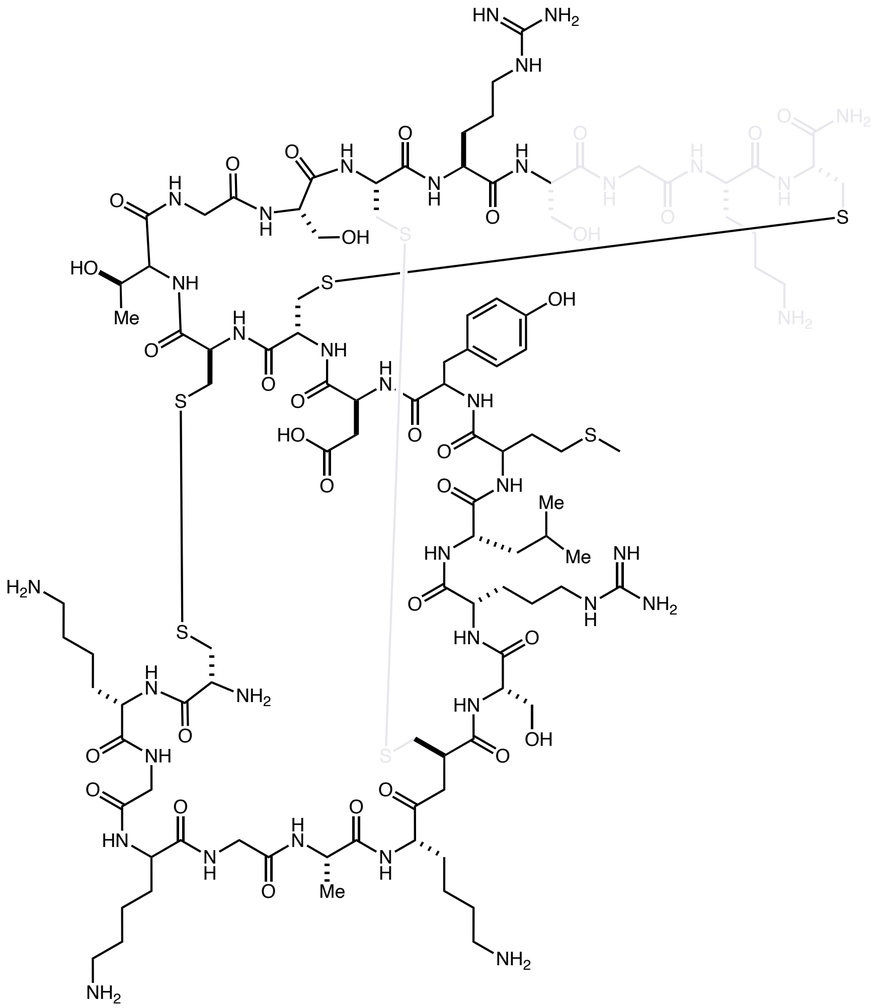
(chronic pain for cancer patients)

only FDA approved non-opioid agent

1,000 fold** more powerful than **morphine

no optimisation from venom compound

Limitations of Ziconotide



PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

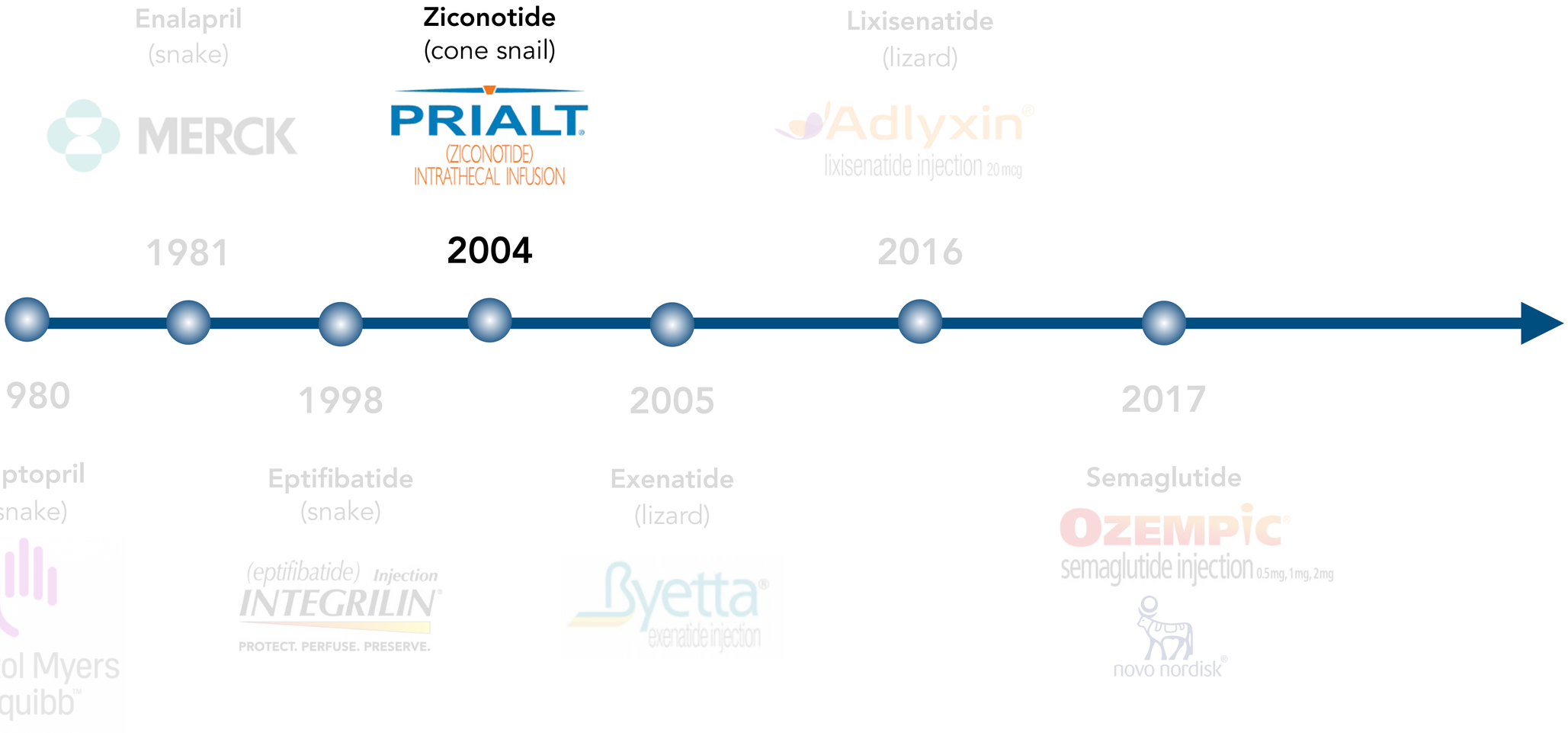
molecular weight = 2.6 kDa

oral bioavailability issues

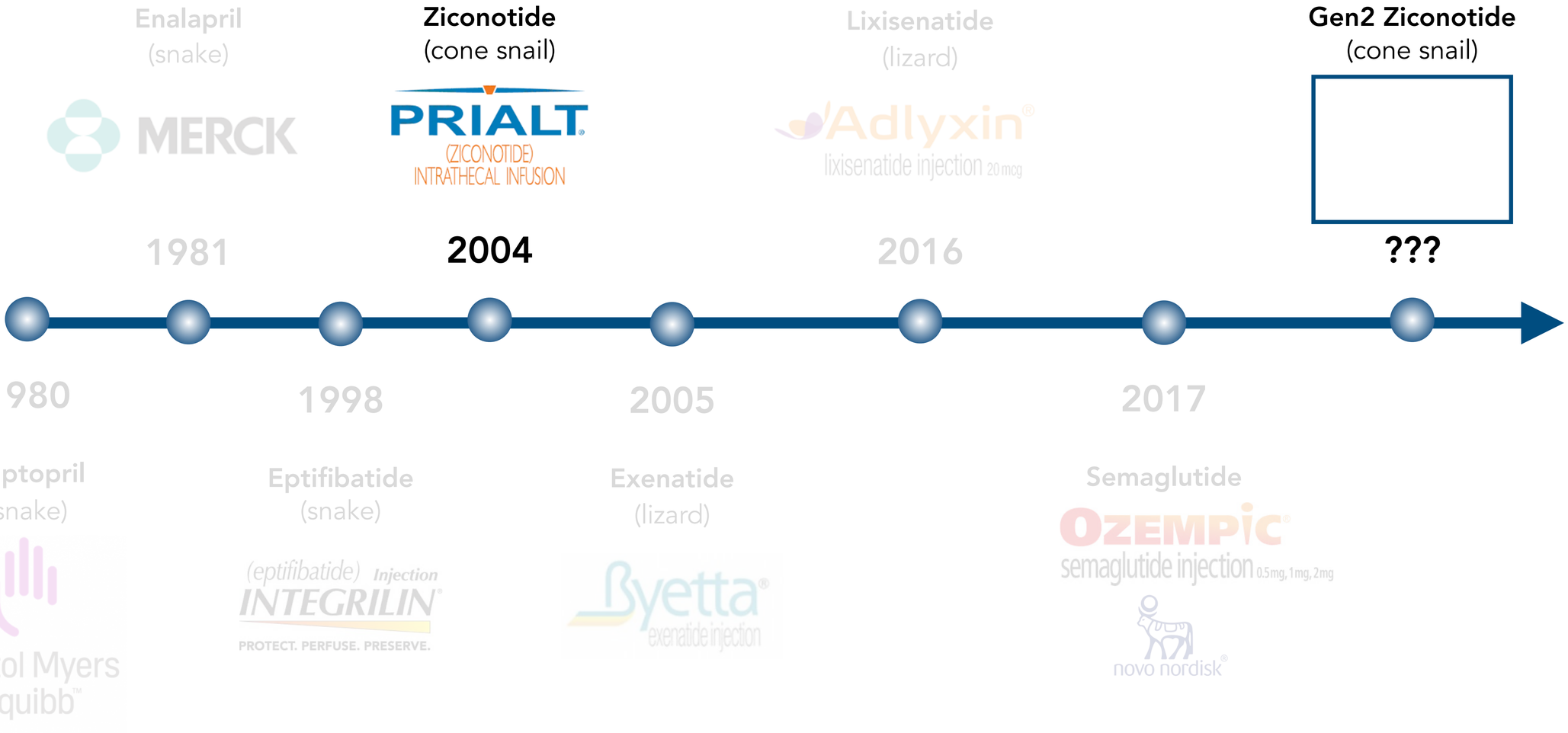
only available as an intravenous injection (2024)

2023 - 2024 - nearly 800 new publications

Limitations of Ziconotide



Limitations of Ziconotide



Outlook

Captopril
(snake)

Bristol Myers Squibb™

1980

Enalapril
(snake)

MERCK

1981

Eptifibatide
(snake)

(eptifibatide) Injection
INTEGRILIN®
PROTECT. PERFUSE. PRESERVE.

1998

Ziconotide
(cone snail)

PRIALT®
(ZICONOTIDE)
INTRATHECAL INFUSION

2004

Exenatide
(lizard)

Byetta®
exenatide injection

2005

Lixisenatide
(lizard)

Adlyxin®
lixisenatide injection 20 mcg

2016

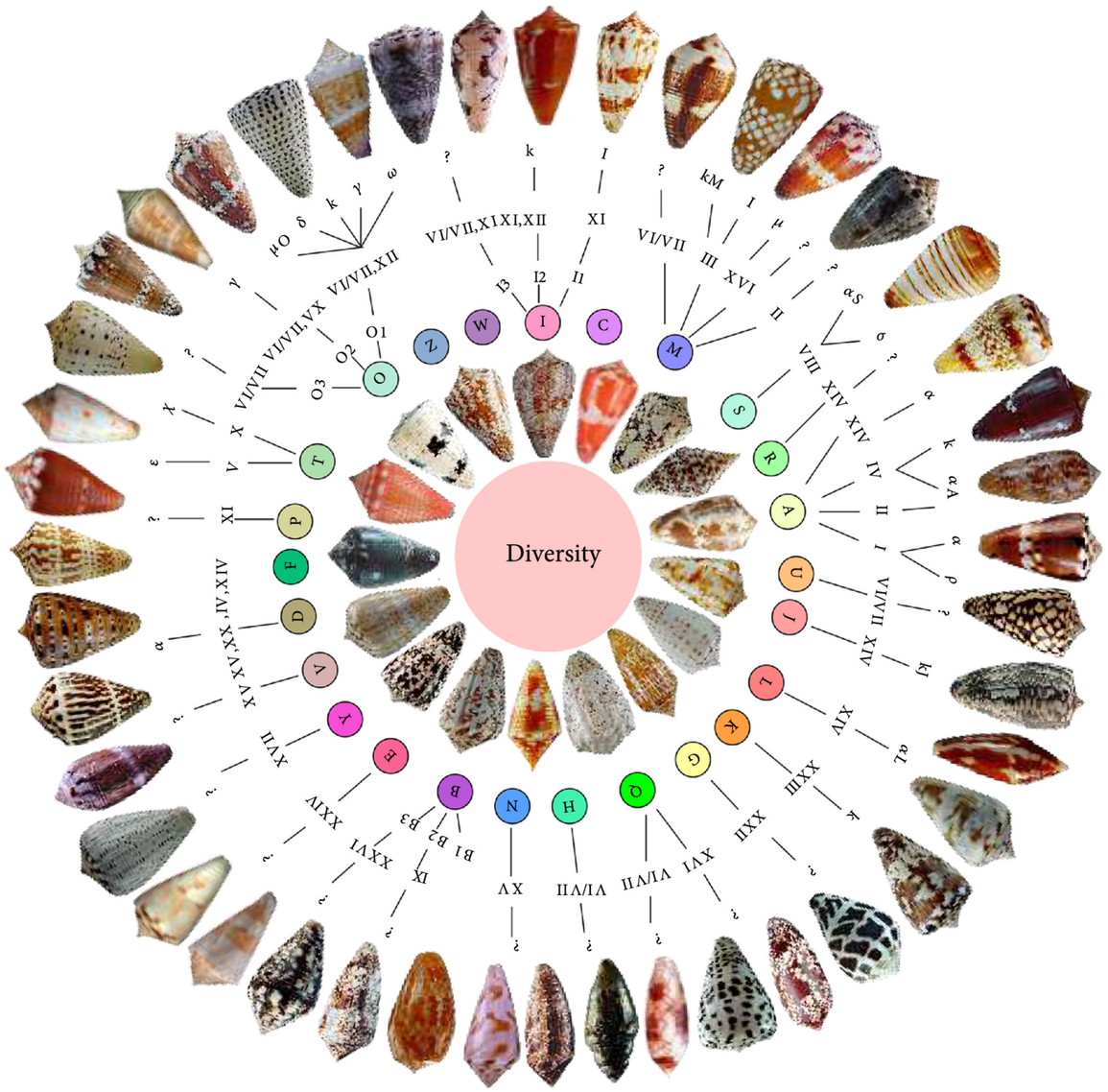
Semaglutide

OZEMPIC®
semaglutide injection 0.5mg, 1mg, 2mg
novo nordisk®

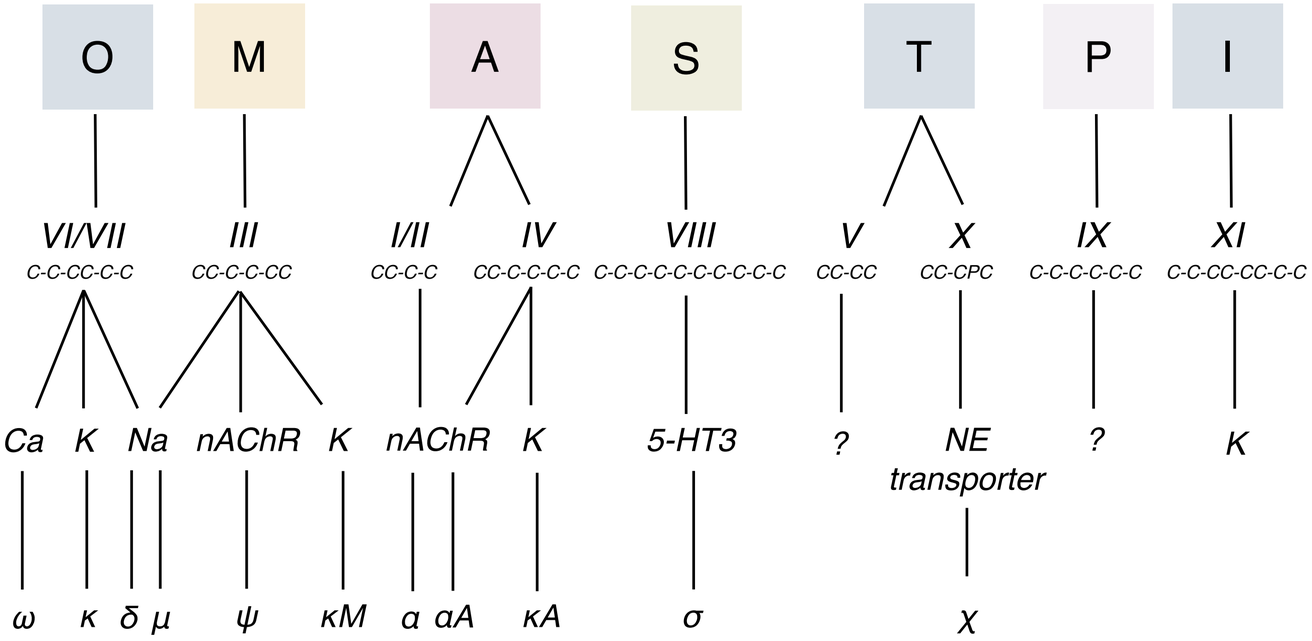
2017

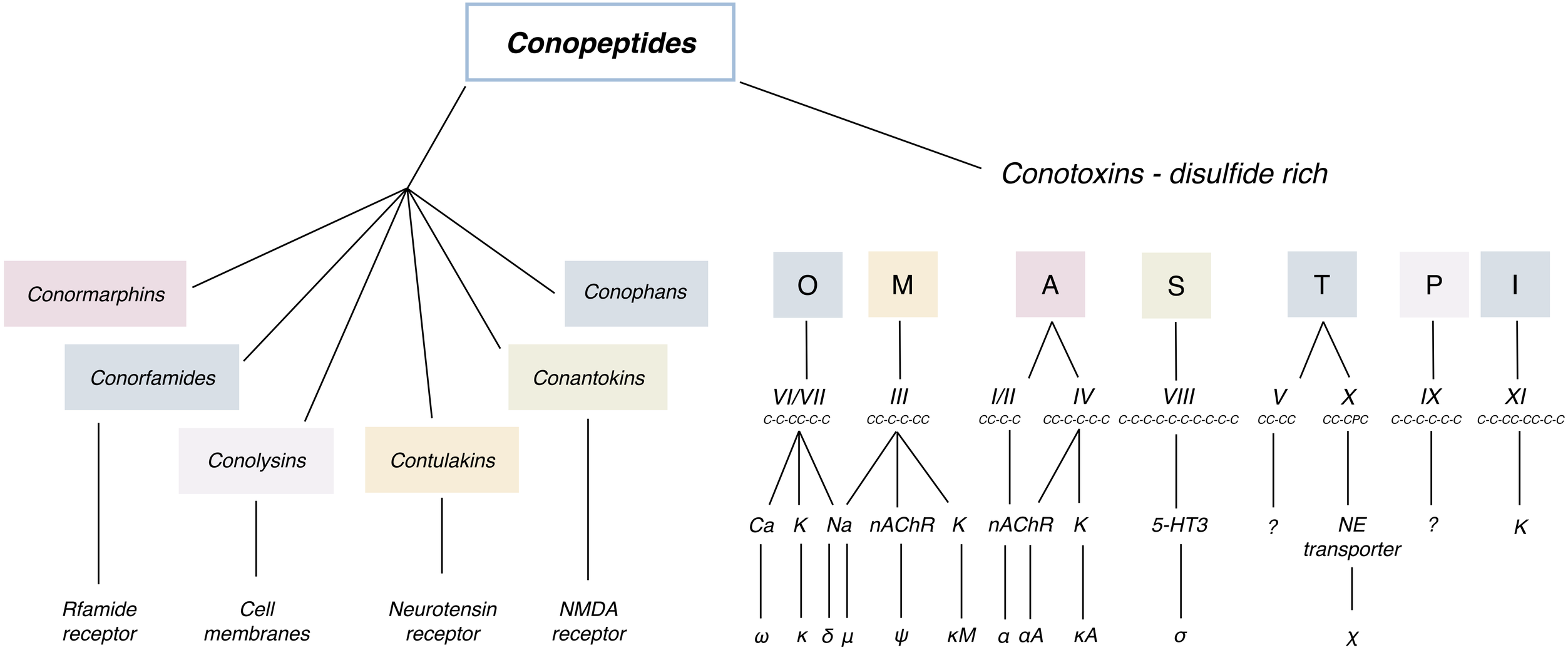
venoms are a rich source of peptide therapeutics….

Conotoxins



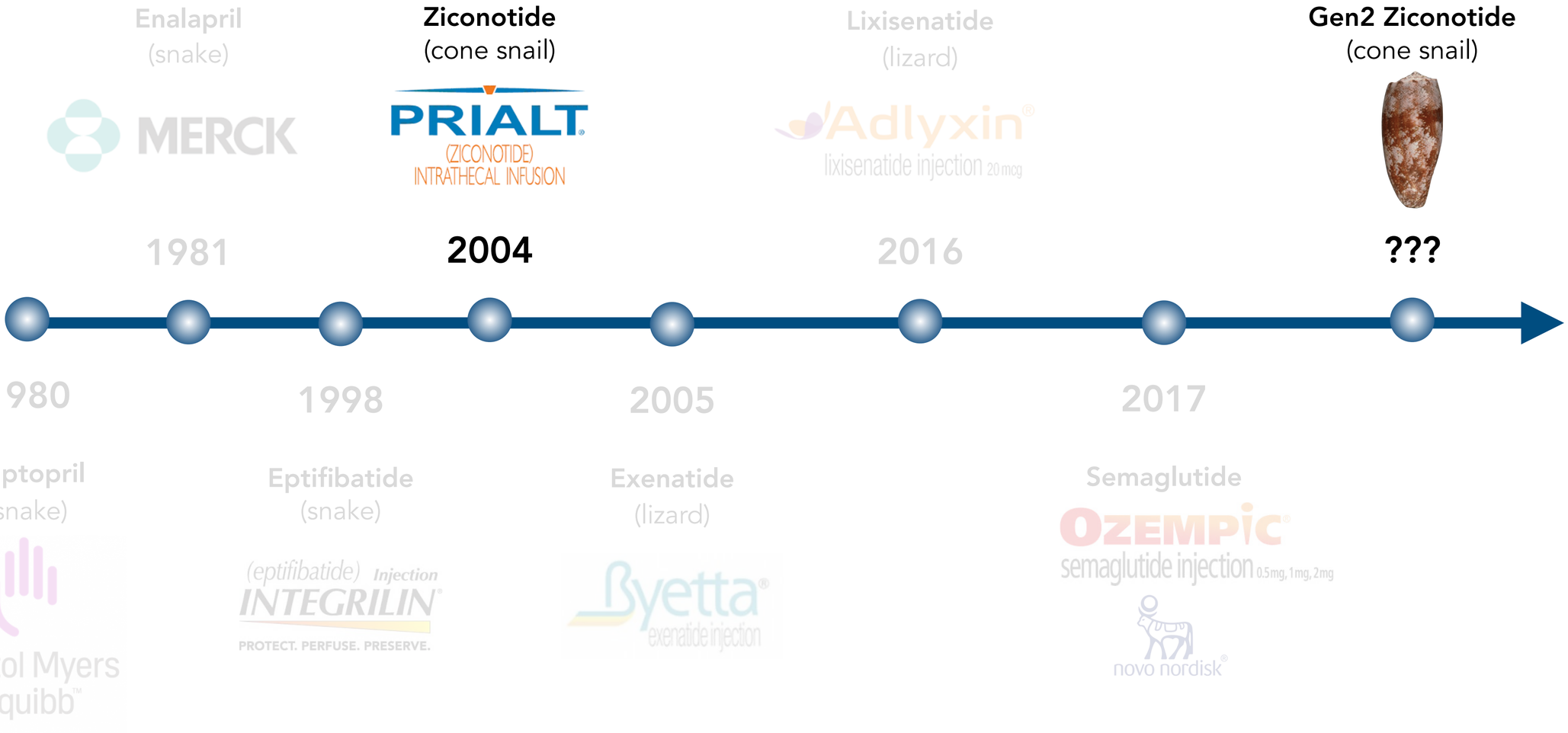
Conotoxins - disulfide rich





wide range of receptor targets

Limitations of Ziconotide



Questions?