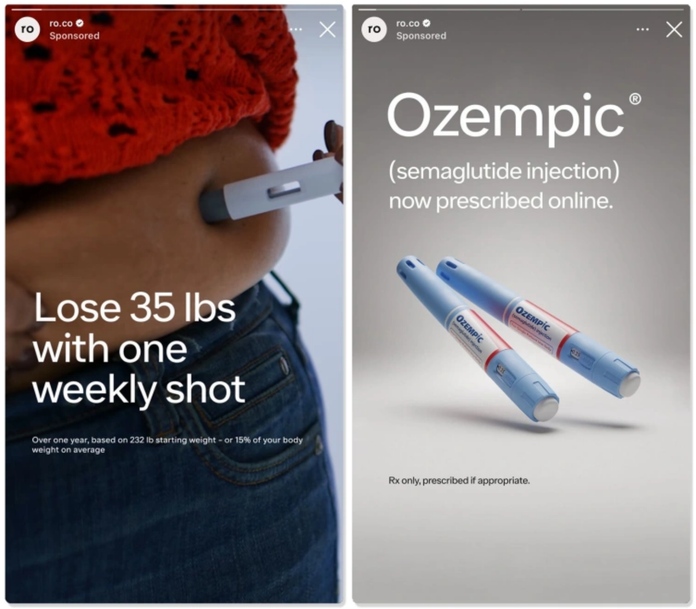
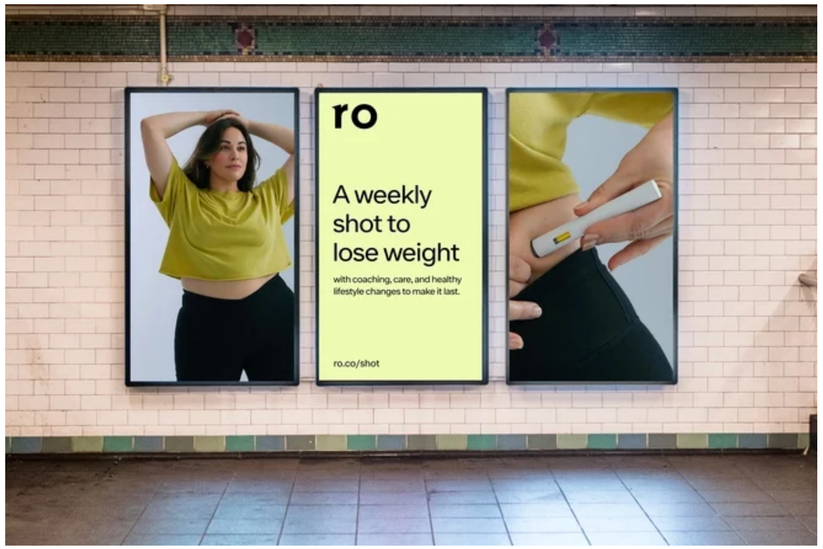
GLP-1 Receptor Agonists: Design and Development

Lauren Harstad
March 28, 2025

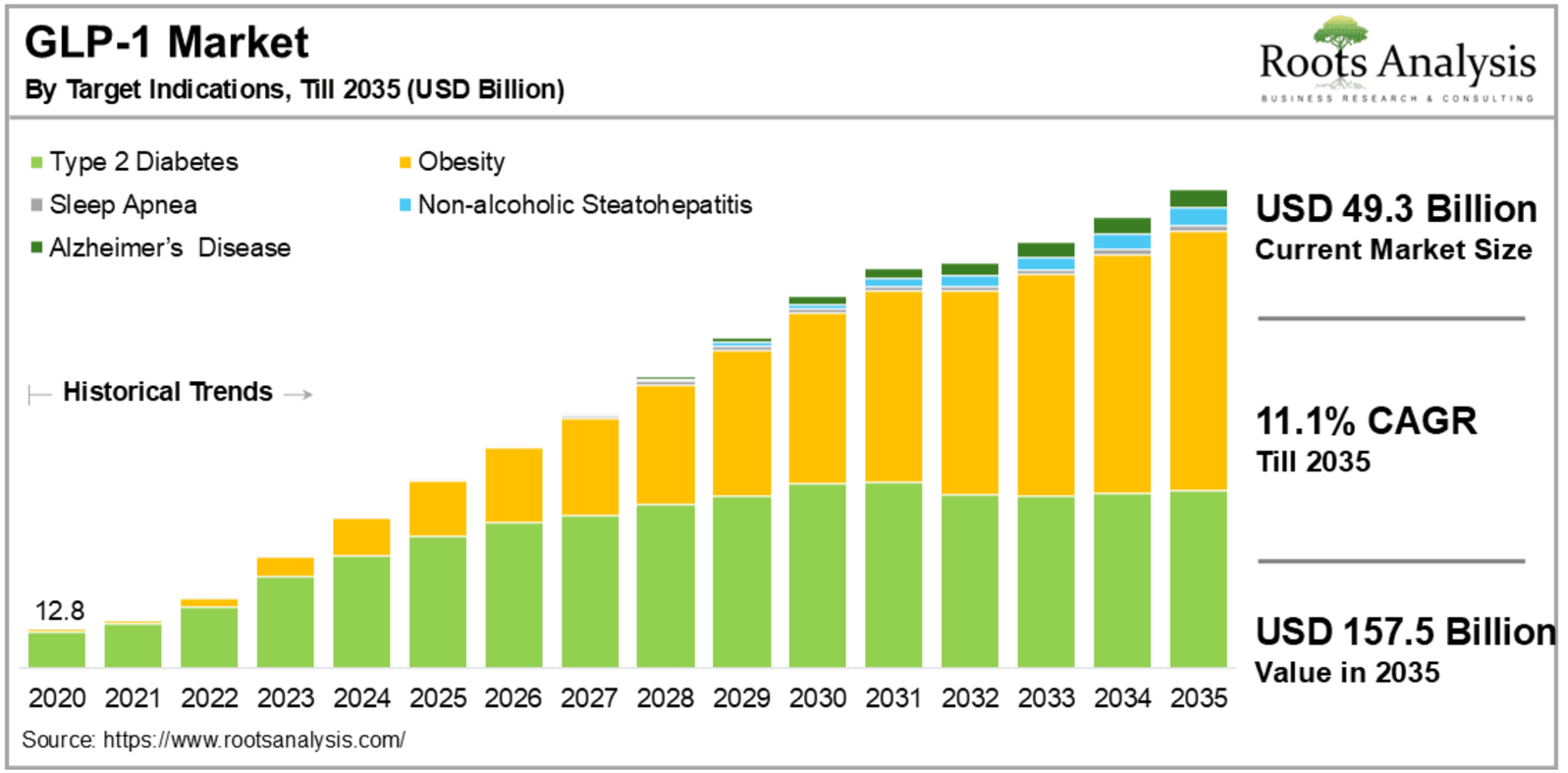
OZEMPIC®

semaglutide injection 0.5mg, 1mg, 2mg





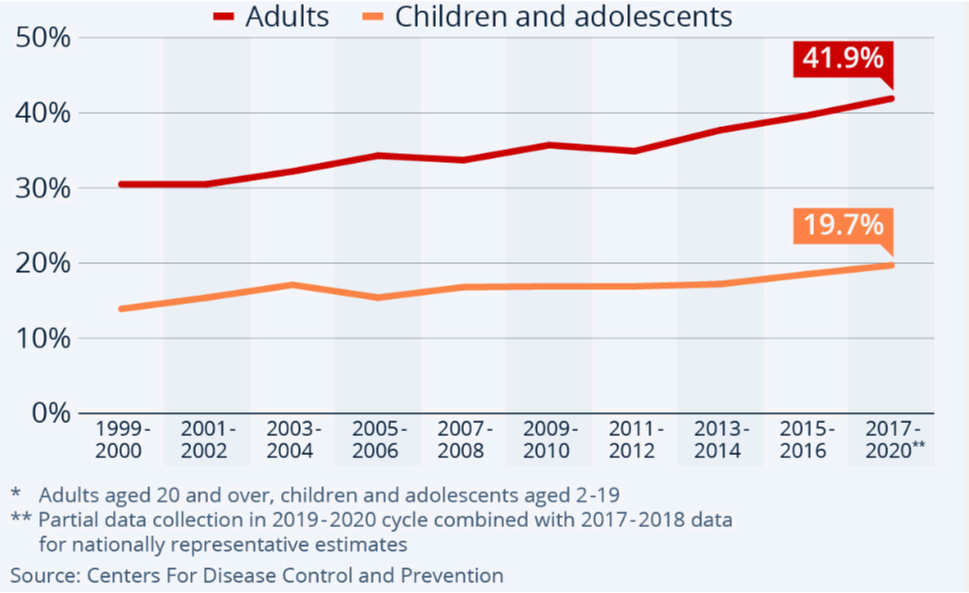
Economics of GLP-1 Analogues



- There are currently 7 FDA approved GLP-1R analogues with many more in the pipeline
- The global market for GLP-1 drugs is valued around $50 billion and is poised for significant growth

Obesity and Type 2 Diabetes

- >40% of US adults aged 20+ suffer from obesity
- $190 billion/year is spent in the US for obesity-related illness
- Obesity-related chronic diseases are one of the leading causes of death



Müller, T.D. *et. al. Nat. Rev. Drug Discov.* **2022**, *21,* 201. CDC National Diabetes Statistics Report 2021.

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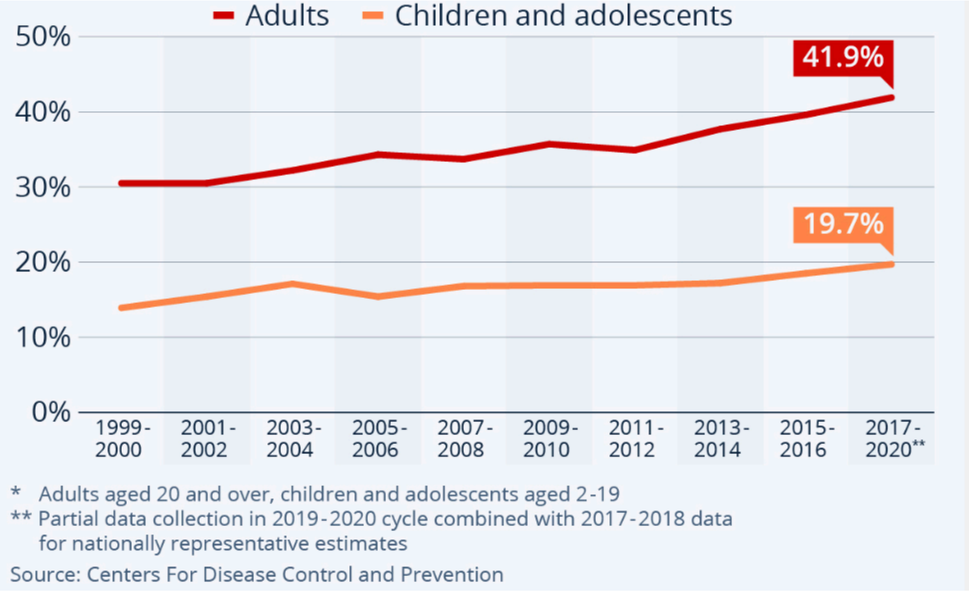
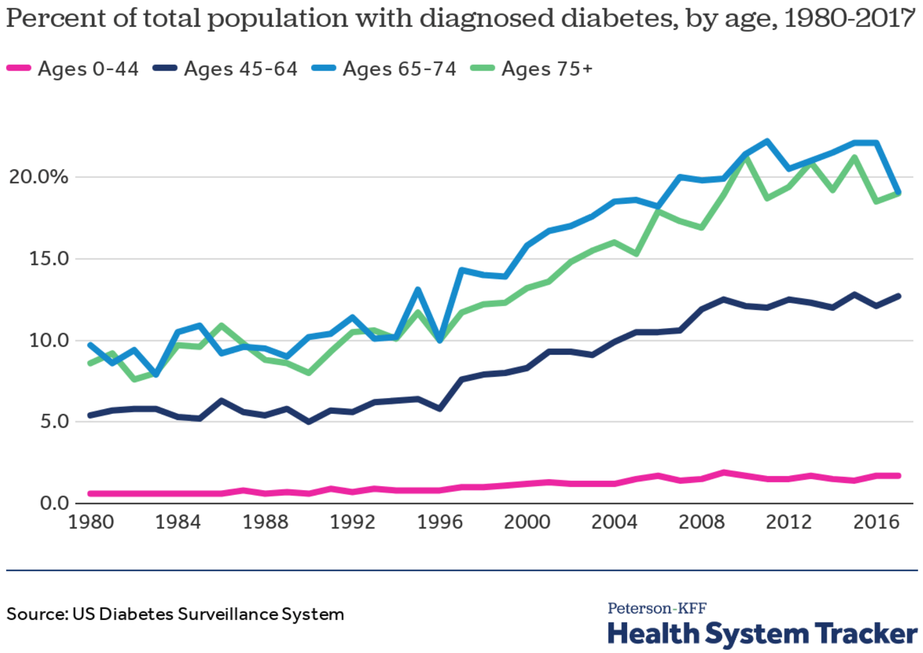


- T2D affects 38.4 million people in the US as of 2021
- This represents ~12% of the total population
- Incidence increases with age, affecting ~30% of people over 65



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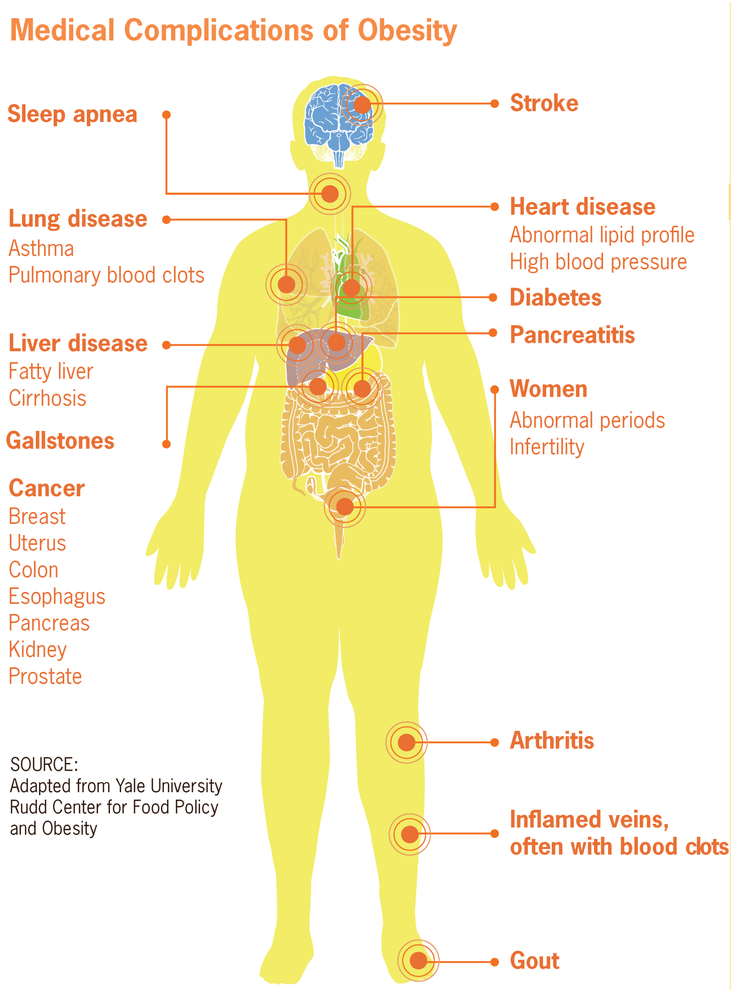
Obesity and Type 2 Diabetes

Leading Causes of Death in the US (2022)

- Heart disease: 702,880
- Cancer: 608,371
- Accidents (unintentional injuries): 227,039
- COVID-19: 186,552
- Stroke (cerebrovascular diseases): 165,393
- Chronic lower respiratory diseases: 147,382
- Alzheimer's disease: 120,122
- Diabetes: 101,209
- Nephritis, nephrotic syndrome, and nephrosis: 57,937
- Chronic liver disease and cirrhosis: 54,803



CDC National Center for Health Statistics. CDC Archive.

GLP-1 Receptor Agonists: Design and Development

Development

- Medicinal chemistry
- Clinical Trials
- Mechanism of Action

Synthesis

- General strategies
- Process scale

State of the Field

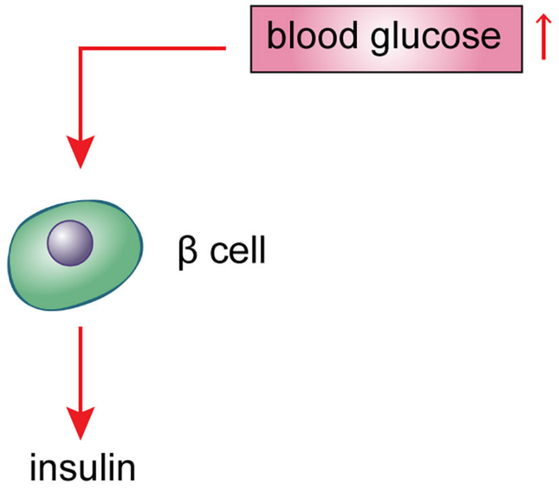
- Oral GLP-1R agonists
- Current research
- Future drug development

GLP-1 Receptor Agonists: Design and Development

Development

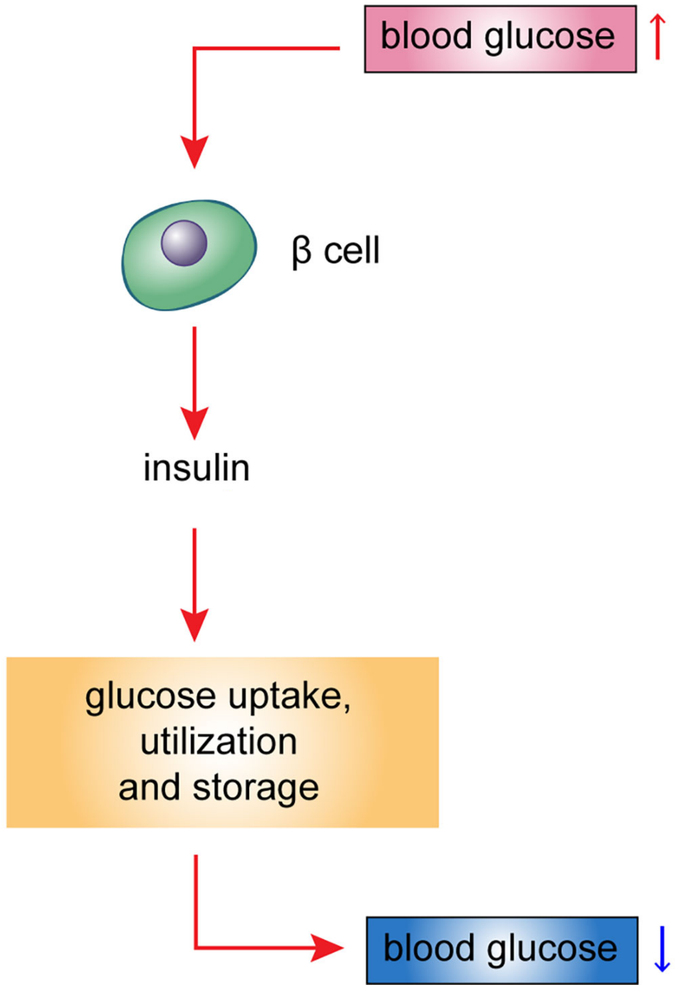
- Medicinal chemistry
- Clinical Trials
- Mechanism of Action

Insulin Signaling



Jia, Y. *et. al. Front. Endocrinol.* **2022**, *21,* 928016.

Insulin Signaling



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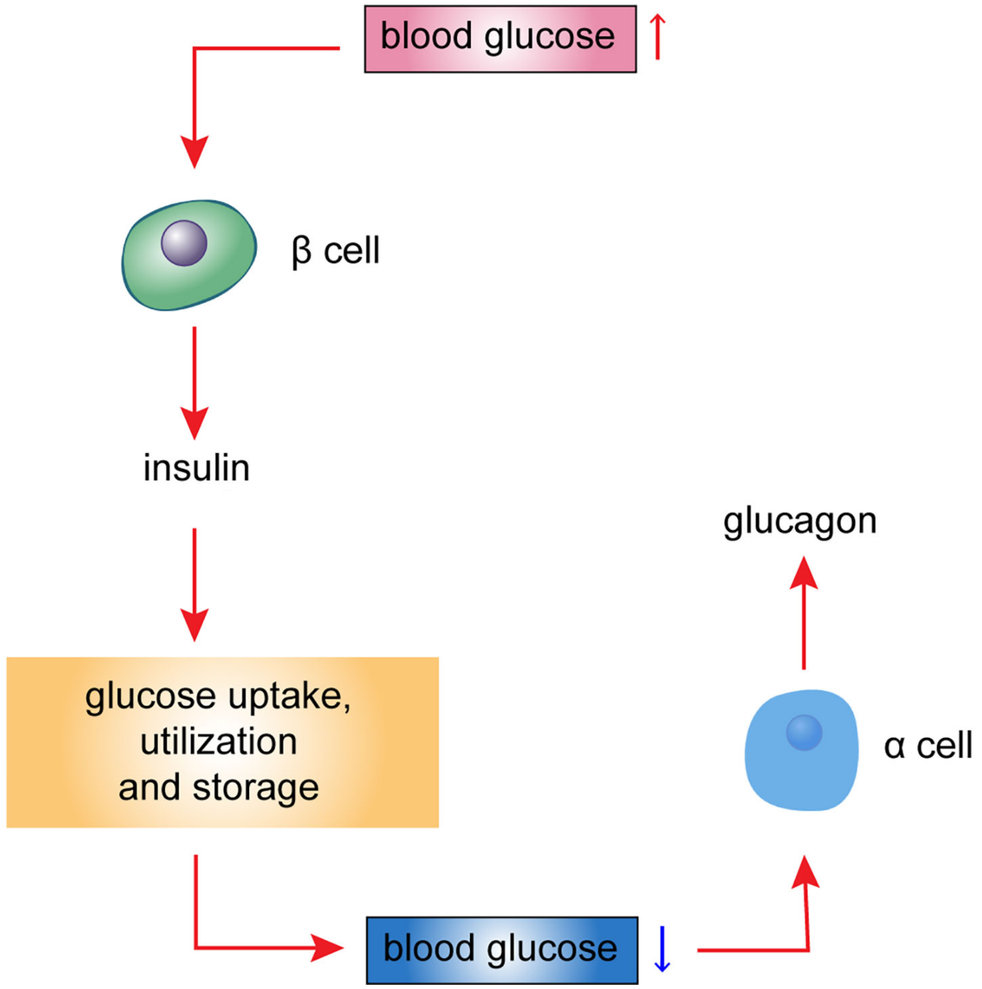

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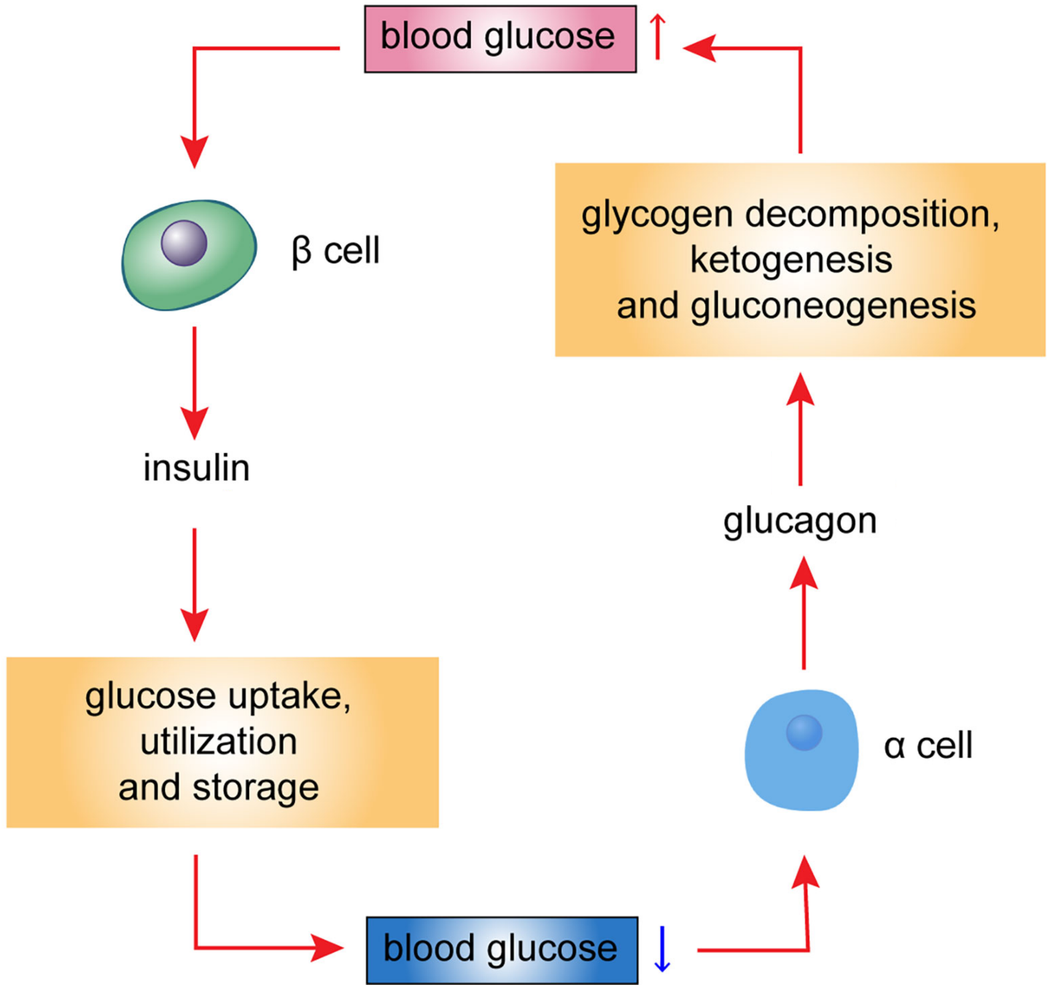

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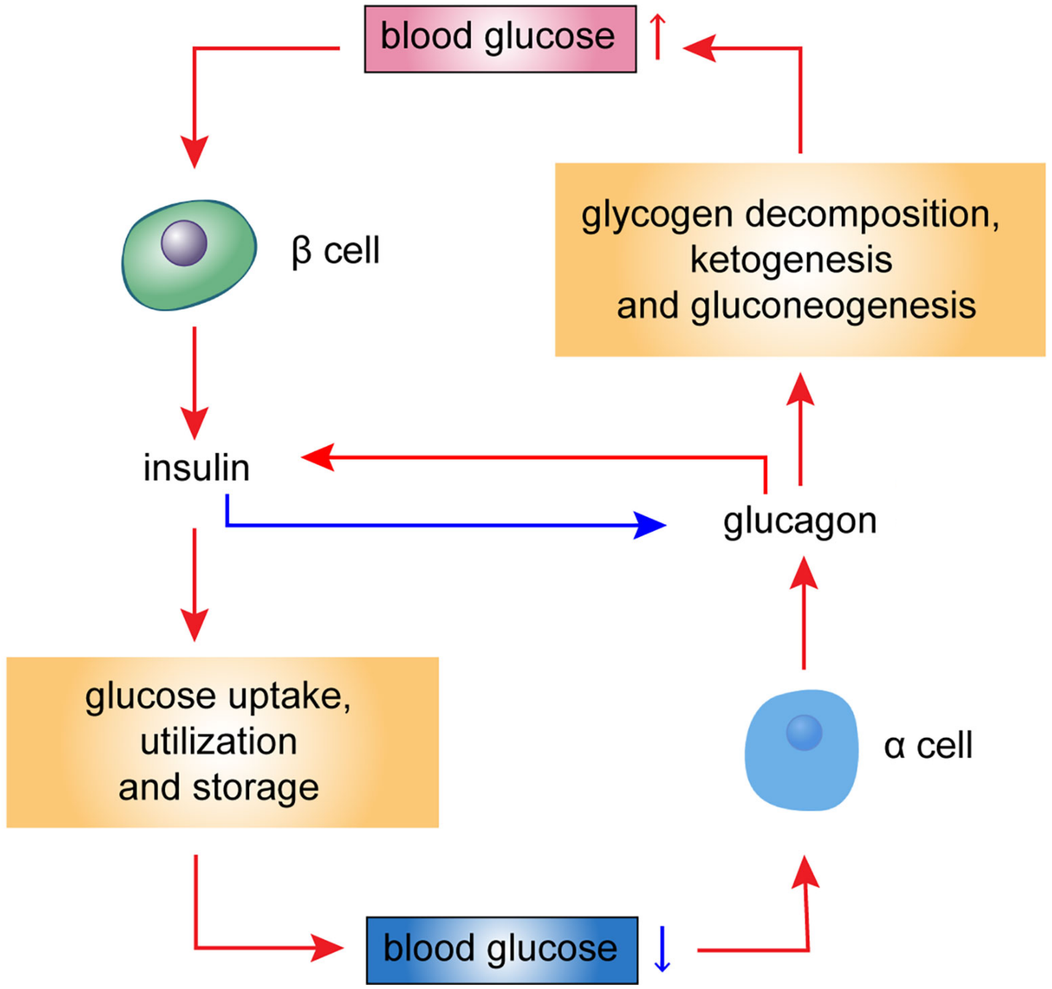

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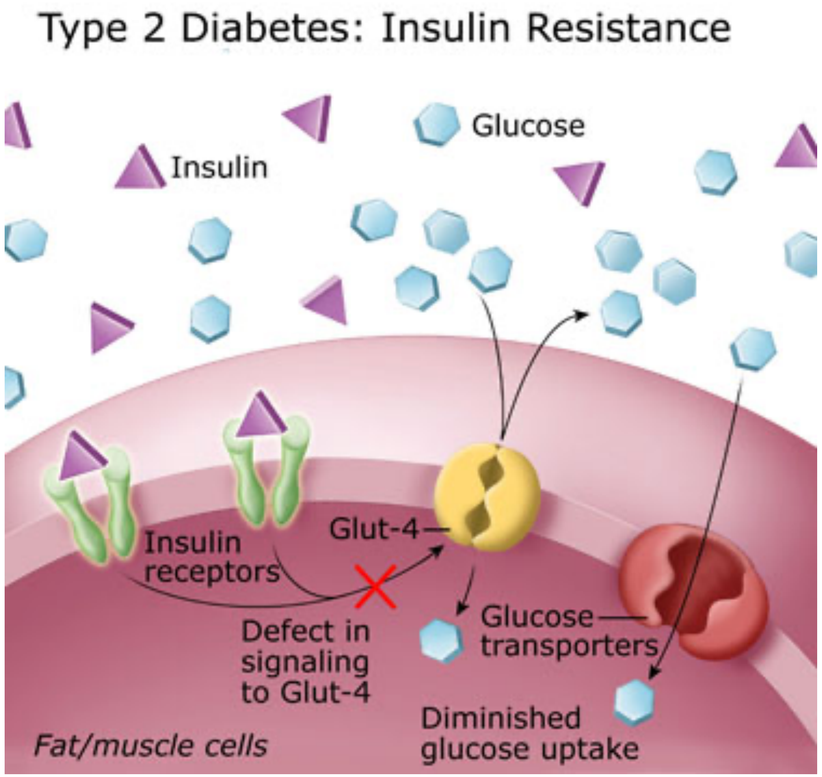
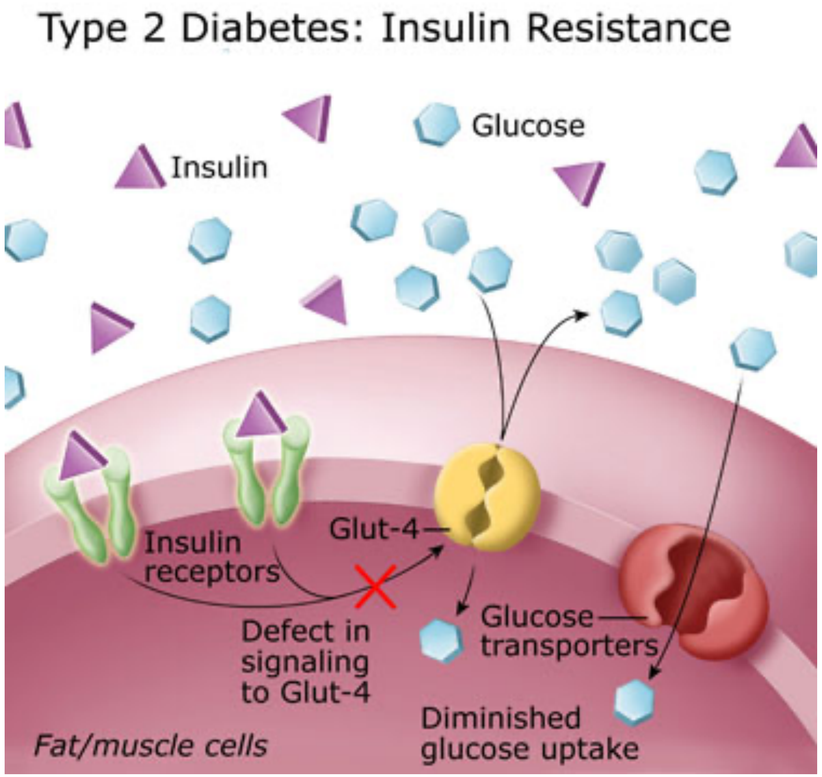
Type 2 Diabetes

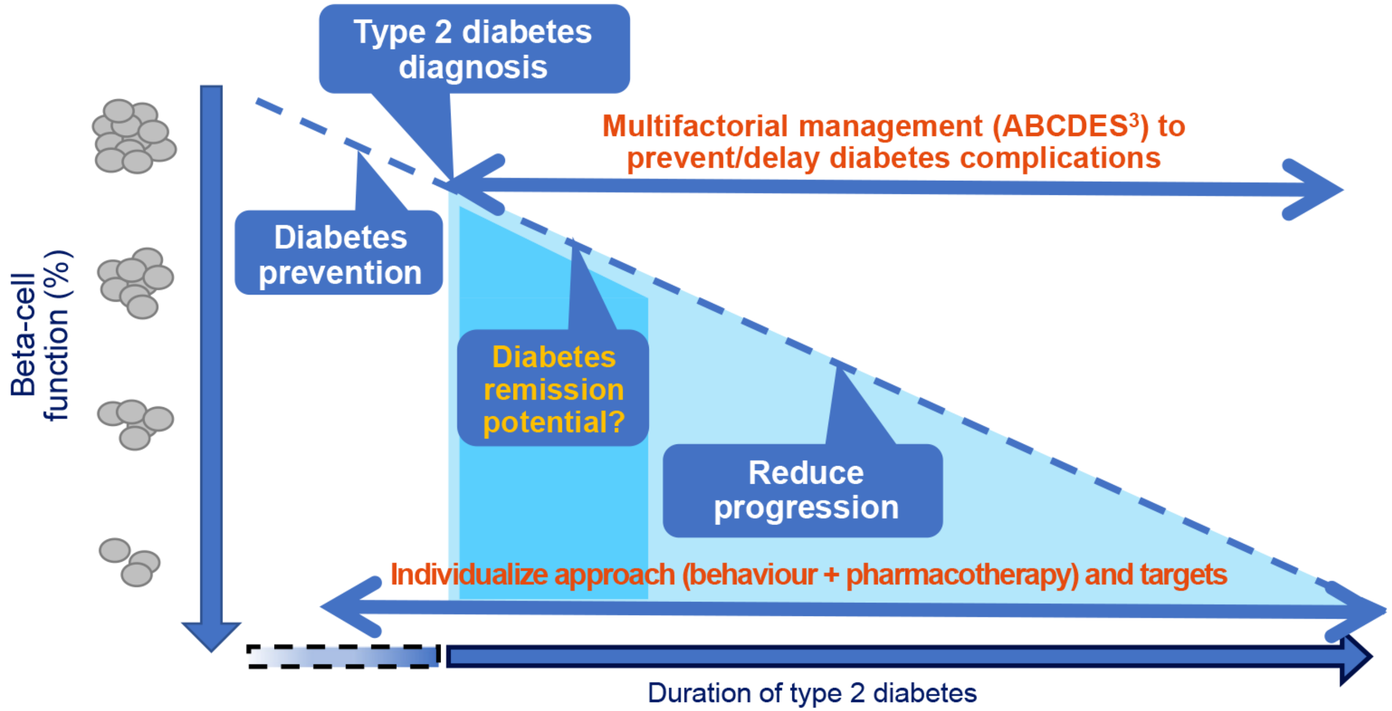


- In type 2 diabetes (T2D), the body does not make enough insulin, or insulin receptors no longer recognize insulin
- Glucose cannot be taken up by cells, resulting in persistent high blood sugar

Alcock, EvolutionMedicine. Diabetes Canada Clinical Practice Guidelines.

Type 2 Diabetes

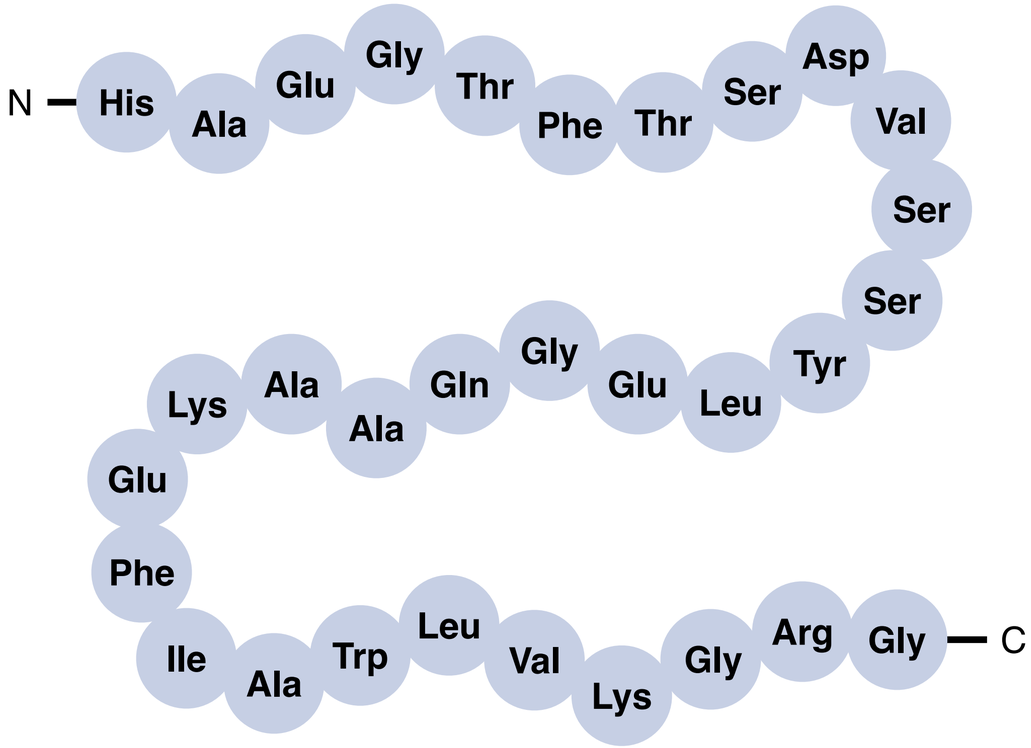




- In type 2 diabetes (T2D), the body does not make enough insulin, or insulin receptors no longer recognize insulin
- Glucose cannot be taken up by cells, resulting in persistent high blood sugar
- Characterized by decreased Beta-cell function as the disease progresses

Alcock, EvolutionMedicine. Diabetes Canada Clinical Practice Guidelines.

Glucagon-like Peptide 1 (GLP-1)



- Incretin hormone (gut hormone released after eating)
- Signals GLP-1 receptors on beta-cells to release insulin
- responsible for 70% of insulin secretion

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

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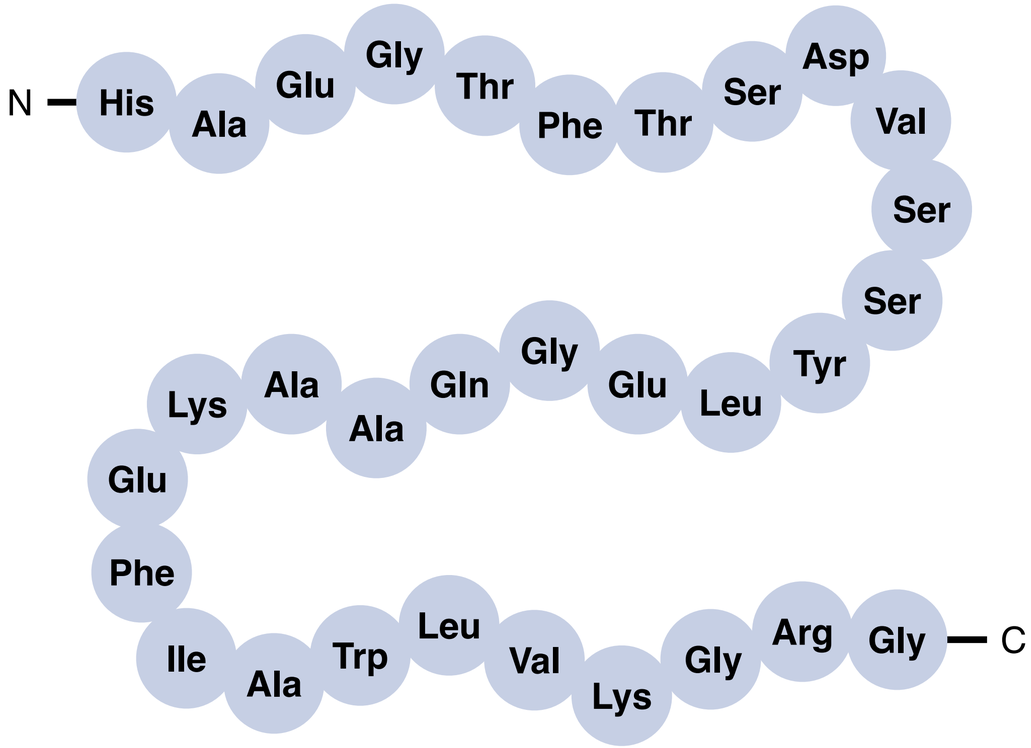

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What happens when we dose GLP-1?

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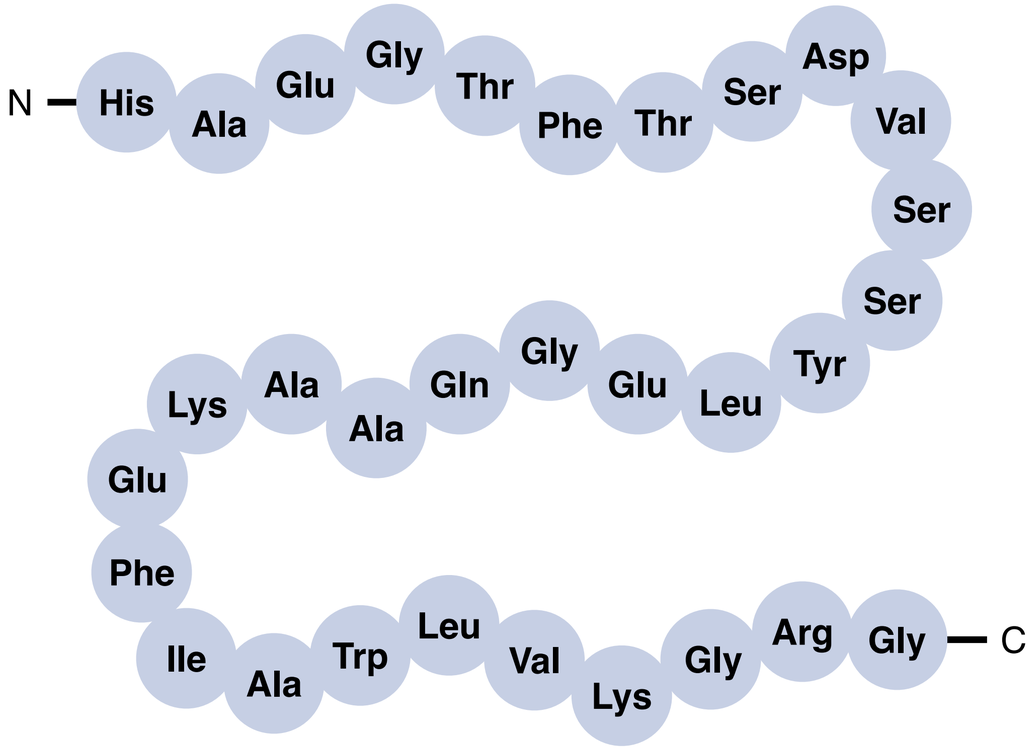

- Incretin hormone (gut hormone released after eating)
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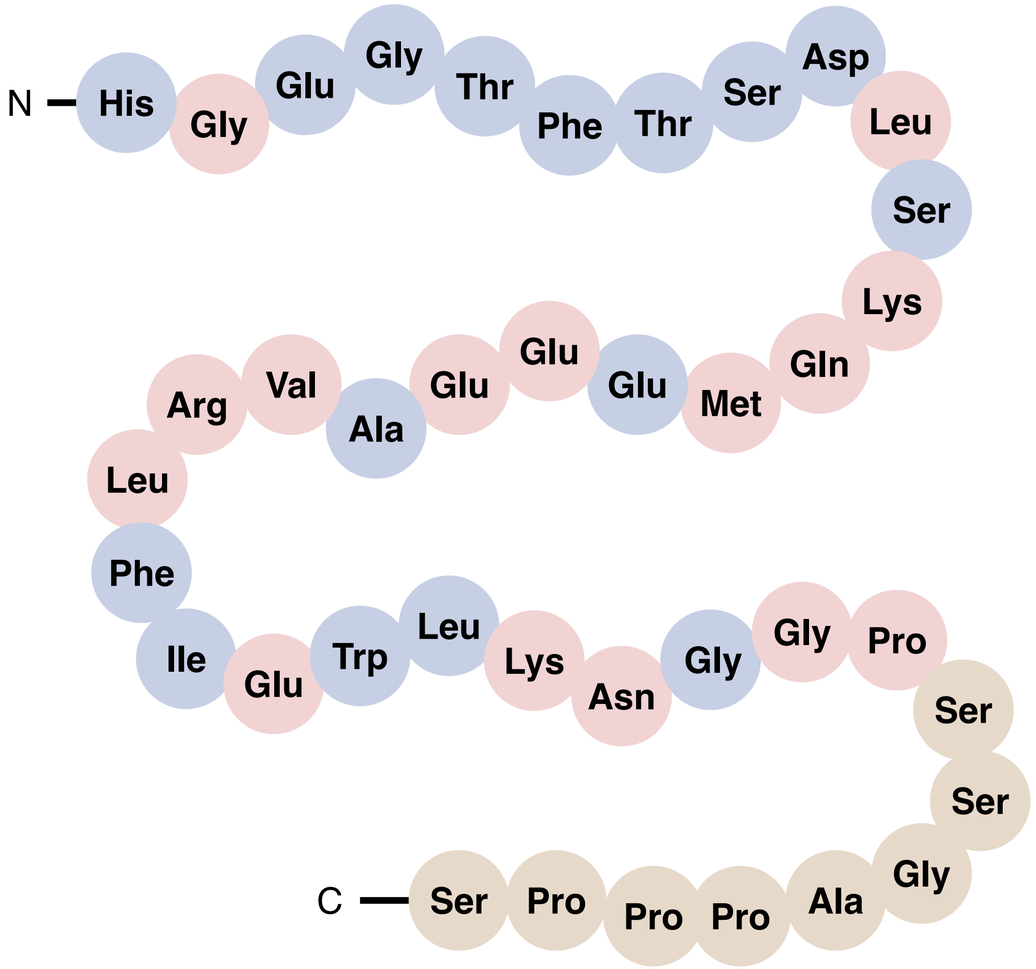
What happens when we dose GLP-1?

- very short half life of ~ 1.5 h
- quickly broken down by dipeptidyl peptidase IV (DPP-IV)

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

Exenatide Development

- naturally-occurring peptide from Heloderma lizard venom
- 53% homology to human GLP-1
- resistant to DPP-IV degradation, leading to a longer $t_{1/2}$



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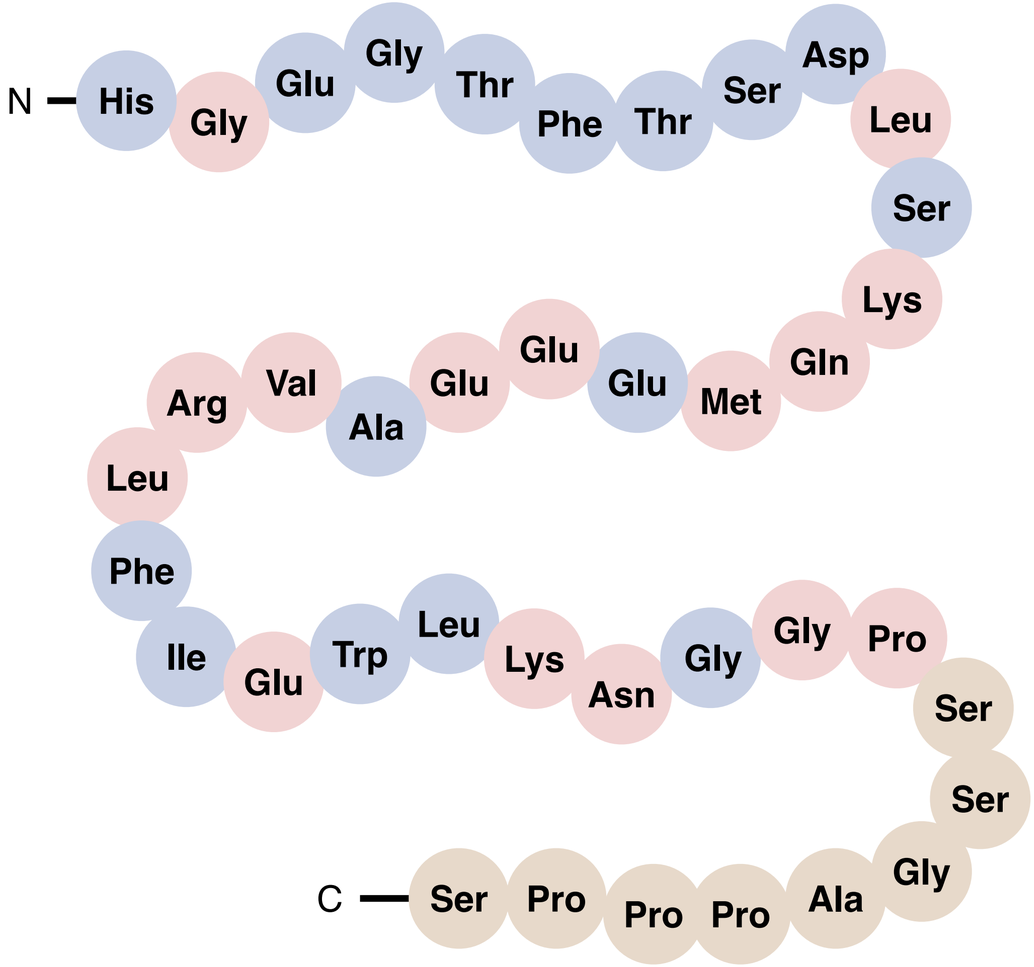

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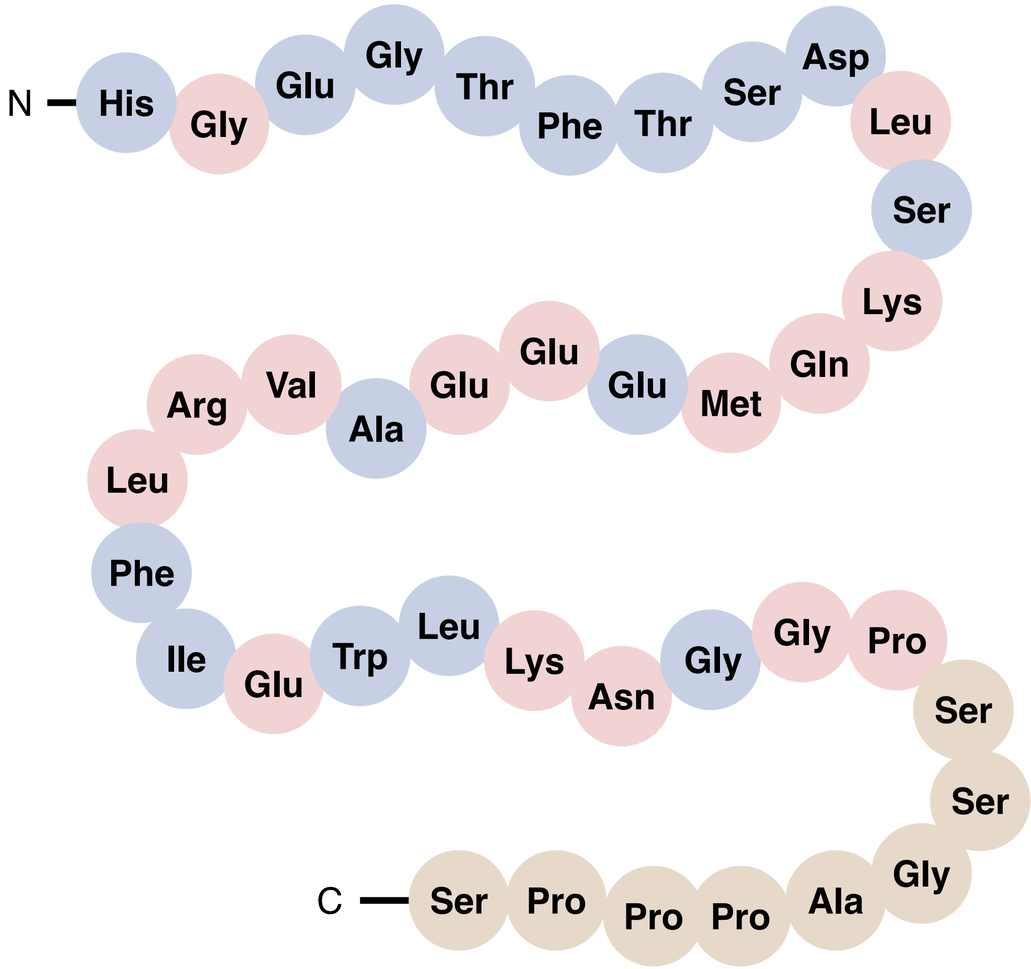

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Byetta faces competition from oral T2D drugs, and is often prescribed as an “add-on” to Metformin

Parkes, D.G.; Mace, K.F.; Trautmann, M.E. *Expert Opin. Drug Discov.* **2012**, *8*, 219.

GLP-1 Analogues as T2D Treatments

Dr. Lotte Bjerre Knudsen

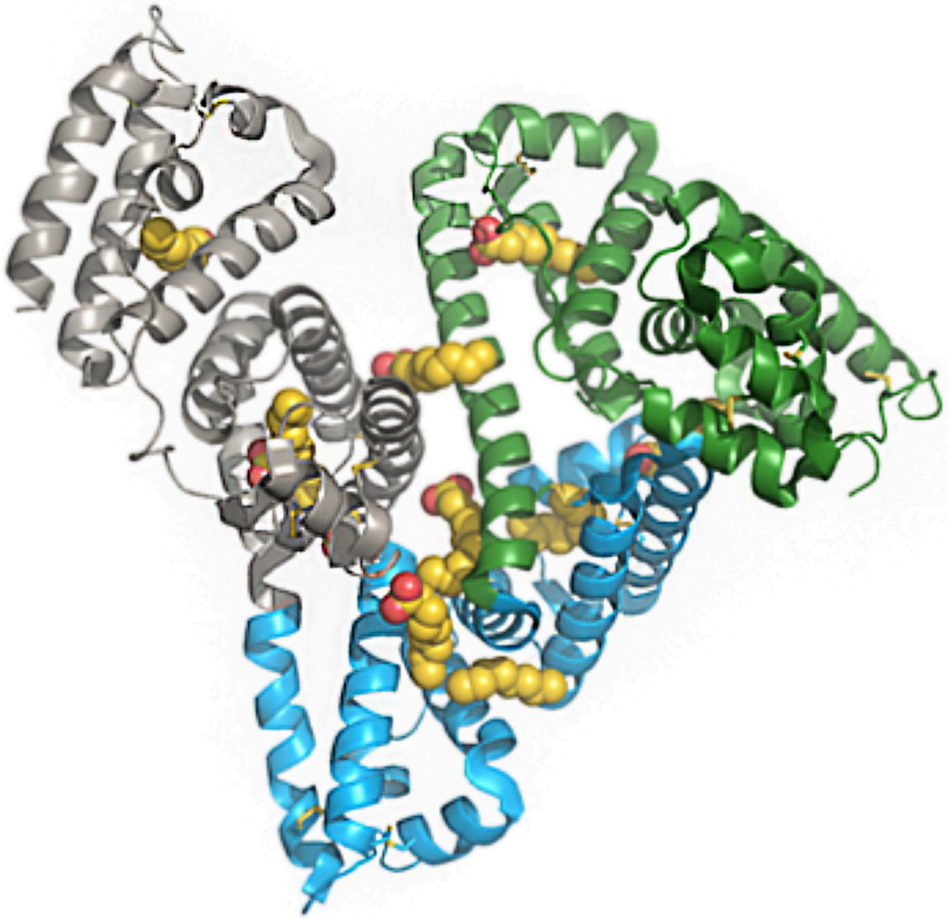
began the development of liraglutide in the mid 1990s

Novo Nordisk (Denmark)

big name in diabetes care, long history of insulin production and development

How can we develop a long-acting GLP-1 analogue effective for the treatment of T2D?

Human Serum Albumin (HSA)



- Protein found in human plasma
- Highly abundant (35g / L)
- Long half life of several weeks

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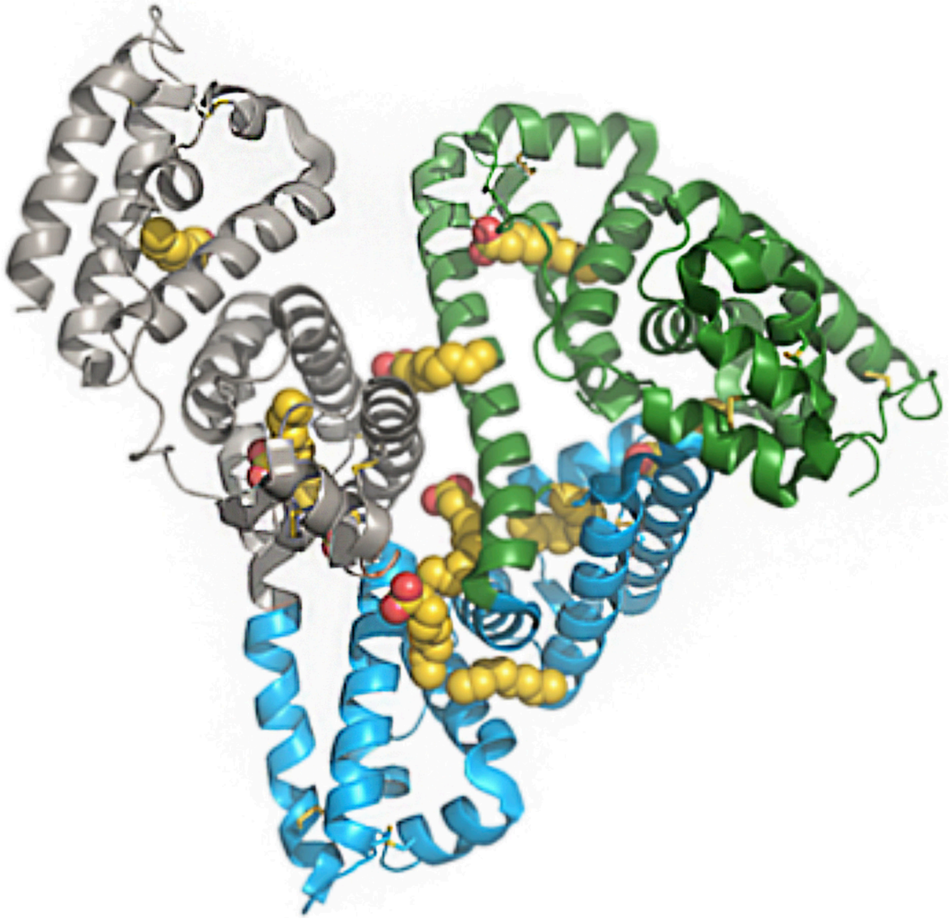

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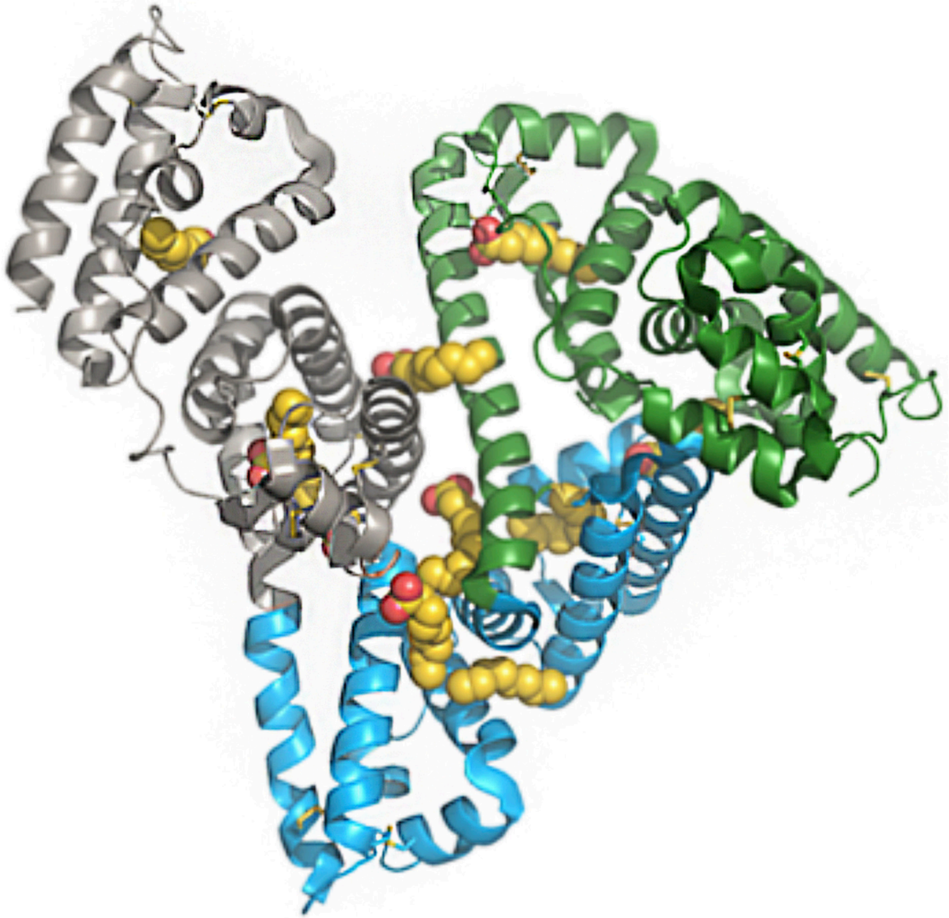

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Can albumin binding be used to improve the half life of a GLP-1 analogue?

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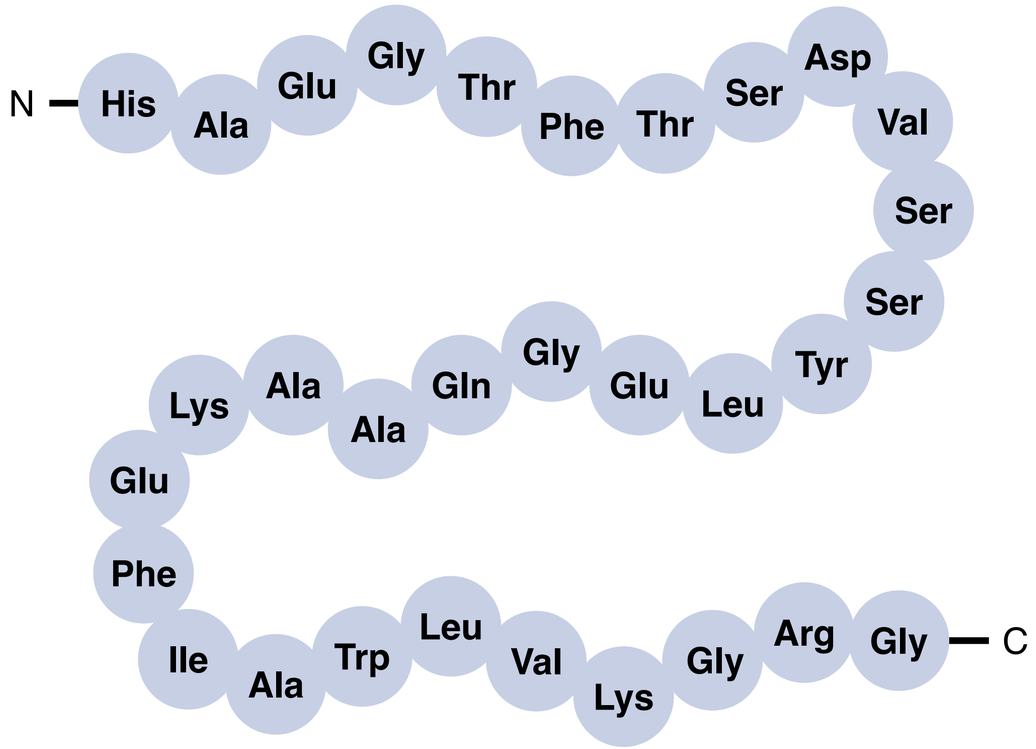
Liraglutide Development

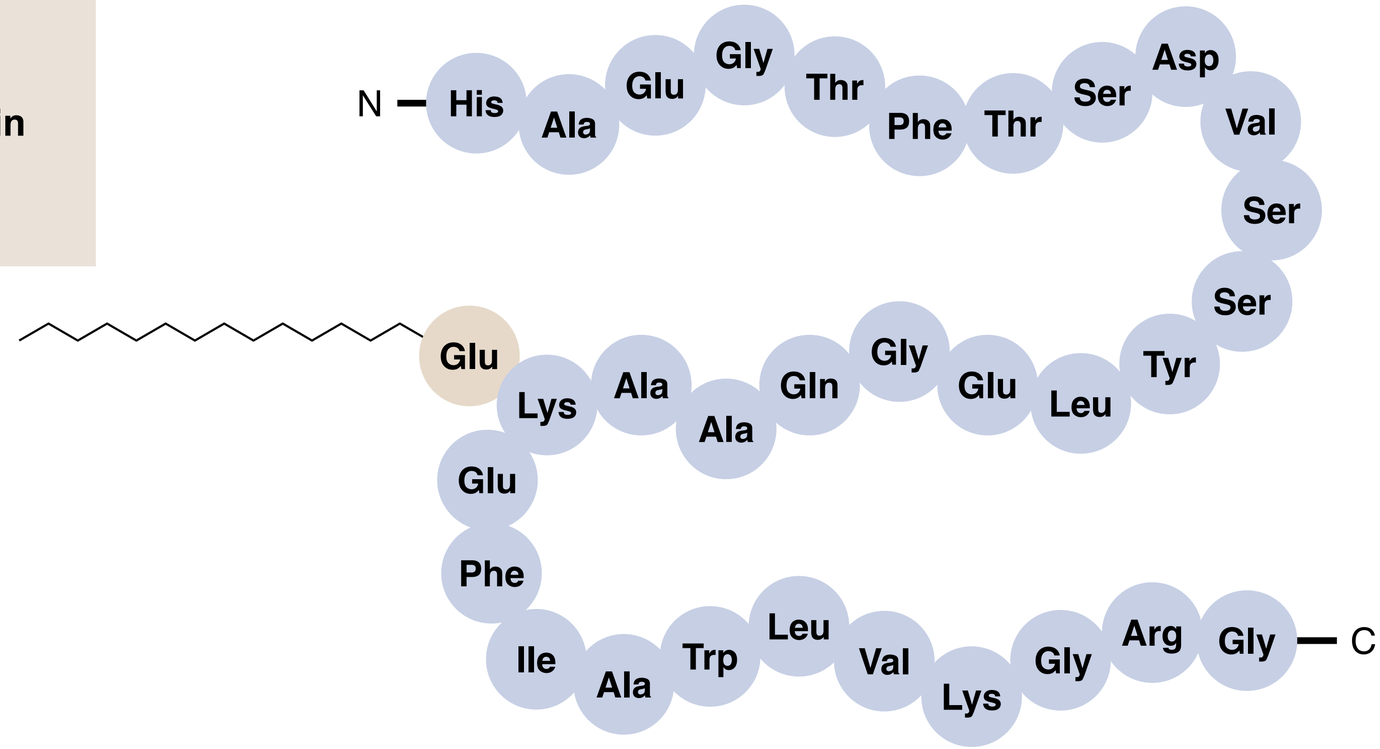


Starting from native GLP-1…

Knudsen, L.B. *et. al. J. Med. Chem.* **2000**, *43,* 1664. Madsen, K. *et. al. J. Med. Chem.* **2007**, *50*, 6126.

Liraglutide Development

fatty acid chain promotes albumin binding



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Liraglutide Development

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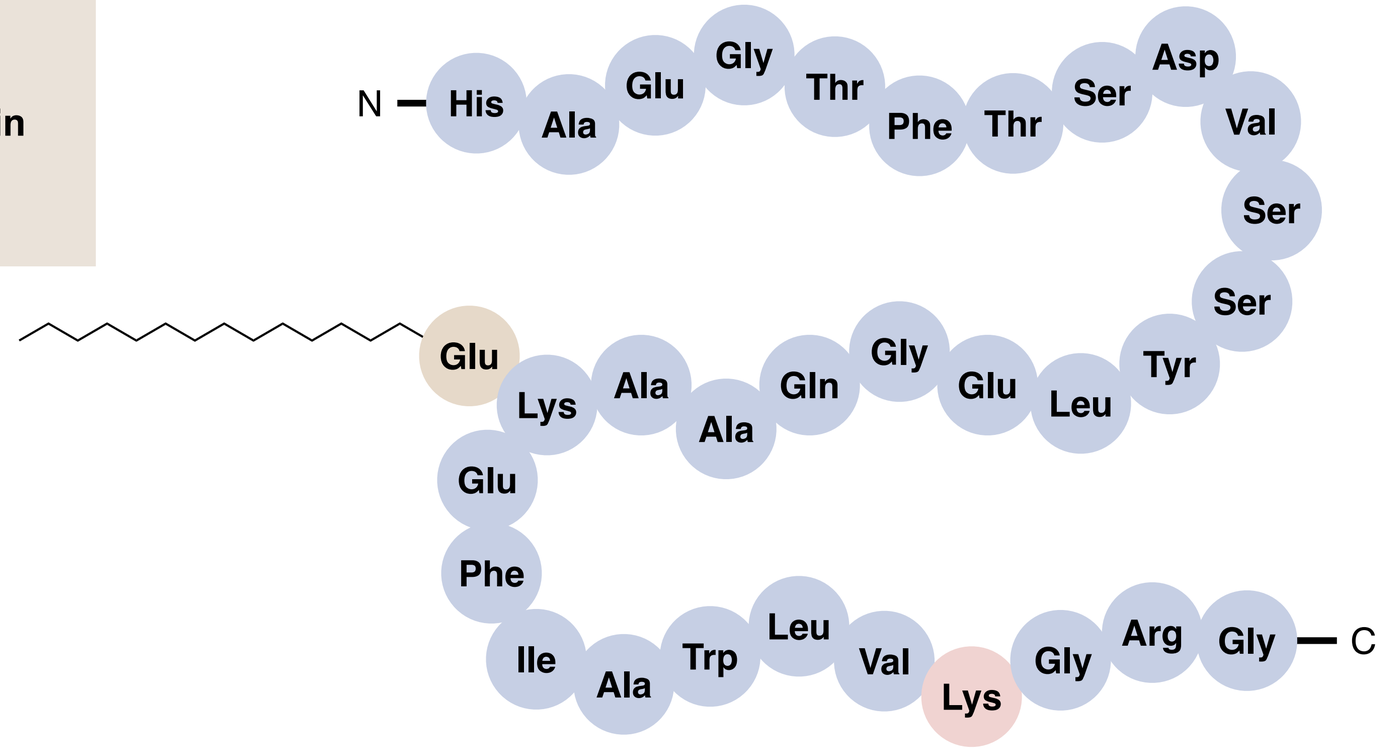

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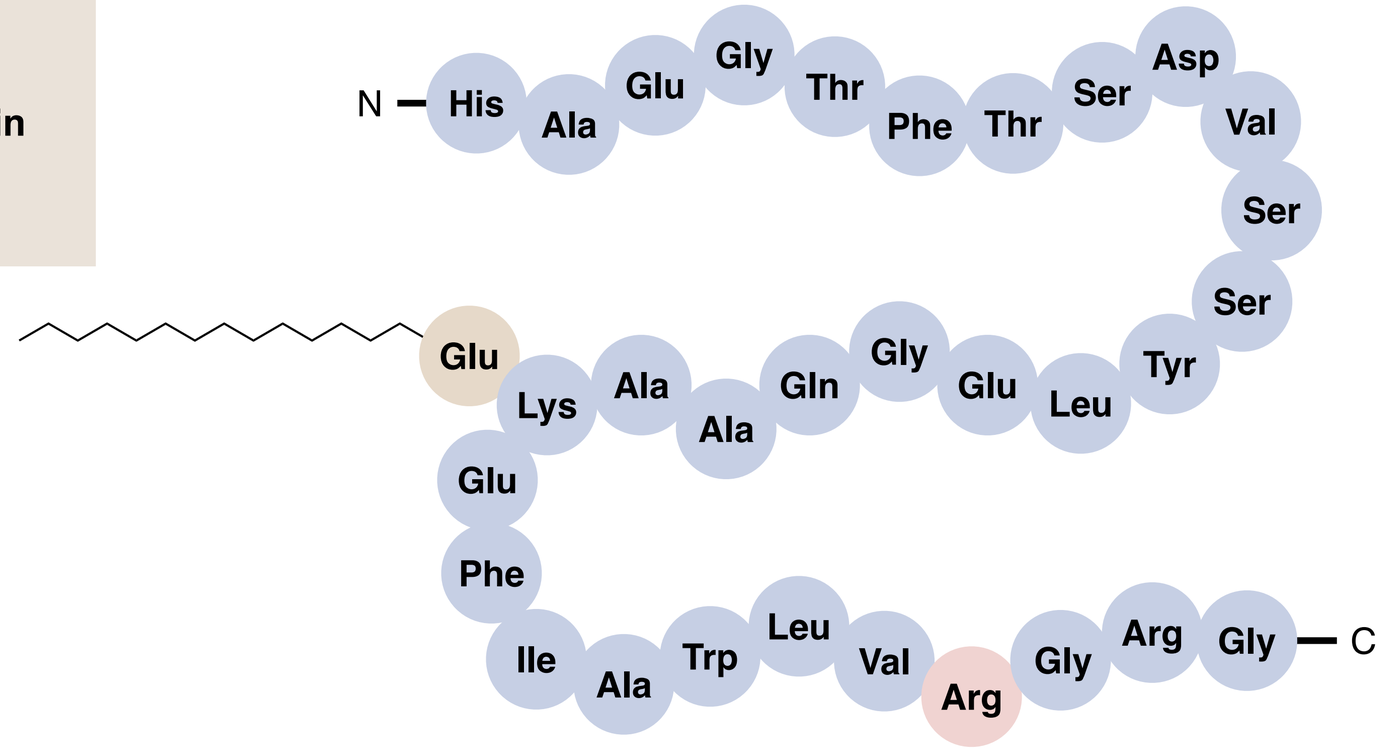

Replacing lysine with arginine will streamline synthesis

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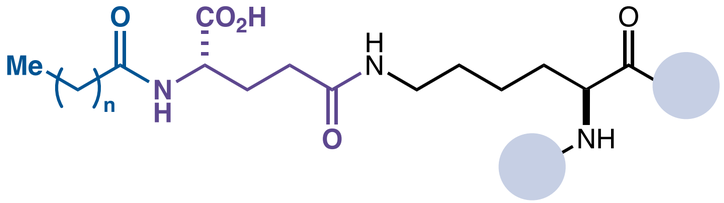
Liraglutide Development



Fatty Acid

Glutamic Acid (Spacer)

Lysine

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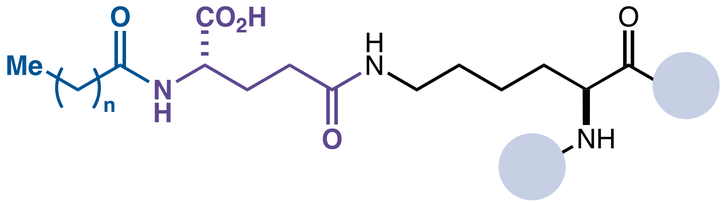
Liraglutide Development



Fatty Acid | Glutamic Acid (Spacer) | Lysine

Chain Length	EC_{50}	$t_{1/2}$
GLP-1		
n = 8		
n = 9		
n = 10		
n = 12		
n = 14		
n = 16		

A "good" drug would have a low EC_{50} and a long half life

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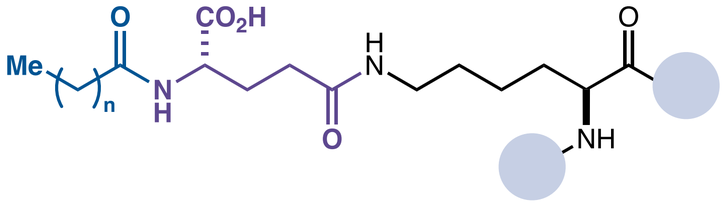
Liraglutide Development

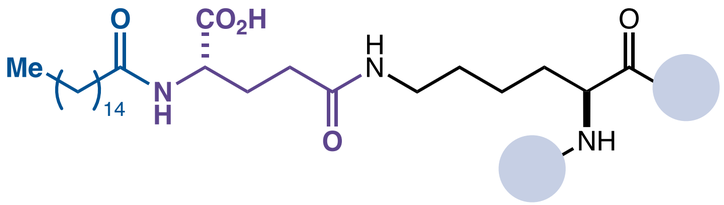


Fatty Acid | Glutamic Acid (Spacer) | Lysine

Chain Length	EC_{50}	$t_{1/2}$
GLP-1	55	1.2
n = 8	39	0.8
n = 9	66	5.1
n = 10	29	7.6
n = 12	27	9.0
n = 14	61	16
n = 16	170	21

Knudsen, L.B. *et. al. J. Med. Chem.* **2000**, *43,* 1664. Madsen, K. *et. al. J. Med. Chem.* **2007**, *50*, 6126.

Liraglutide Development



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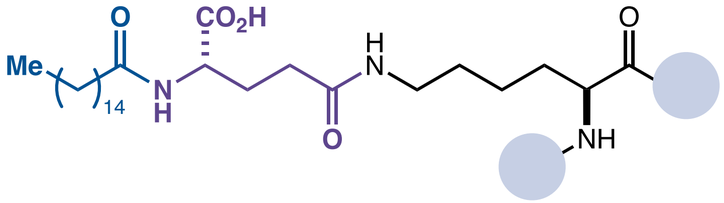

Fatty Acid | Glutamic Acid (Spacer) | Lysine

Spacer	EC_{50}	$t_{1/2}$
y-Glu		
D-y-Glu		
a-Glu		
TEG		
GABA		
B-Ala		
no spacer		

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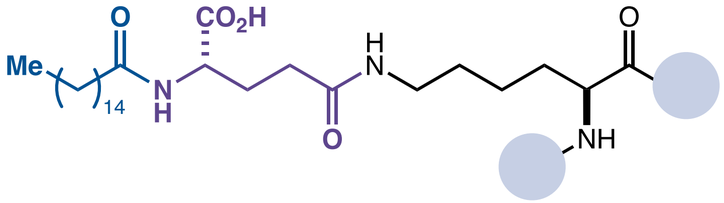
Liraglutide Development



Fatty Acid | Glutamic Acid (Spacer) | Lysine

Spacer	EC_{50}	$t_{1/2}$
y-Glu	61	16
D-y-Glu	74	22
a-Glu	76	12
TEG	1570	13
GABA	84	31
B-Ala	113	8.8
no spacer	4440	21

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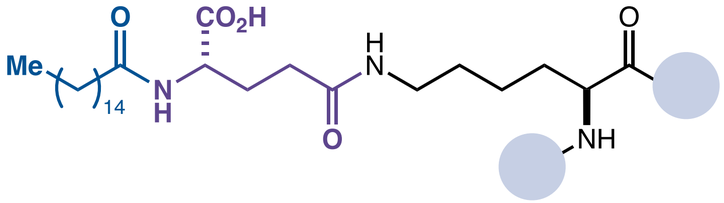

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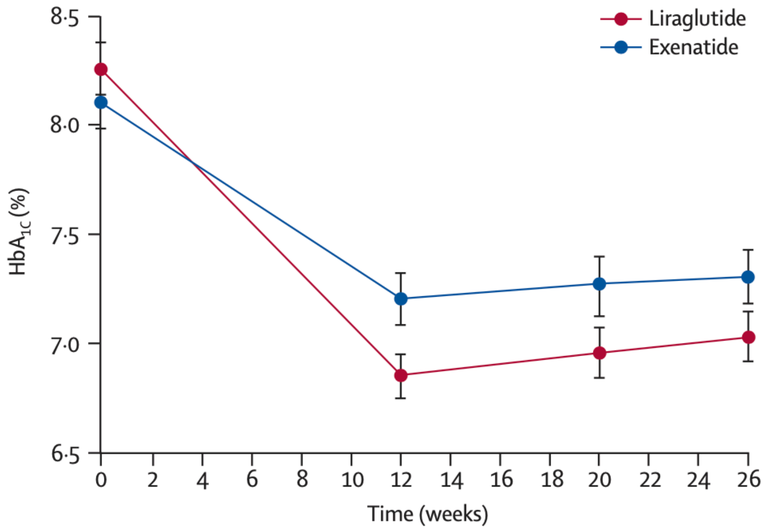
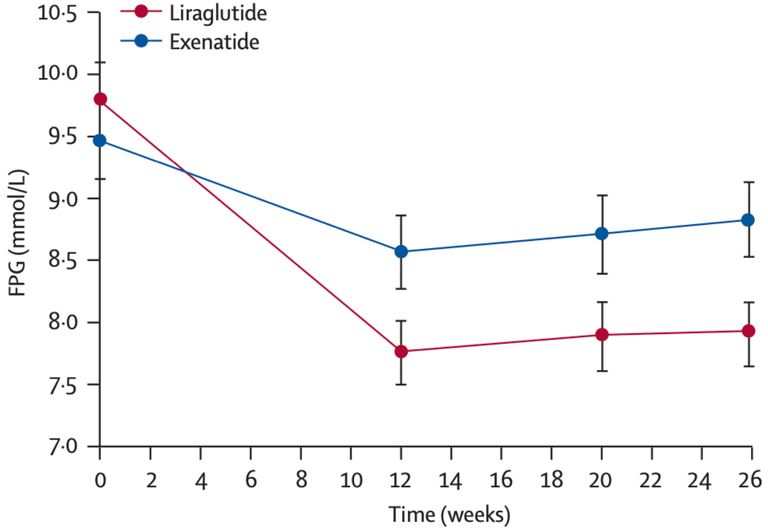
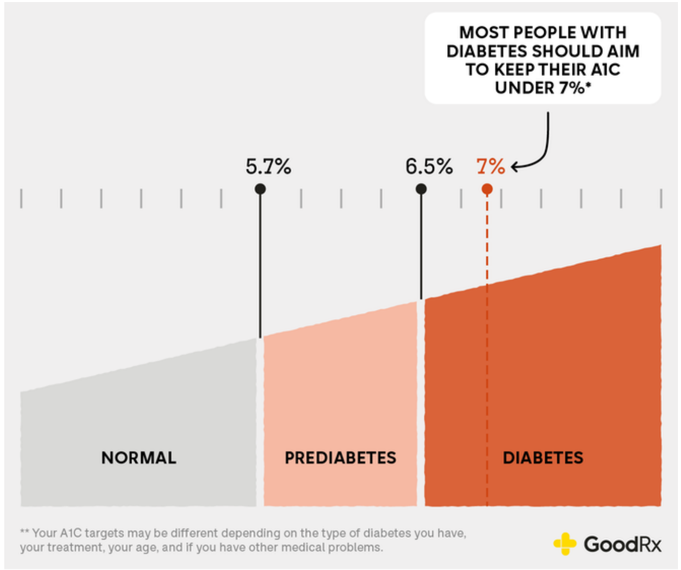
Liraglutide Phase 3 Clinical Trials (T2D)







- 1.8 mg daily dose for patients with T2D
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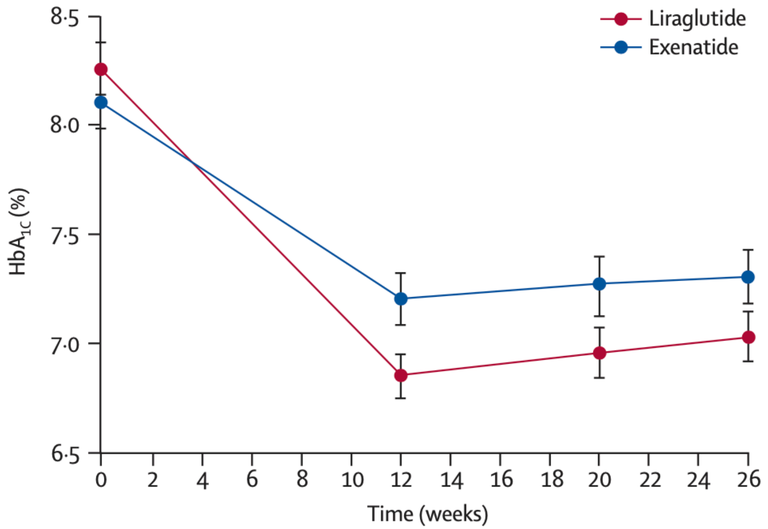
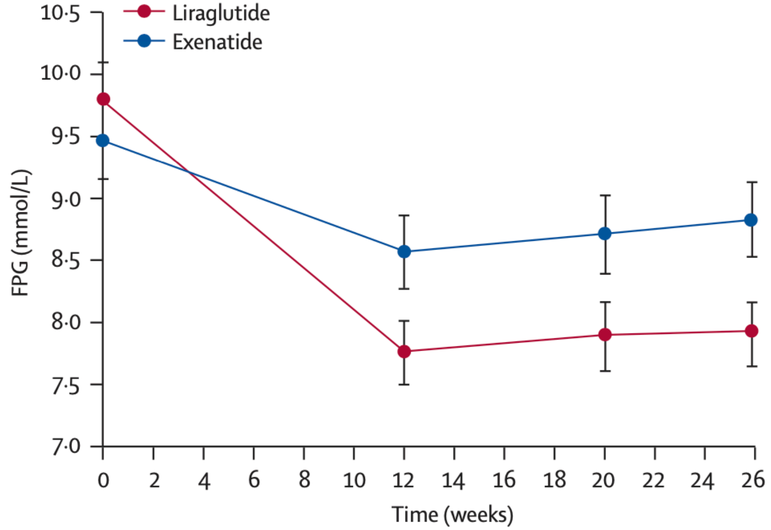
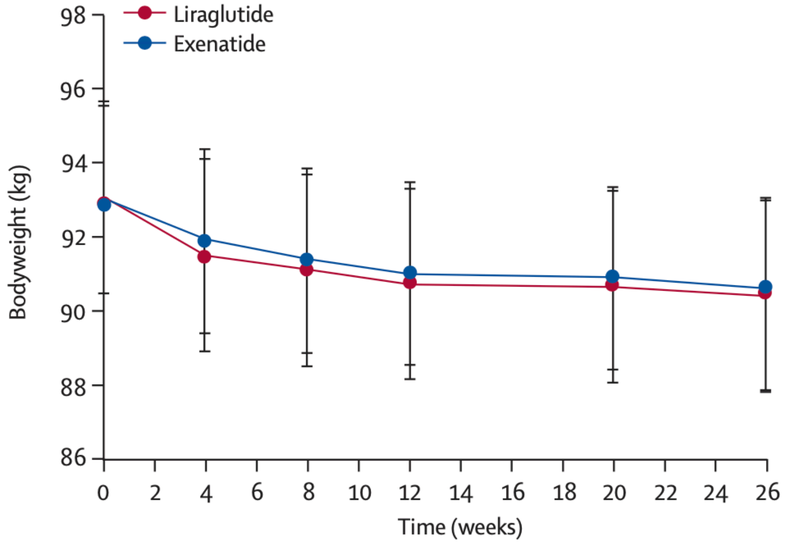
Buse, J.B. *et. al. Lancet* **2009**, *374,* 39.

Liraglutide Phase 3 Clinical Trials (T2D)







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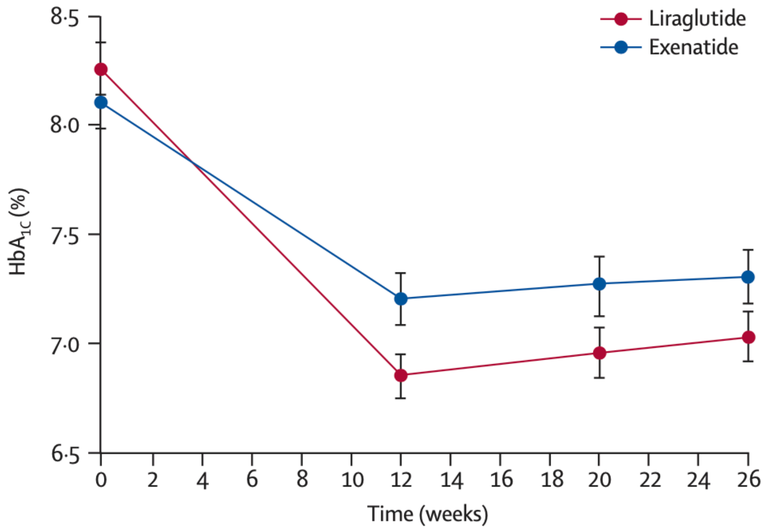

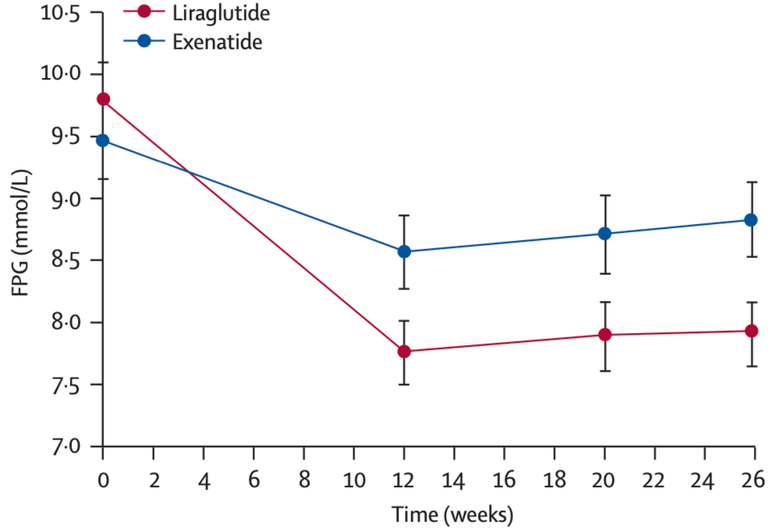

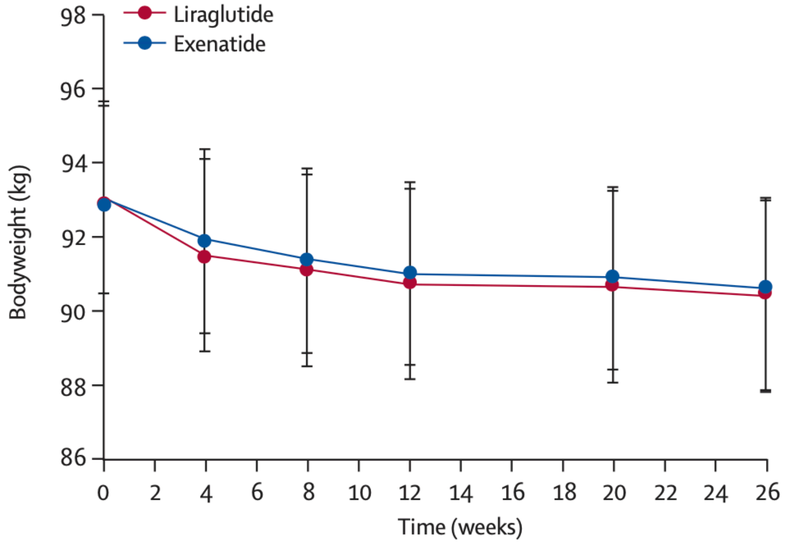

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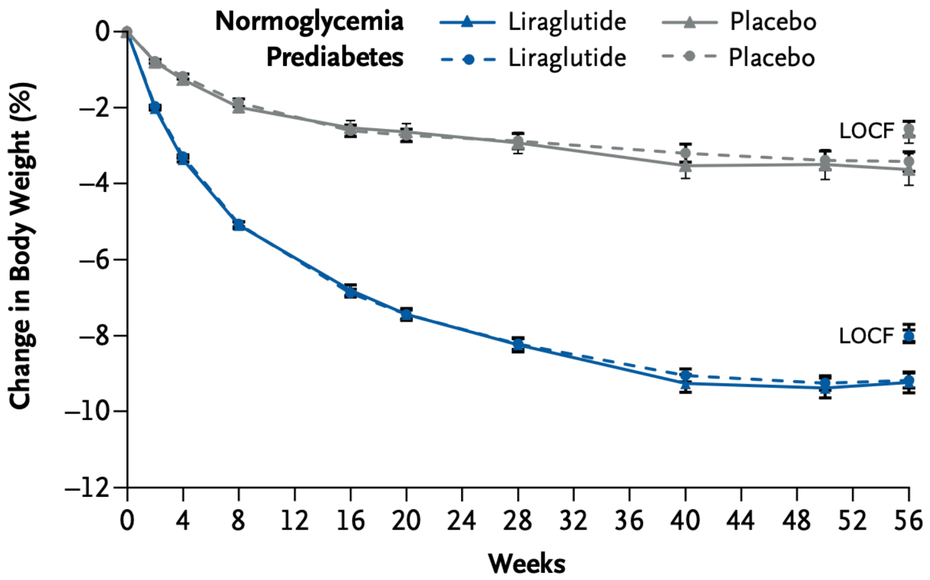
Liraglutide is approved for T2D in 2010 under the brand name Victoza

Buse, J.B. *et. al. Lancet* **2009**, *374,* 39.

Liraglutide Phase 3 Clinical Trials (Weight Loss)



- 3.0 mg daily dose for patients with obesity (not T2D)
- Participants lose ~8% of their body weight on average

Pi-Sunyer, X. *et. al. New Engl. J. Med.* **2015**, *373,* 11.

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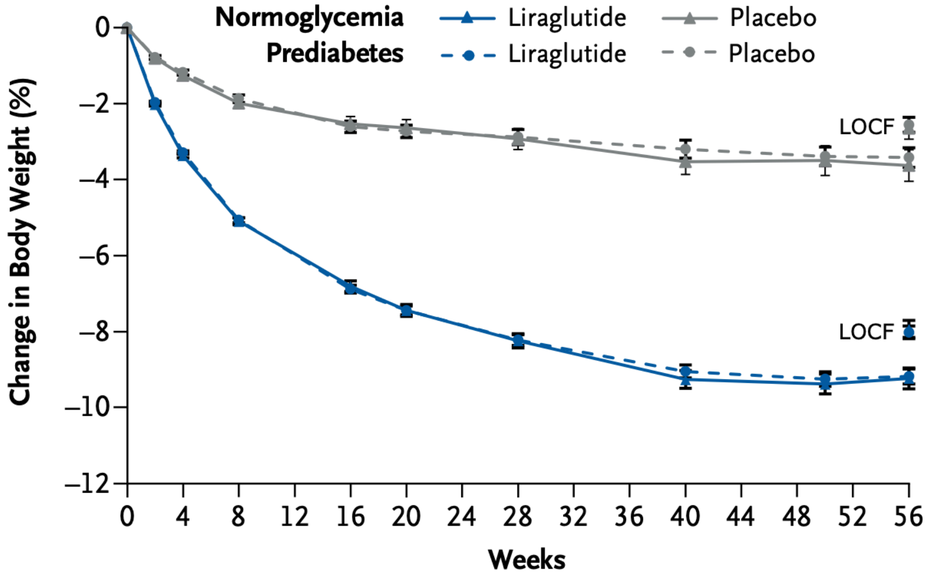

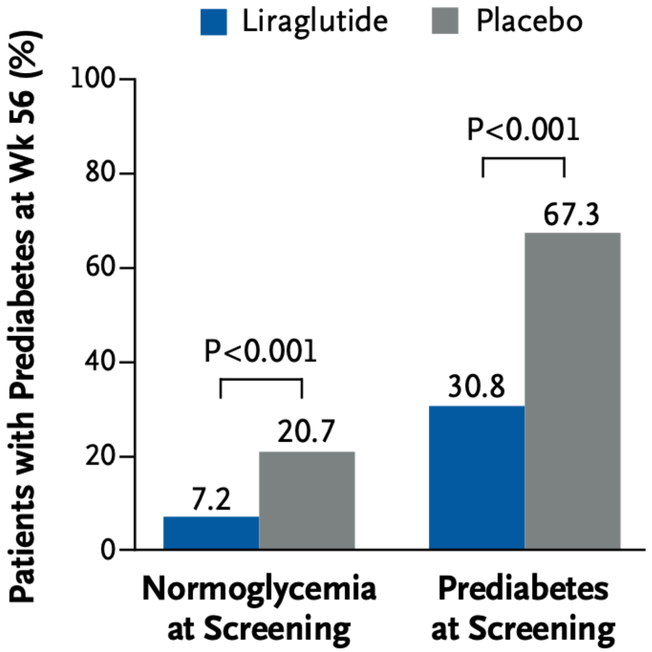

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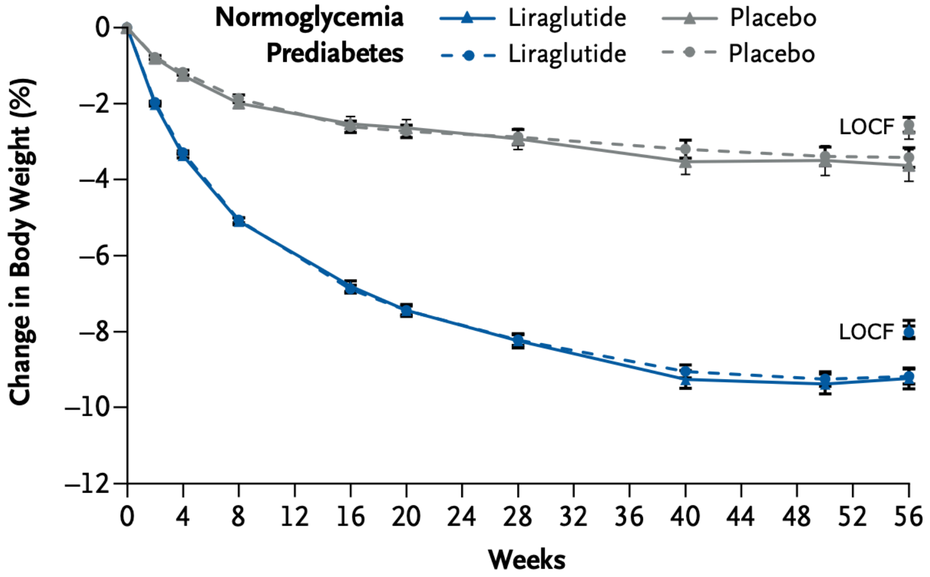

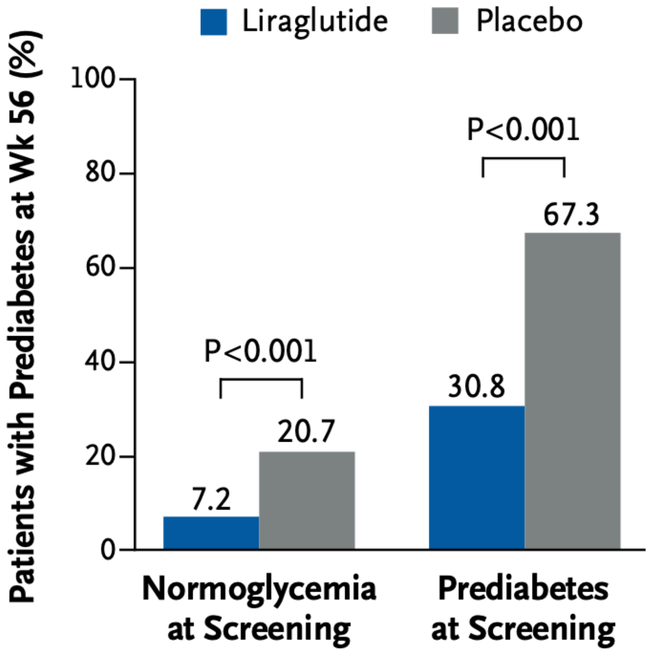

- 3.0 mg daily dose for patients with obesity (not T2D)
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Liraglutide is approved for obesity in 2014 under the brand name Saxenda

Pi-Sunyer, X. *et. al. New Engl. J. Med.* **2015**, *373,* 11.

Why does Liraglutide cause weight loss?

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

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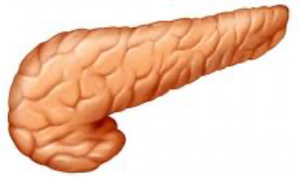

Lowering blood sugar levels by signaling GLP-1

receptors on the pancreas does not explain weight loss

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

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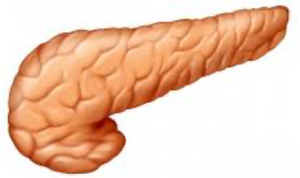
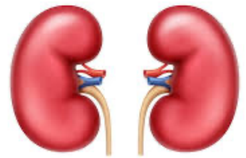


GLP-1 receptors are found in many areas of the body



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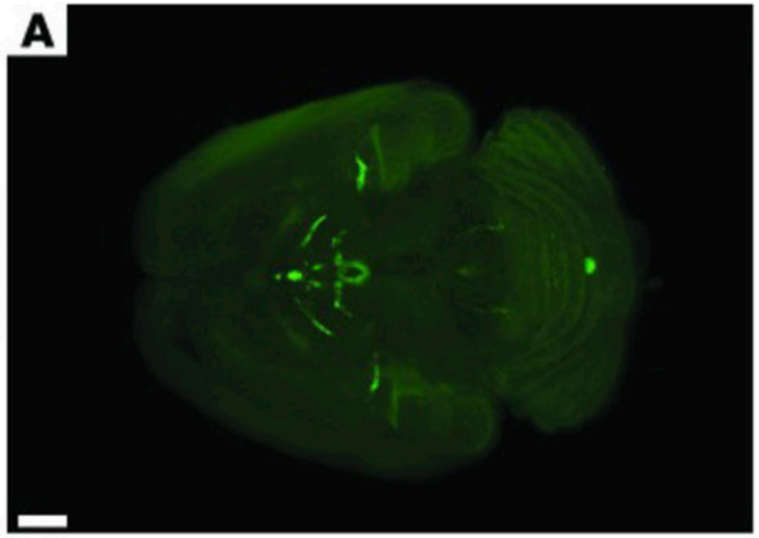

- Fluorescent version of liraglutide shown to cross the BBB to access the hypothalamus

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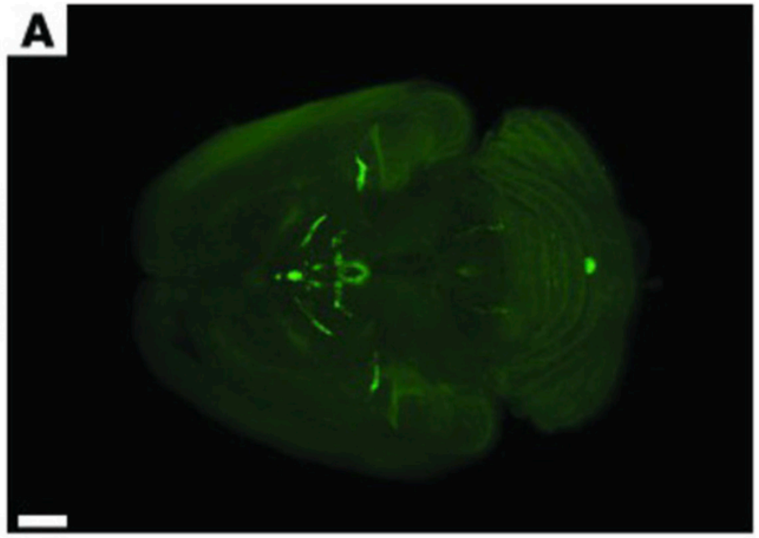
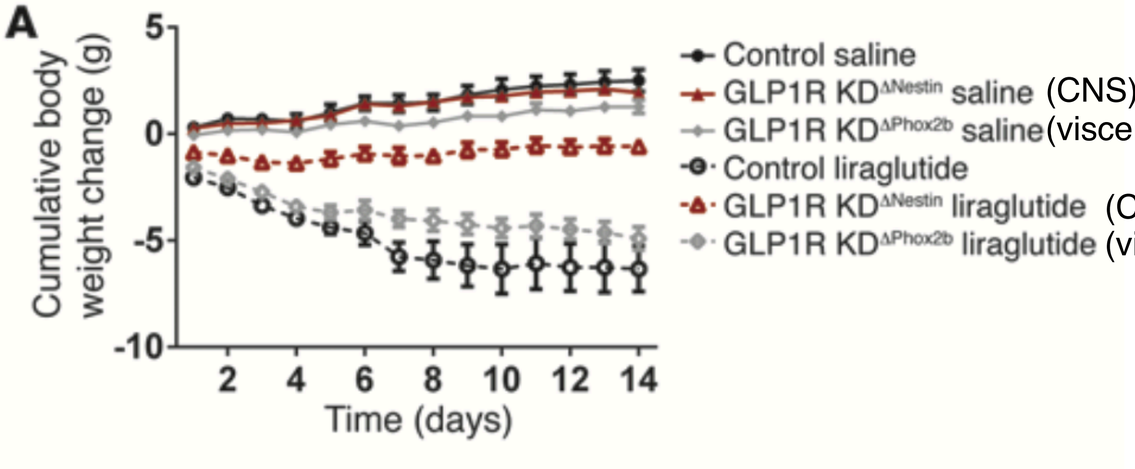


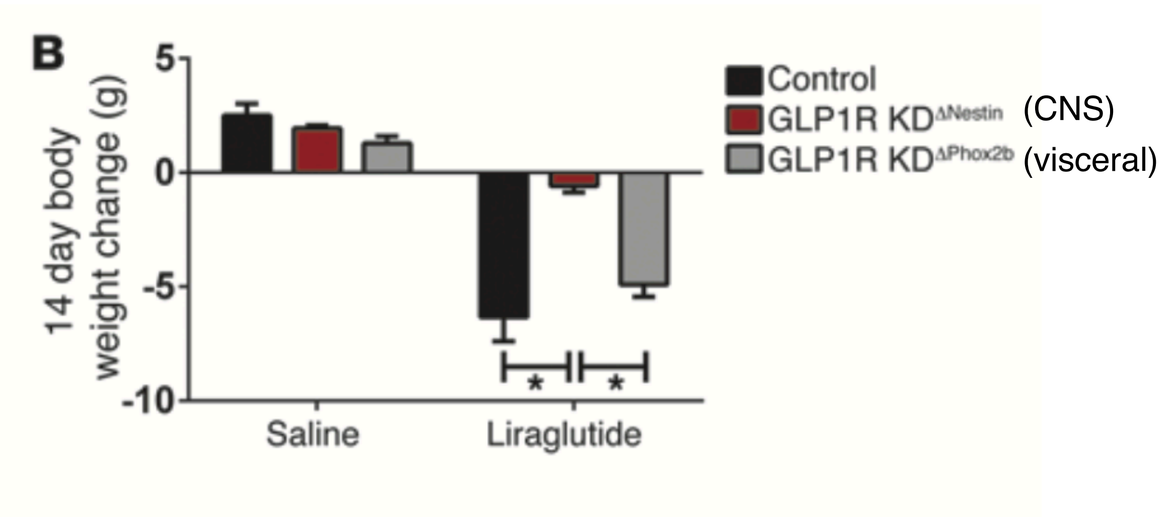
- Fluorescent version of liraglutide shown to cross the BBB to access the hypothalamus
- Liraglutide was not observed in the brain in mice lacking functional GLP-1Rs

Liraglutide enters the brain in a GLP-1R dependent manner

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

Why does Liraglutide cause weight loss?

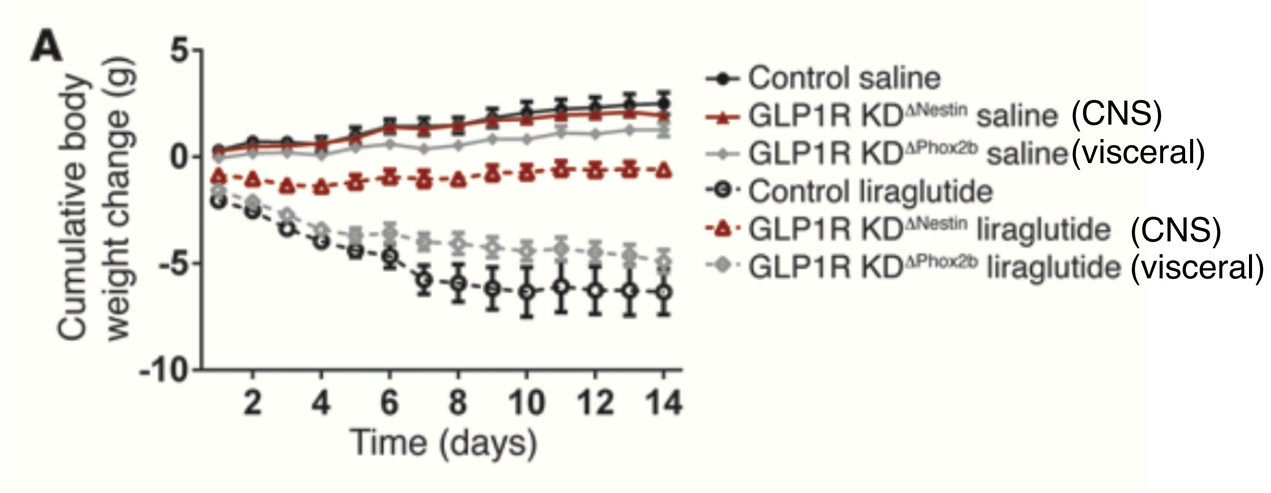


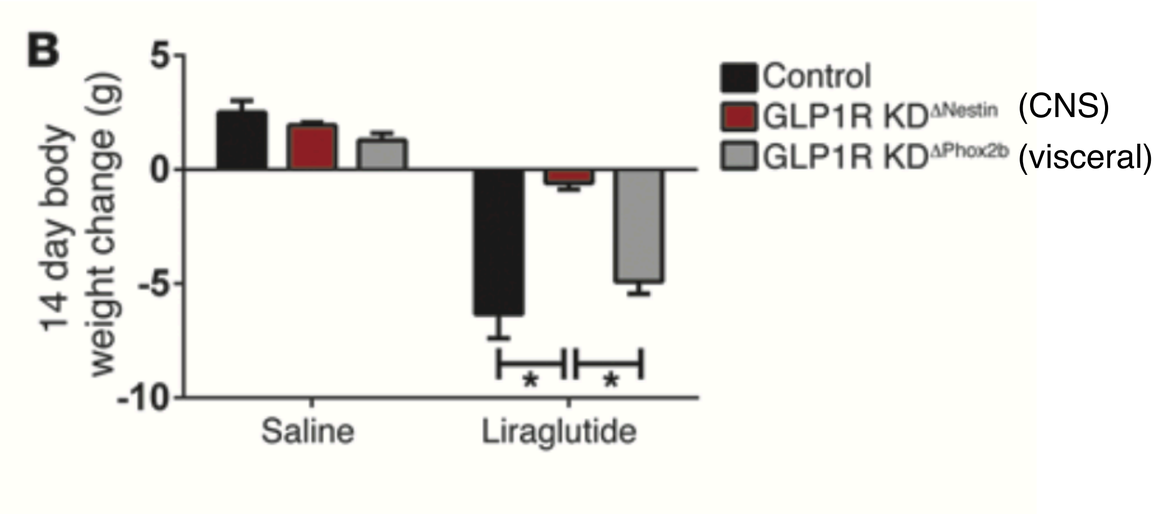


- Mice were generated with GLP-1R knockdowns in the CNS or the visceral nerves
- The CNS GLP-1 receptors are implicated in weight loss with liraglutide administration

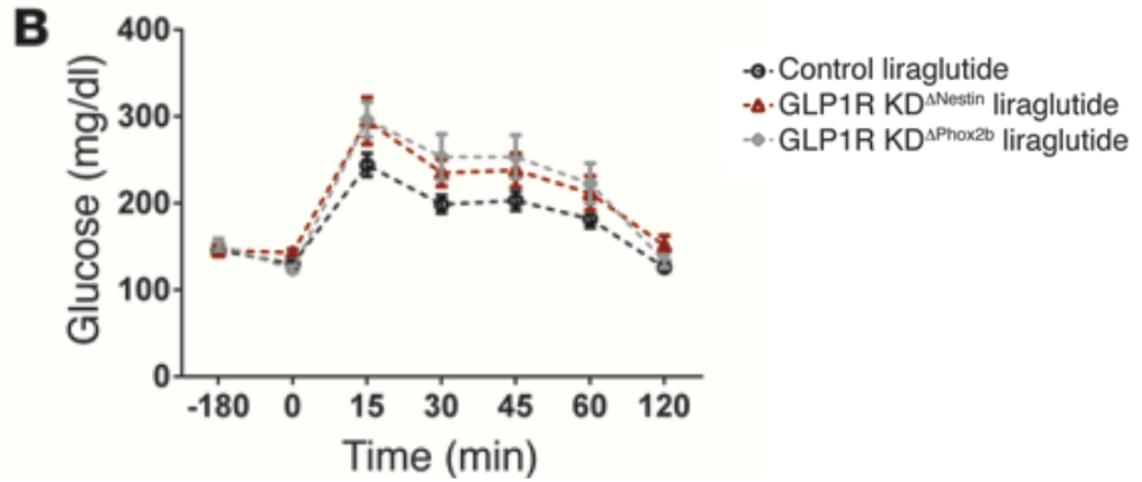
Sisley, S. *et. al. J. Clin. Invest.* **2014**, *124,* 2456.

Why does Liraglutide cause weight loss?





- Mice were generated with GLP-1R knockdowns in the CNS or the visceral nerves
- The CNS GLP-1 receptors are implicated in weight loss with liraglutide administration
- Neither CNS or visceral nerve GLP-1Rs were implicated in liraglutide's glucose lower effects



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Next Gen GLP-1 Analogues

Can we develop a GLP-1 analogue for once weekly dosing?

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

Next Gen GLP-1 Analogues

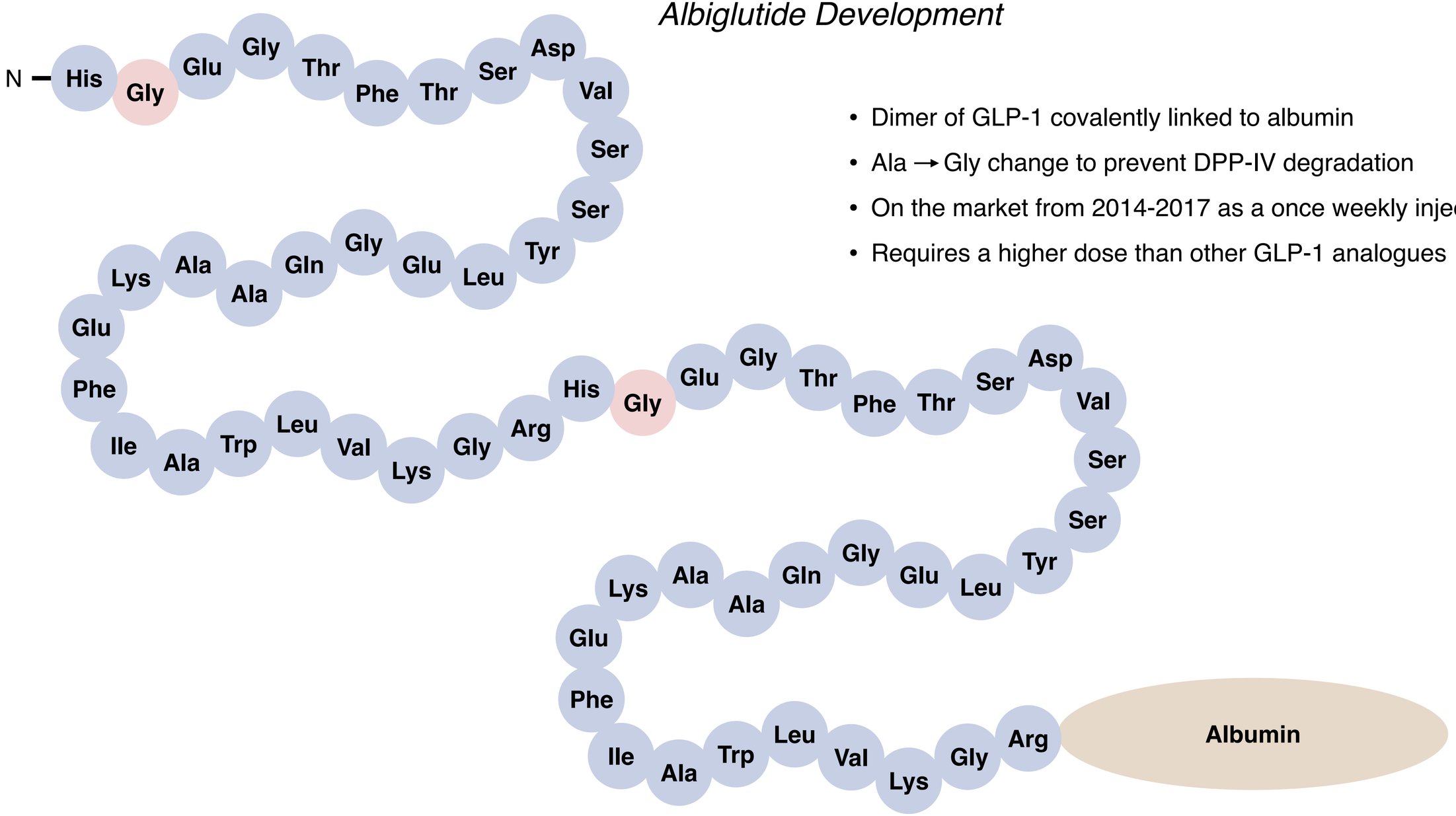
Can we develop a GLP-1 analogue for once weekly dosing?

Idea:

Can we covalently link GLP-1 to albumin to further increase its lifetime?

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

Albiglutide Development



- Dimer of GLP-1 covalently linked to albumin
- Ala → Gly change to prevent DPP-IV degradation
- On the market from 2014-2017 as a once weekly injection
- Requires a higher dose than other GLP-1 analogues

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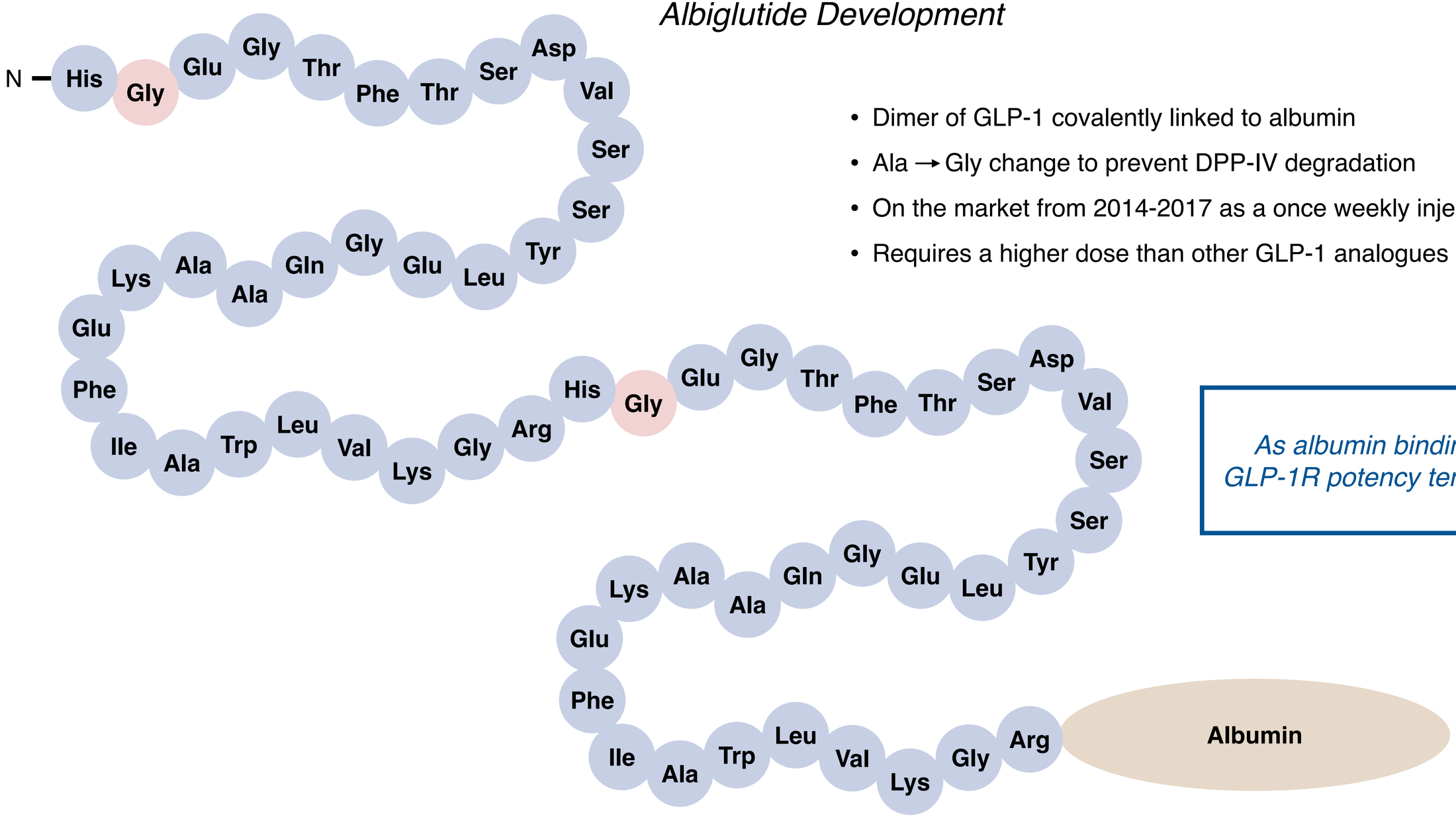

- Dimer of GLP-1 covalently linked to albumin
- Ala → Gly change to prevent DPP-IV degradation
- On the market from 2014-2017 as a once weekly injection
- Requires a higher dose than other GLP-1 analogues

As albumin binding increases, GLP-1R potency tends to decrease

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

Next Gen GLP-1 Analogues

Can we develop a GLP-1 analogue for once weekly dosing?

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Next Gen GLP-1 Analogues

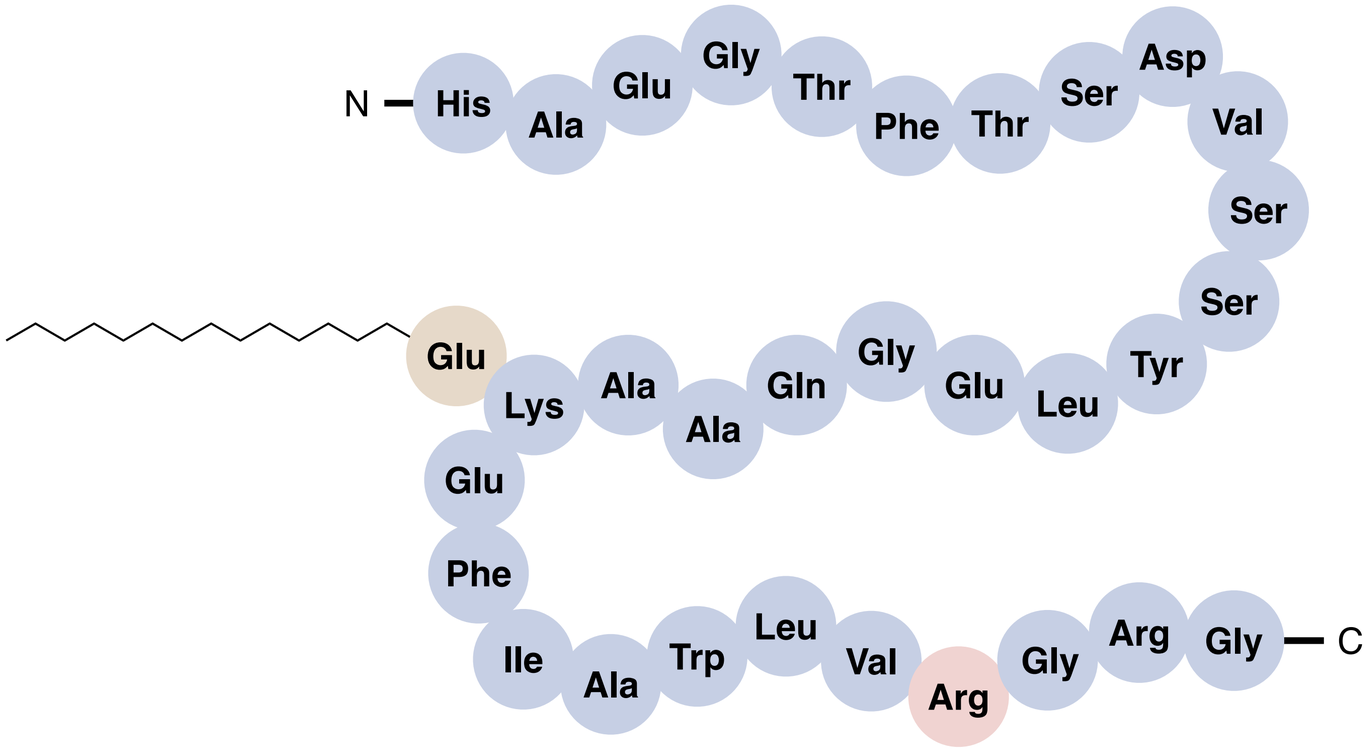
Can we develop a GLP-1 analogue for once weekly dosing?

Goals:

1. Develop a GLP-1 analogue for once weekly dosing by optimizing albumin binding
2. Maintain GLP-1R potency without requiring large doses
3. Make it as similar to native GLP-1 as possible to reduce immunogenicity responses

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

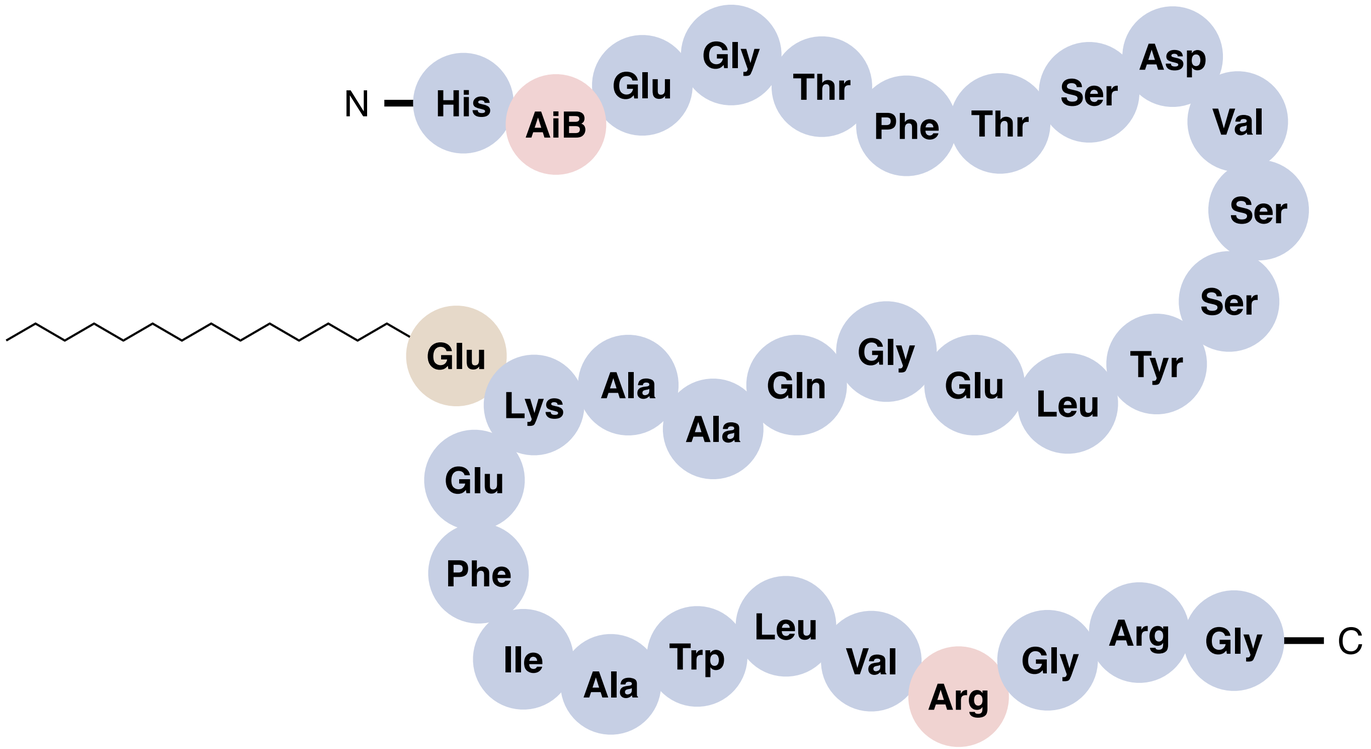
Semaglutide Development



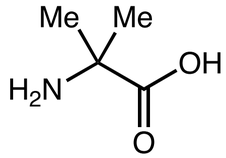
Starting from liraglutide…

Lau, J. *et. al. J. Med. Chem.* **2015**, *58,* 7370.

Semaglutide Development



unnatural amino acid improves DPP-IV stability



aminoisobutyric acid (AiB)

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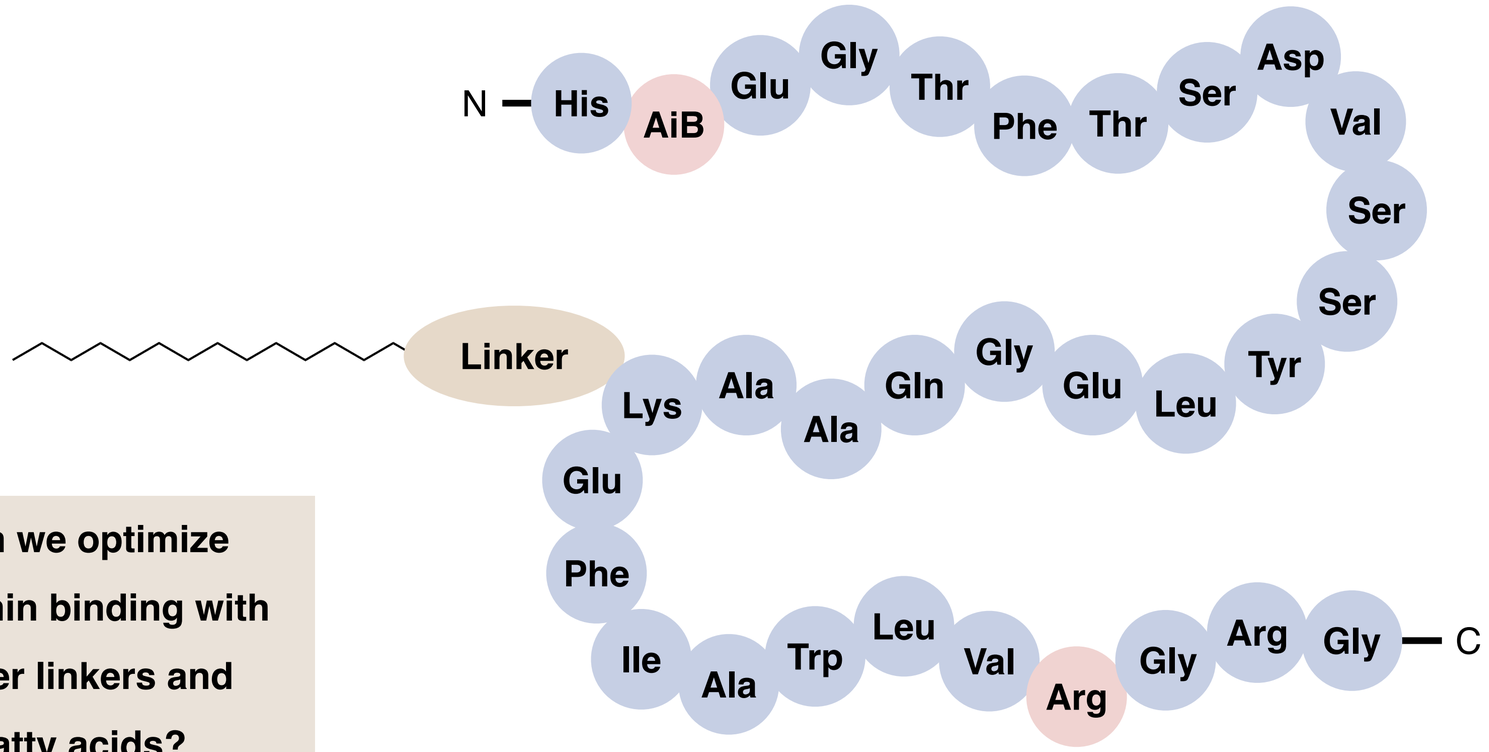
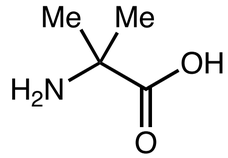
Semaglutide Development



Can we optimize albumin binding with other linkers and fatty acids?

unnatural amino acid improves DPP-IV stability



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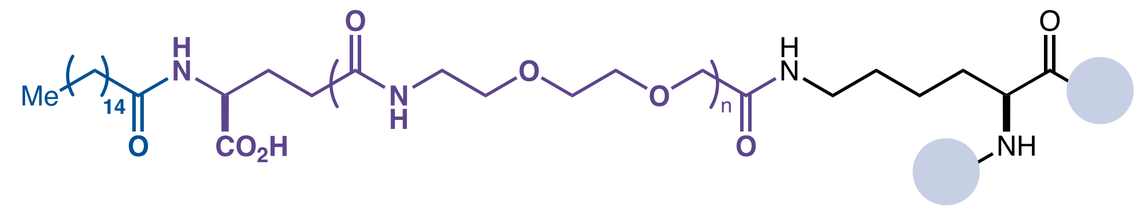

Fatty Acid | Glutamic Acid | OEG Spacer | Lysine

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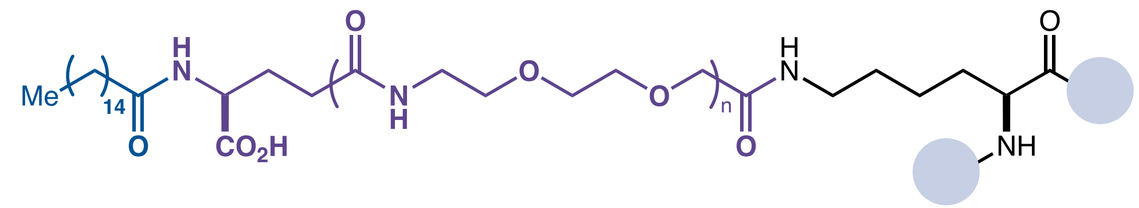

Fatty Acid | Glutamic Acid | OEG Spacer | Lysine

Spacer	**EC_{50}**	**IC_{50} ratio**
no OEG		
n=1		
n=2		
n=3		
n=2, no Glu		

ratio 2%/0% HSA (higher # implies better albumin binding)

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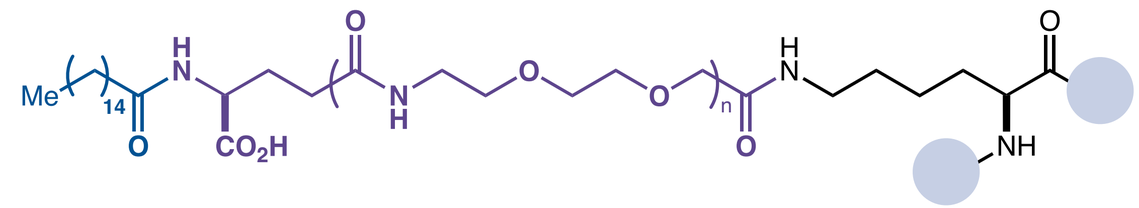

Fatty Acid | Glutamic Acid | OEG Spacer | Lysine

Spacer	EC_{50}	IC_{50} ratio
no OEG	19.2	42
n=1	14.7	21
n=2	2.7	20
n=3	4.3	8
n=2, no Glu	11.1	2.3

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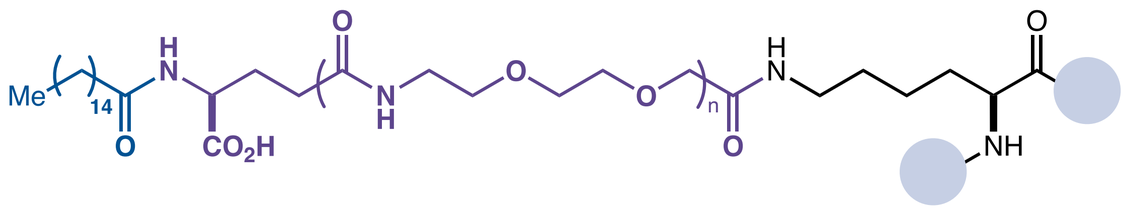

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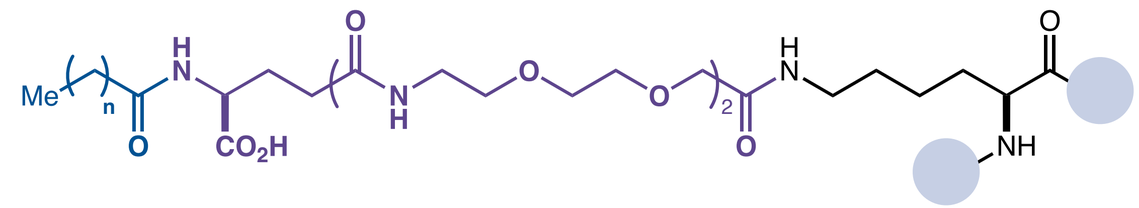

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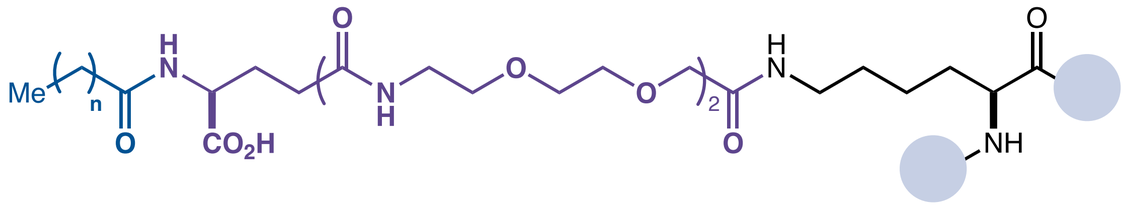

Fatty Acid | Glutamic Acid | OEG Spacer | Lysine

Fatty Acid	EC_{50}	IC_{50} ratio
C16	2.7	20
C18	3.2	50
C20	4.8	4.9

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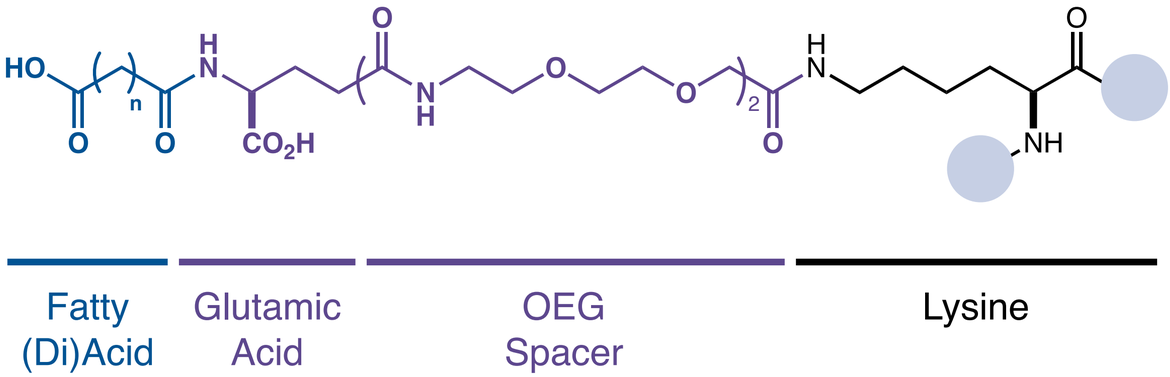
Semaglutide Development



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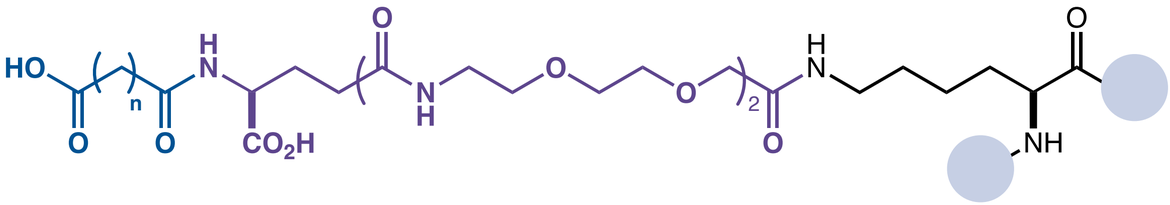

Fatty (Di)Acid | Glutamic Acid | OEG Spacer | Lysine

Fatty Acid	EC_{50}	IC_{50} ratio
C18 (monoacid)	3.2	50
C14 diacid	15.7	3.3
C16 diacid	8.6	22
C18 diacid	6.2	940
C20 diacid	11.5	85
C22 diacid	24.4	116

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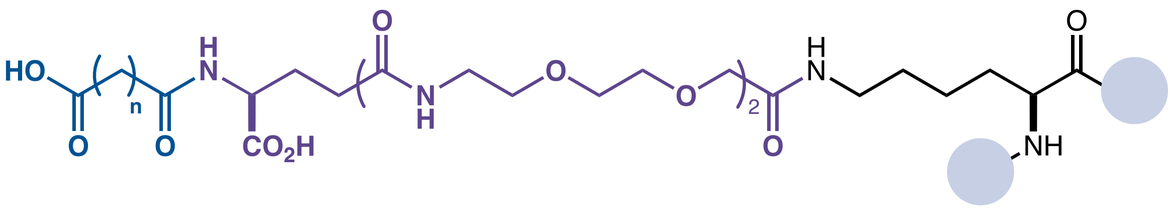
Semaglutide Development



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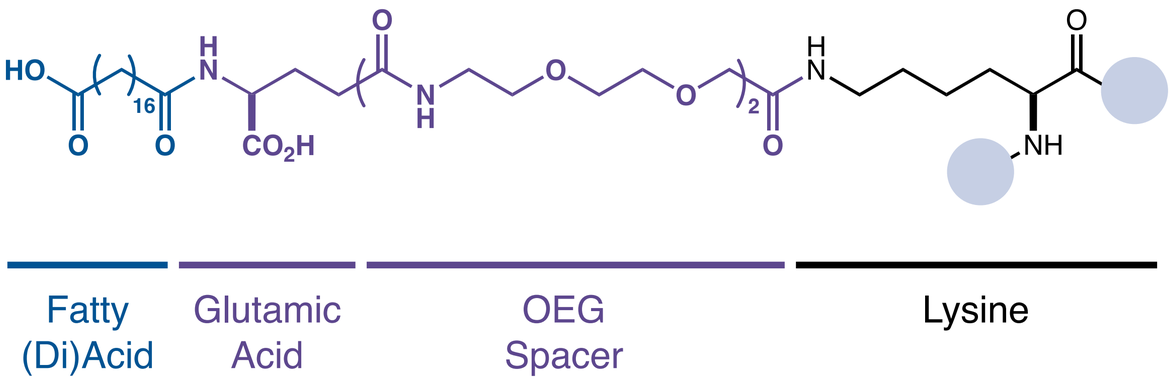
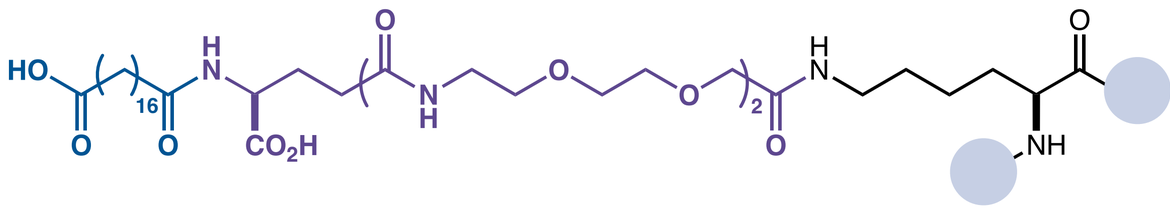
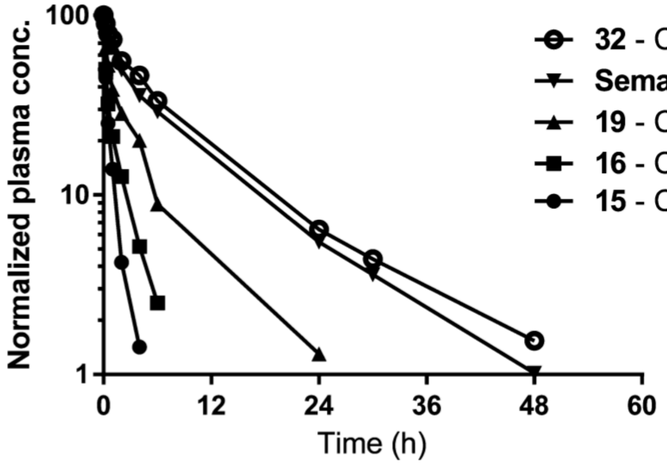


Lau, J. *et. al. J. Med. Chem.* **2015**, *58,* 7370.

Semaglutide Development

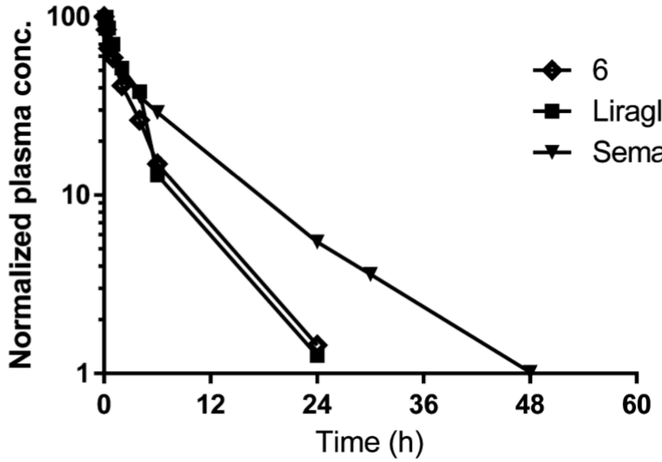


Fatty (Di)Acid | Glutamic Acid | OEG Spacer | Lysine



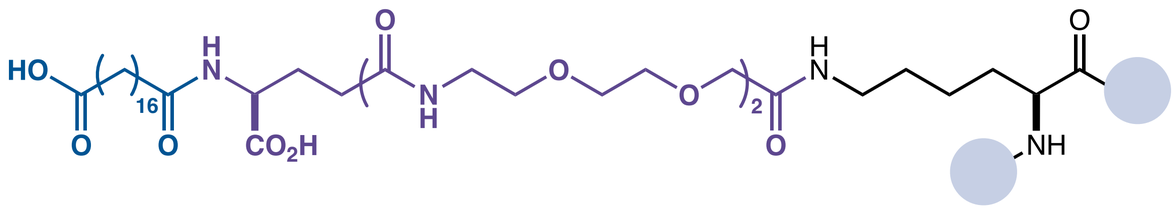
32 - C20 diacid
Semaglutide - C18 diacid
19 - C16 diacid
16 - C14 diacid
15 - C12 diacid

increased protraction in rats compared to liraglutide and other analogues

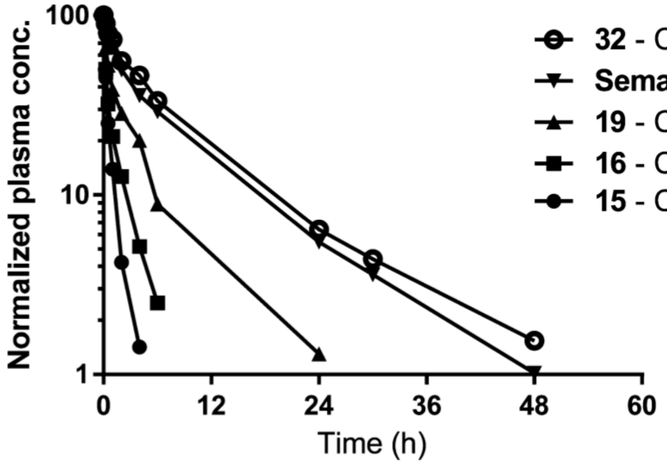


Lau, J. *et. al. J. Med. Chem.* **2015**, *58,* 7370.

Semaglutide Development



Fatty (Di)Acid | Glutamic Acid | OEG Spacer | Lysine



- **32** - C20 diacid
- **Semaglutide** - C18 diacid
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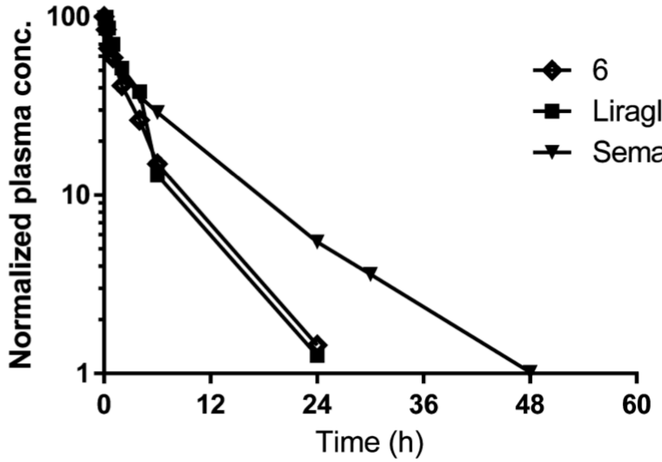
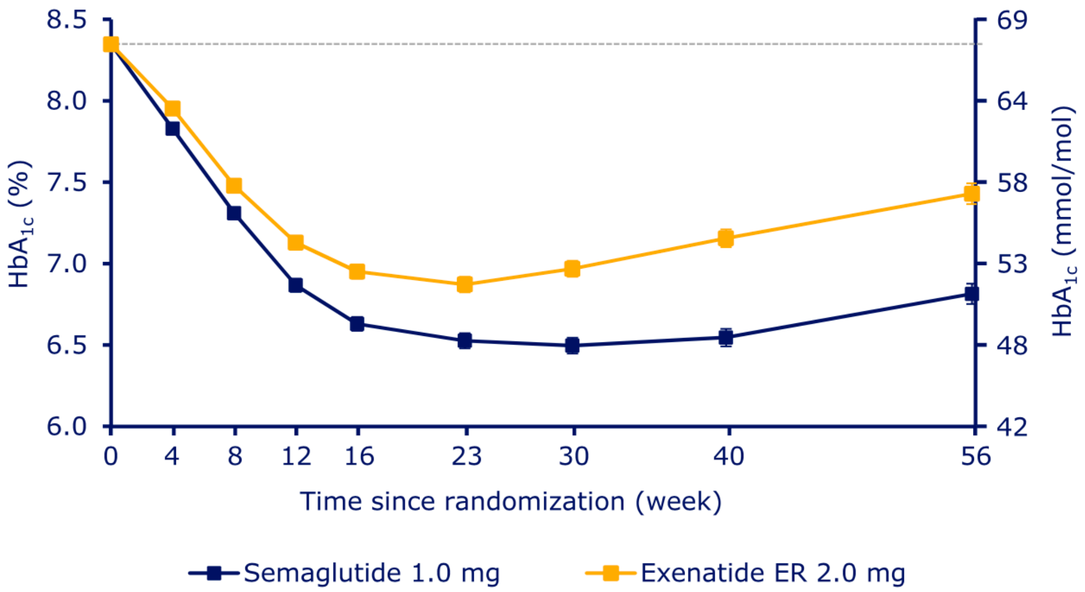
increased protraction in rats compared to liraglutide and other analogues



Semaglutide half life in humans is 165 hours

Lau, J. *et. al. J. Med. Chem.* **2015**, *58,* 7370.

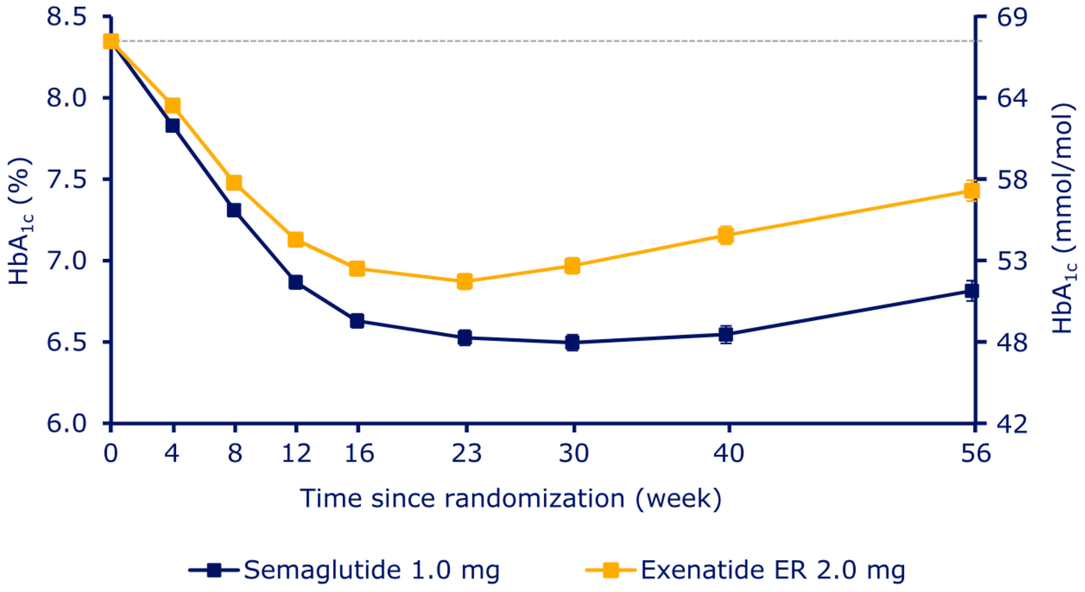
Semaglutide Clinical Trials (Phase 3a)

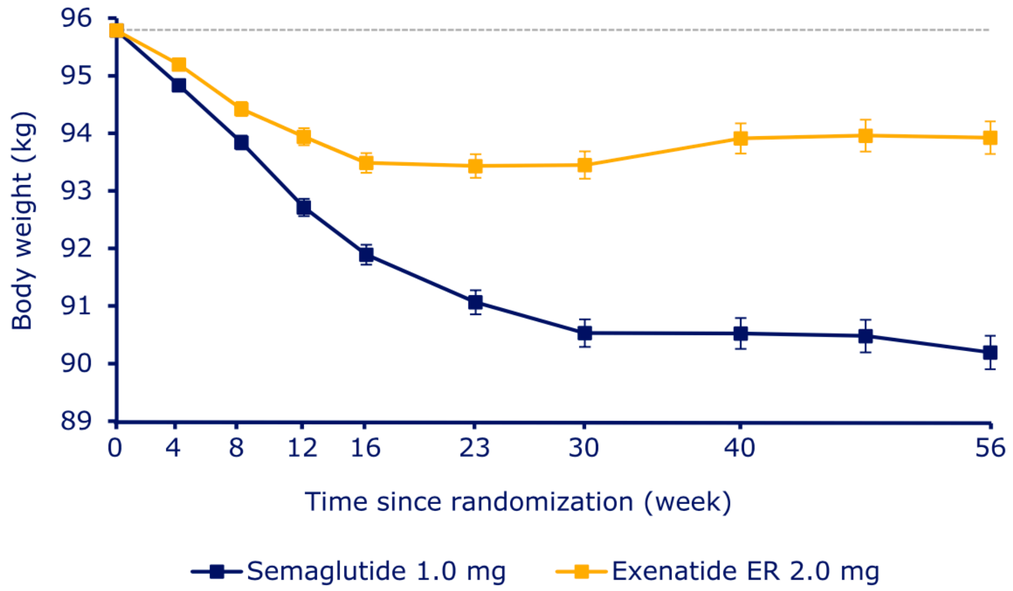


- 1.0 mg weekly dose of semaglutide in T2D patients
- A1c reduced by 1.5%, with 67% of patients reaching levels below 7%
- GI side effects were more common for semaglutide

Ahmann, A.J. *et. al. Diabetes Care* **2018**, *41,* 258.

Semaglutide Clinical Trials (Phase 3a)



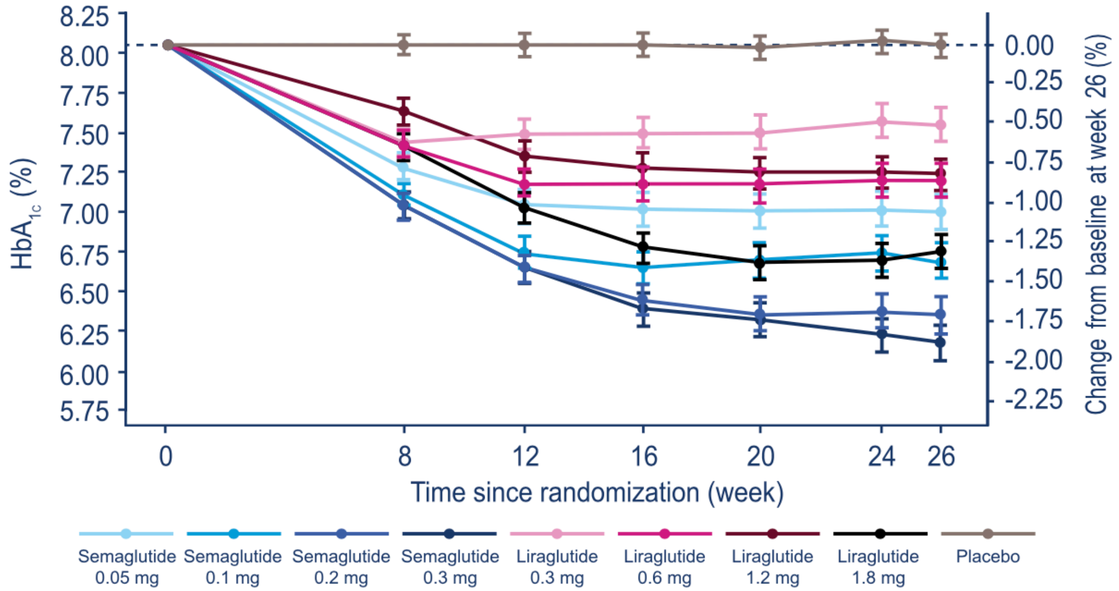


- 1.0 mg weekly dose of semaglutide in T2D patients
- A1c reduced by 1.5%, with 67% of patients reaching levels below 7%
- GI side effects were more common for semaglutide

- Patients lost on average 5.6 kg (compared to 1.9 kg of exenatide)
- Semaglutide is about 3x more effective for weight loss than exenatide

Ahmann, A.J. *et. al. Diabetes Care* **2018**, *41,* 258.

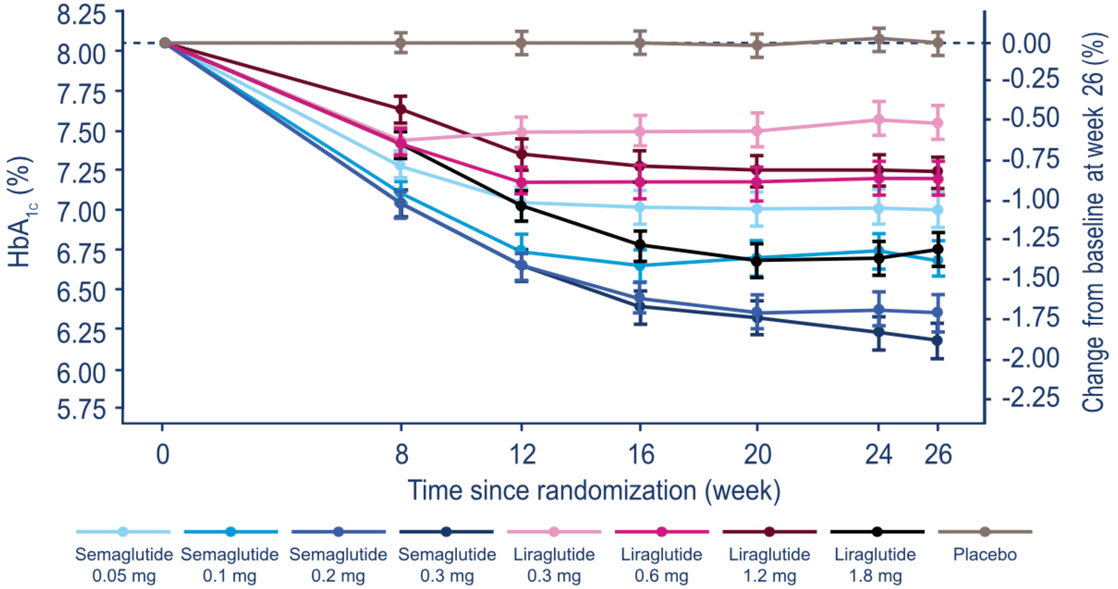
Semaglutide Clinical Trials (Phase 2)

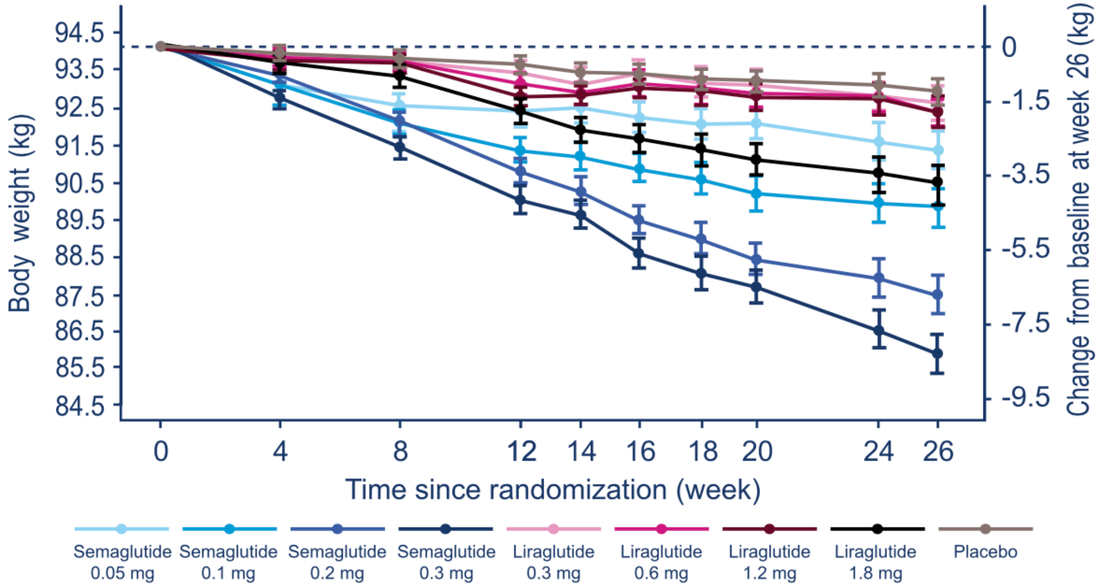


- Daily dose of semaglutide vs liraglutide in T2D patients
- Semaglutide is more effective at reducing A1c and fasting plasma glucose levels
- GI side effects were more common for semaglutide, and increased at higher doses

Lingvay, I. *et. al. Diabetes Care* **2018**, *41,* 1926.

Semaglutide Clinical Trials (Phase 2)



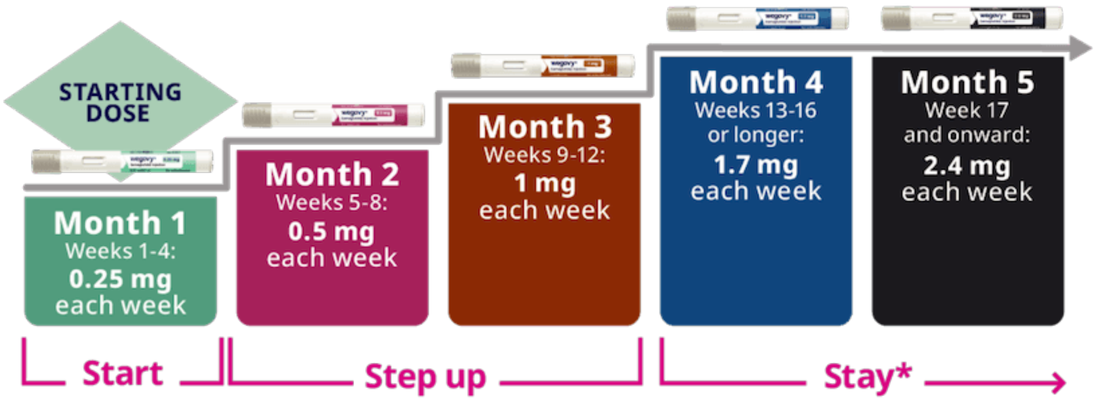


- Daily dose of semaglutide vs liraglutide in T2D patients
- Semaglutide is more effective at reducing A1c and fasting plasma glucose levels
- GI side effects were more common for semaglutide, and increased at higher doses

- Patients lost up to 8.2 kg at the highest dose
- Semaglutide is about 2x more effective for weight loss than liraglutide

Lingvay, I. *et. al. Diabetes Care* **2018**, *41,* 1926.

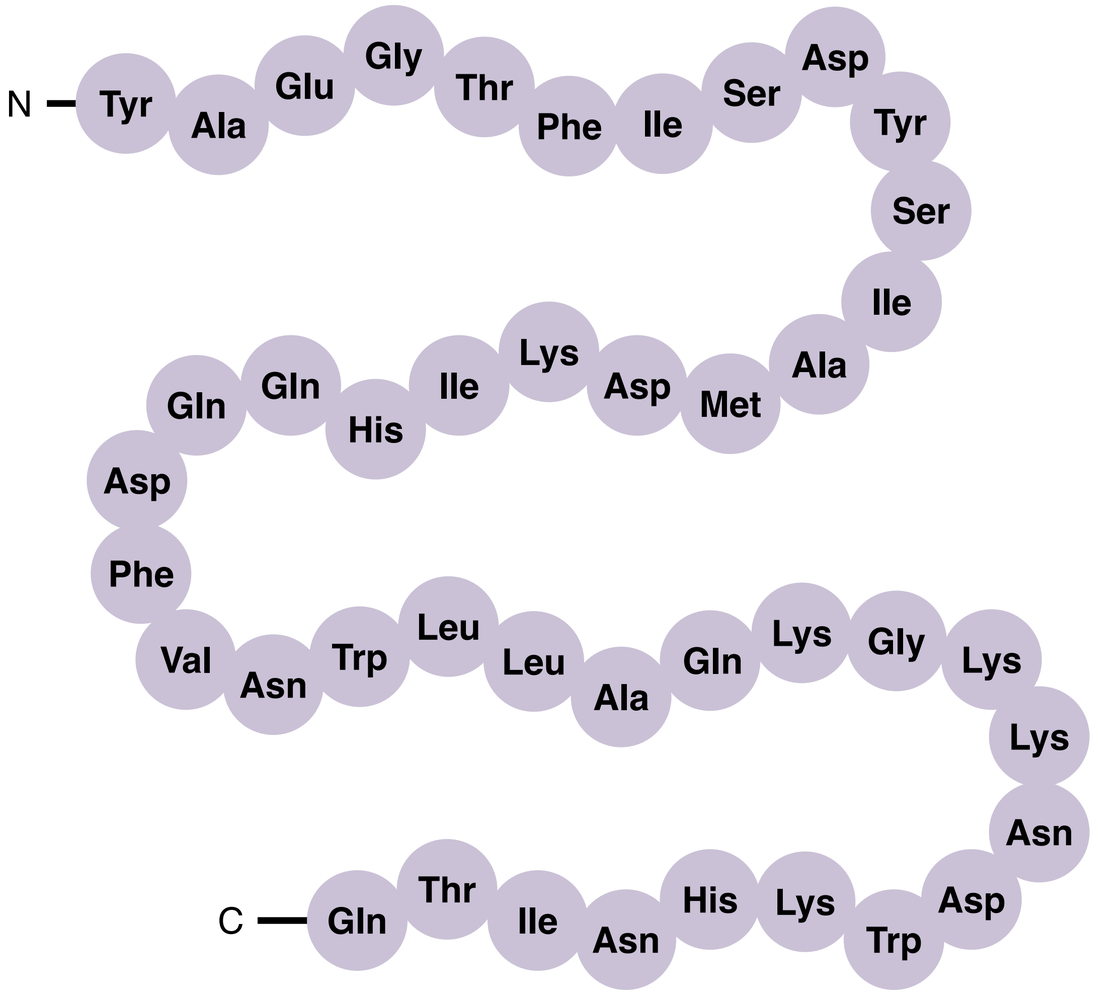
Semaglutide Becomes FDA Approved



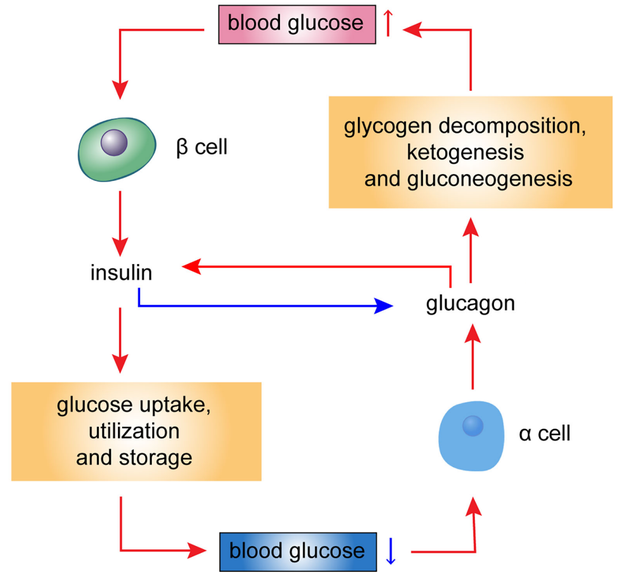
*At month 5 and on, you may either stay at 1.7 mg or increase to 2.4 mg. Work with your health care provider to determine which dose is right for you.

Both drugs require titration to reduce GI side effects

Glucose-dependent Insulinotropic Polypeptide (GIP)

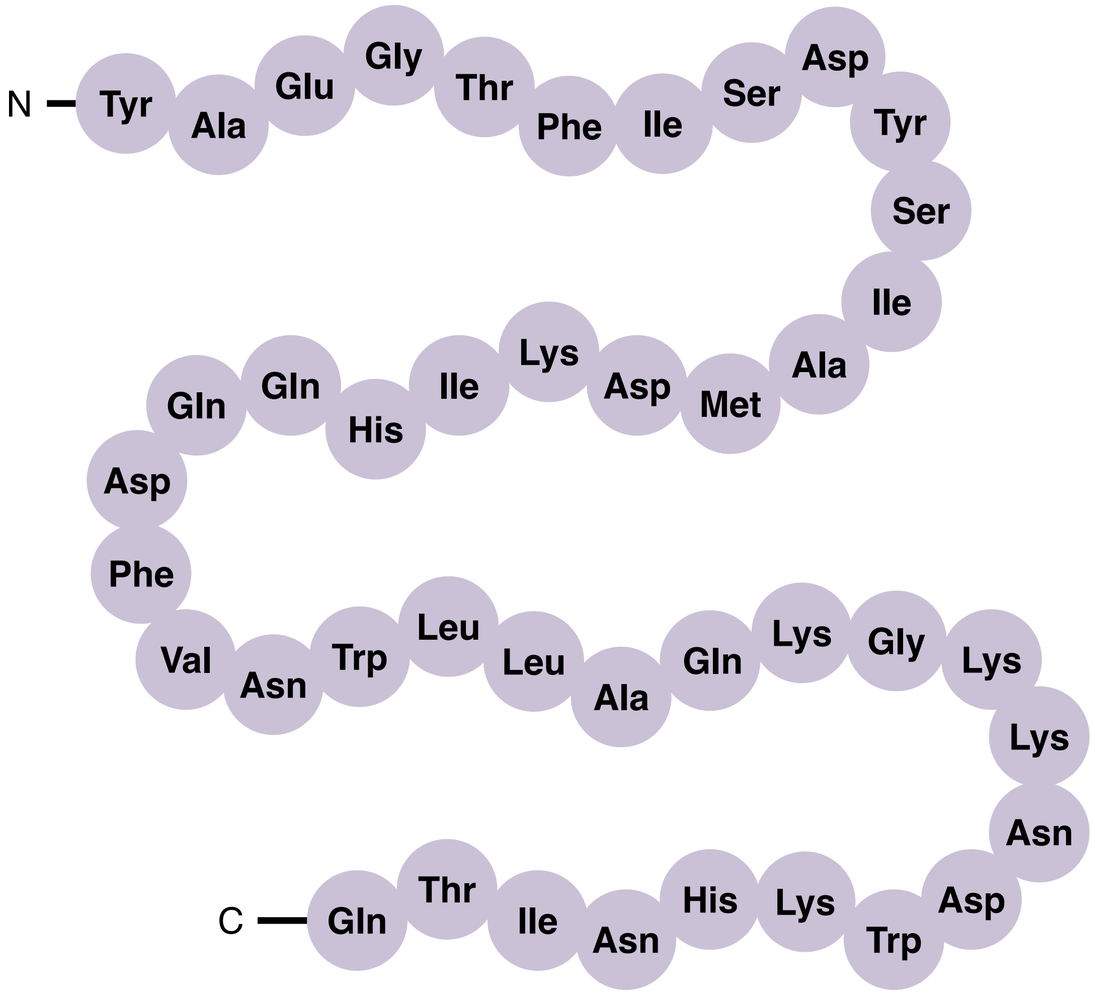


- Incretin hormone (gut hormone released after eating)
- Both glucagonotropic and insulinotropic (can stimulate glucagon secretion under hypoglycemic conditions and insulin under hyperglycemic conditions)

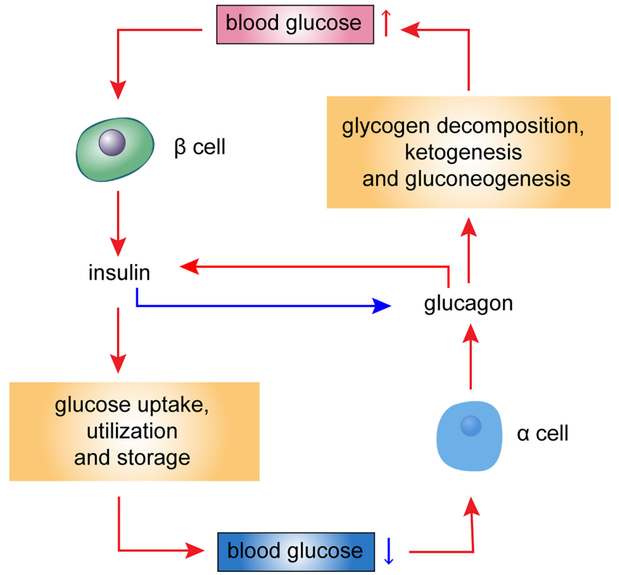


Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

Glucose-dependent Insulinotropic Polypeptide (GIP)

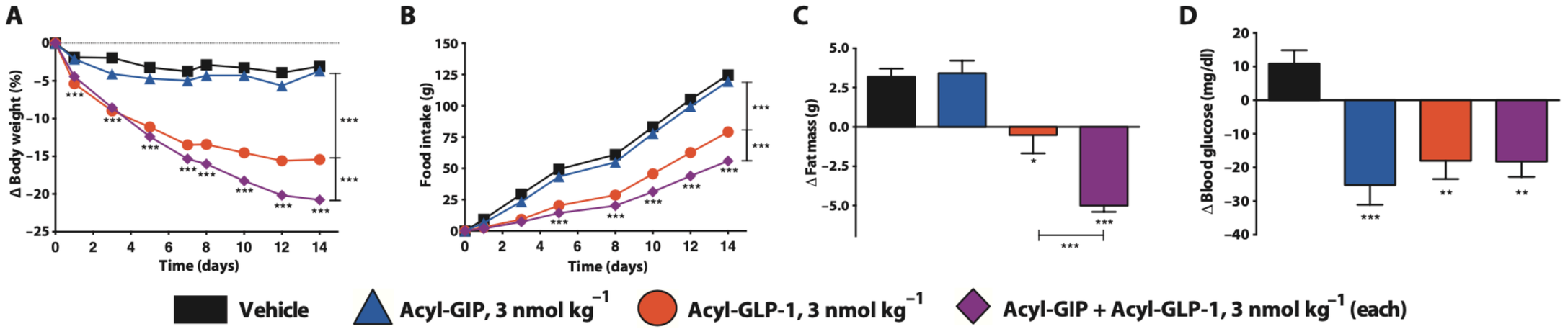


- Incretin hormone (gut hormone released after eating)
- Both glucagonotropic and insulinotropic (can stimulate glucagon secretion under hypoglycemic conditions and insulin under hyperglycemic conditions)
- GIP receptors are present on B-cells as well as in adipose tissue (implicated in T2D and fat accumulation)



Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

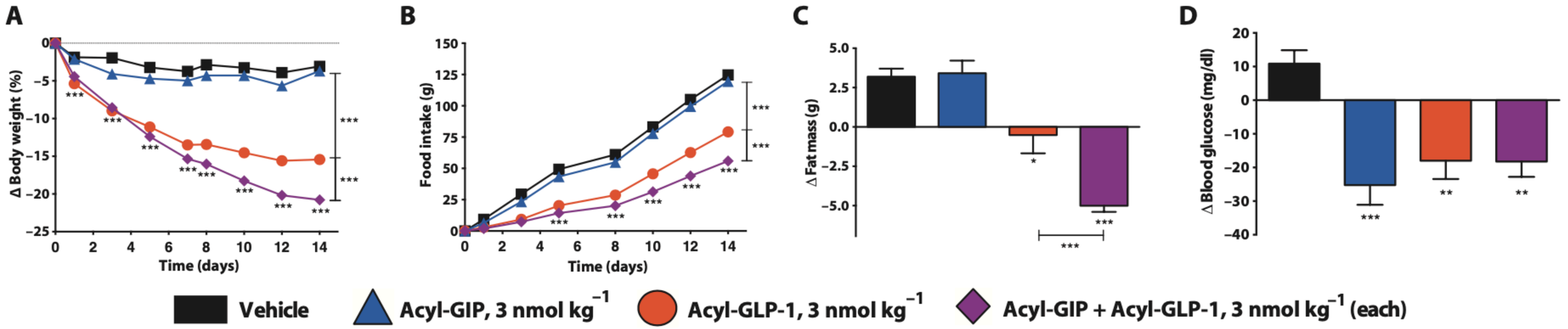
Dual GIP/GLP-1 Receptor Agonists



- Administering mice with both GIP and GLP-1 analogues leads to more weight loss than either analogue alone

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



- Administering mice with both GIP and GLP-1 analogues leads to more weight loss than either analogue alone
- This effect does not hold for glucose levels at the doses tested

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

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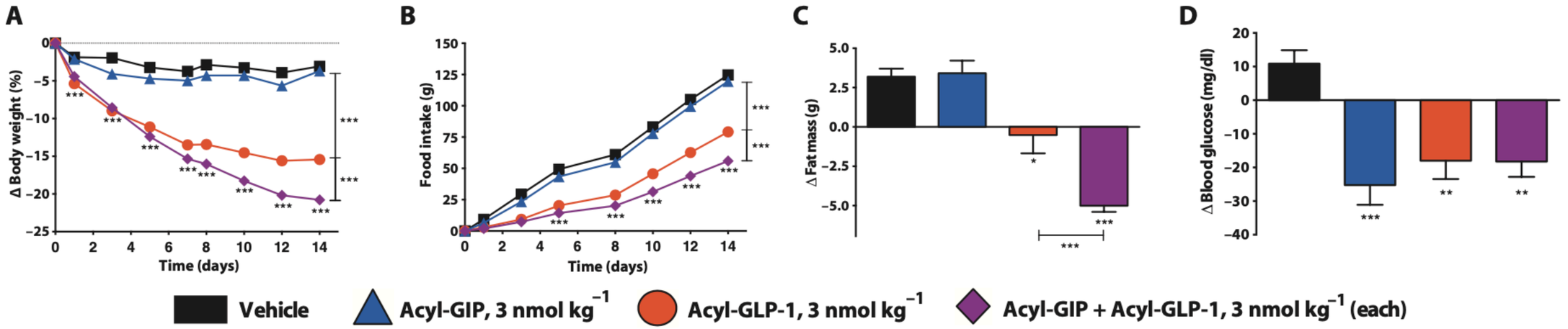

- Administering mice with both GIP and GLP-1 analogues leads to more weight loss than either analogue alone
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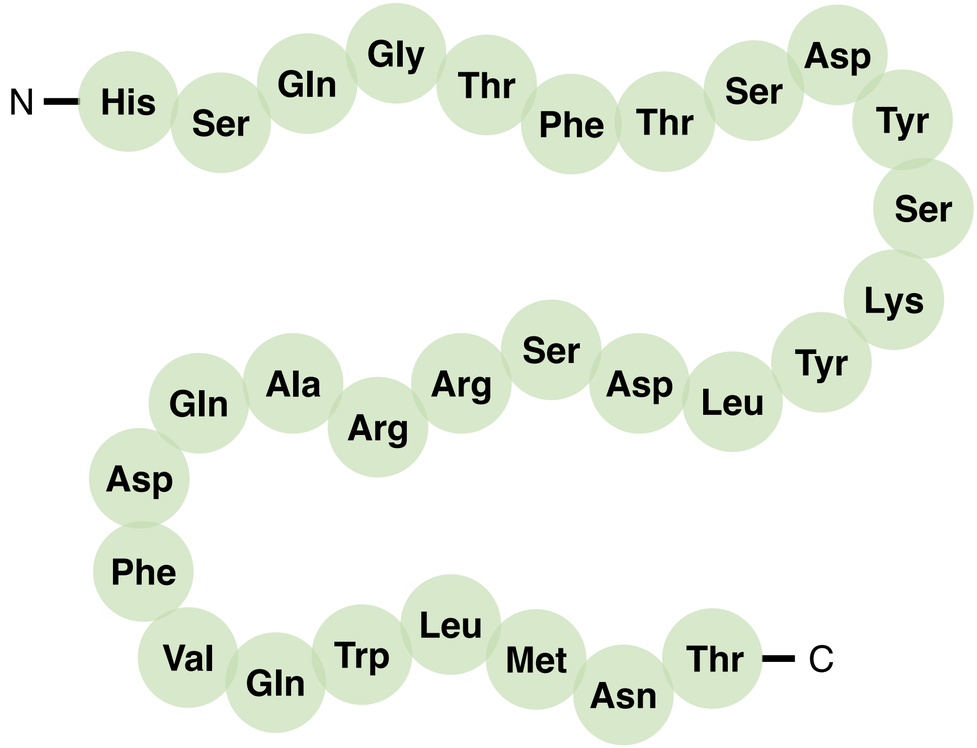
Can we use "rational design" to make a dual GIP and GLP-1 receptor agonist?

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



Compound 1

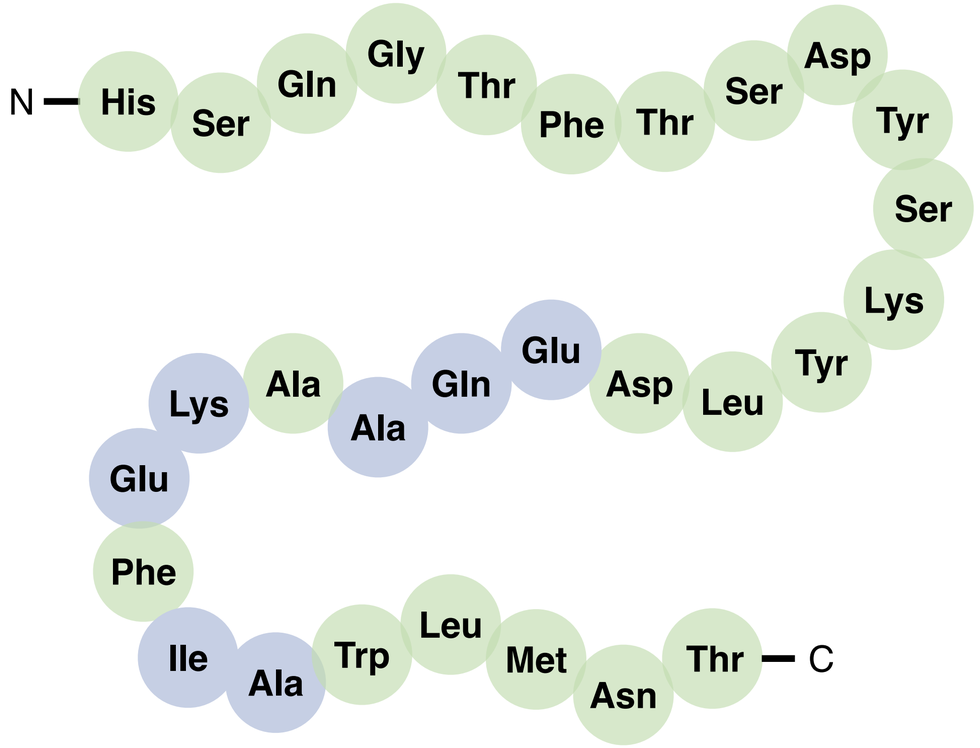
Glucagon

Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03

Both GLP-1 and GIP have sequence similarity to glucagon - it's a good starting place to build a dual agonist

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



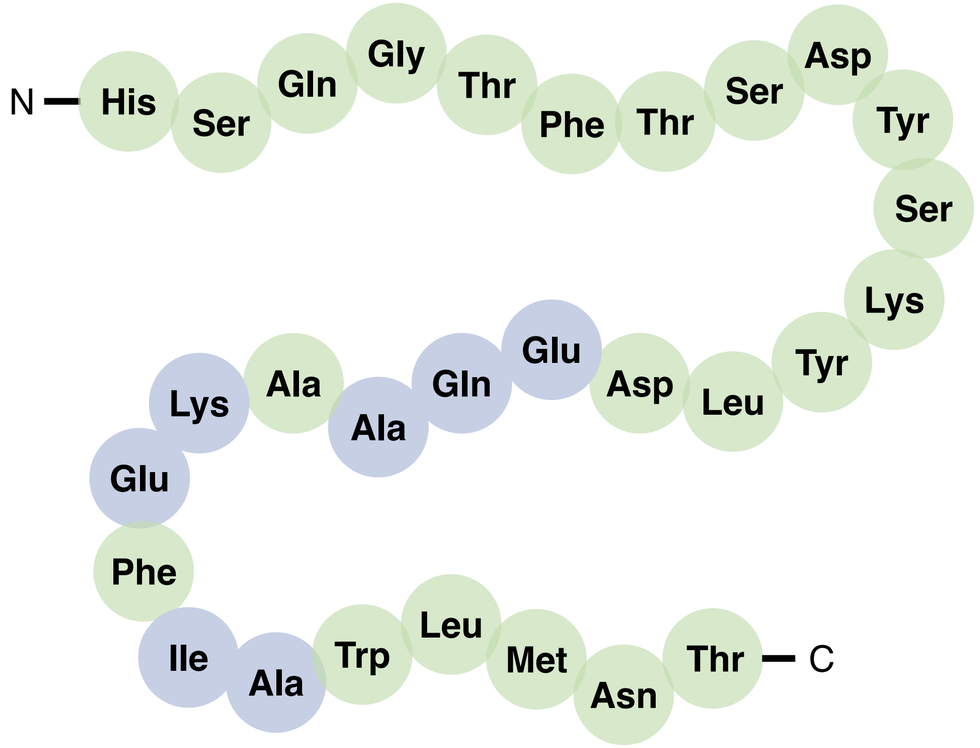
Compound 2

Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03
2	0.02	6.3	0.03

Add in amino acids important for GLP-1 potency

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



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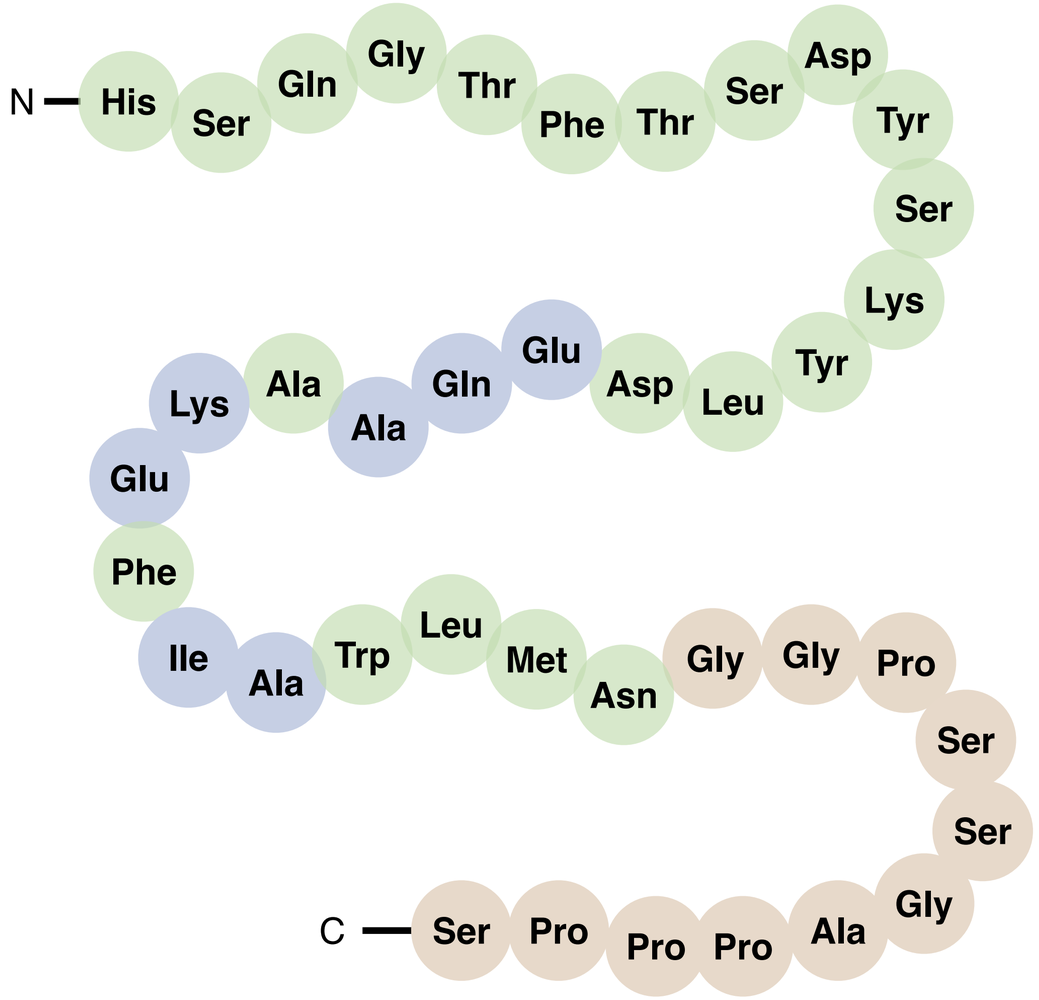


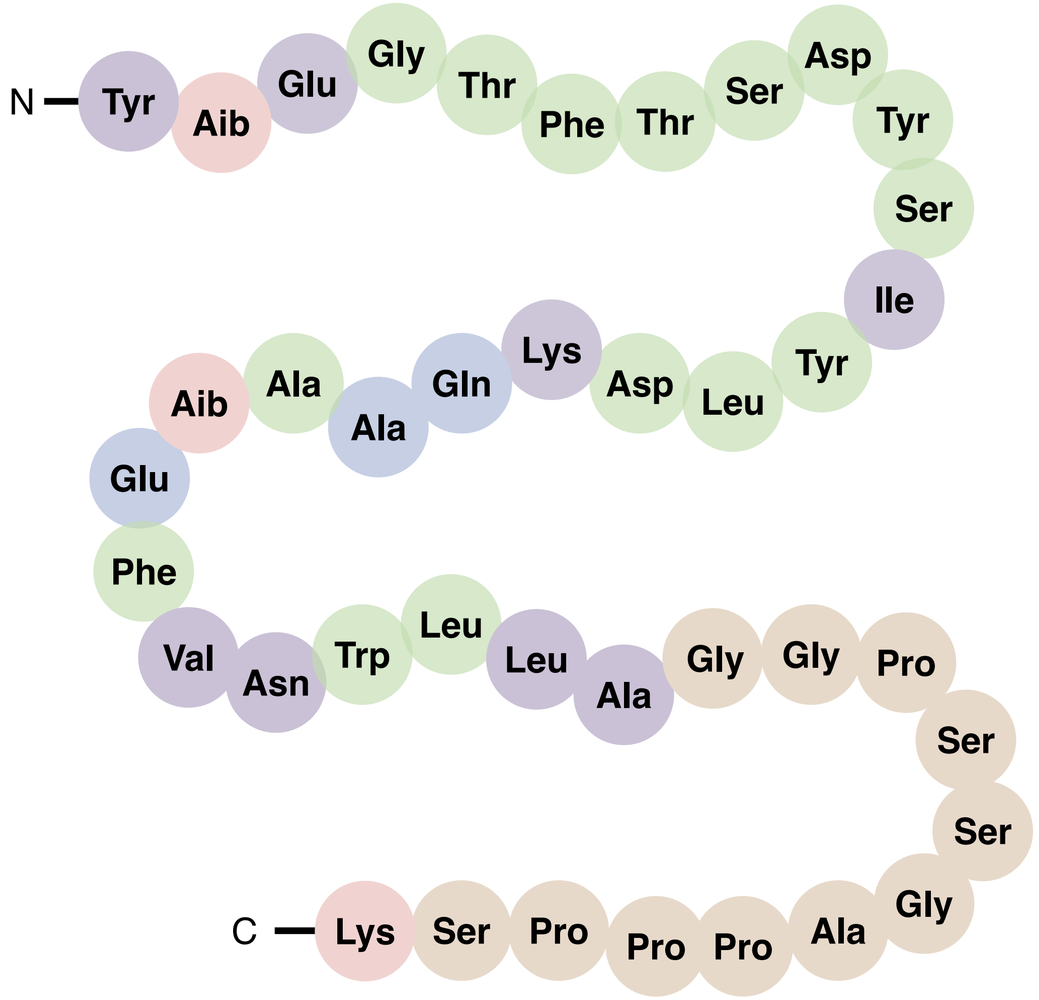
Compound 3

Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03
2	0.02	6.3	0.03
3	0.02	14.6	0.06

Additional amino acids at C-terminus match exenatide

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



Compound 4

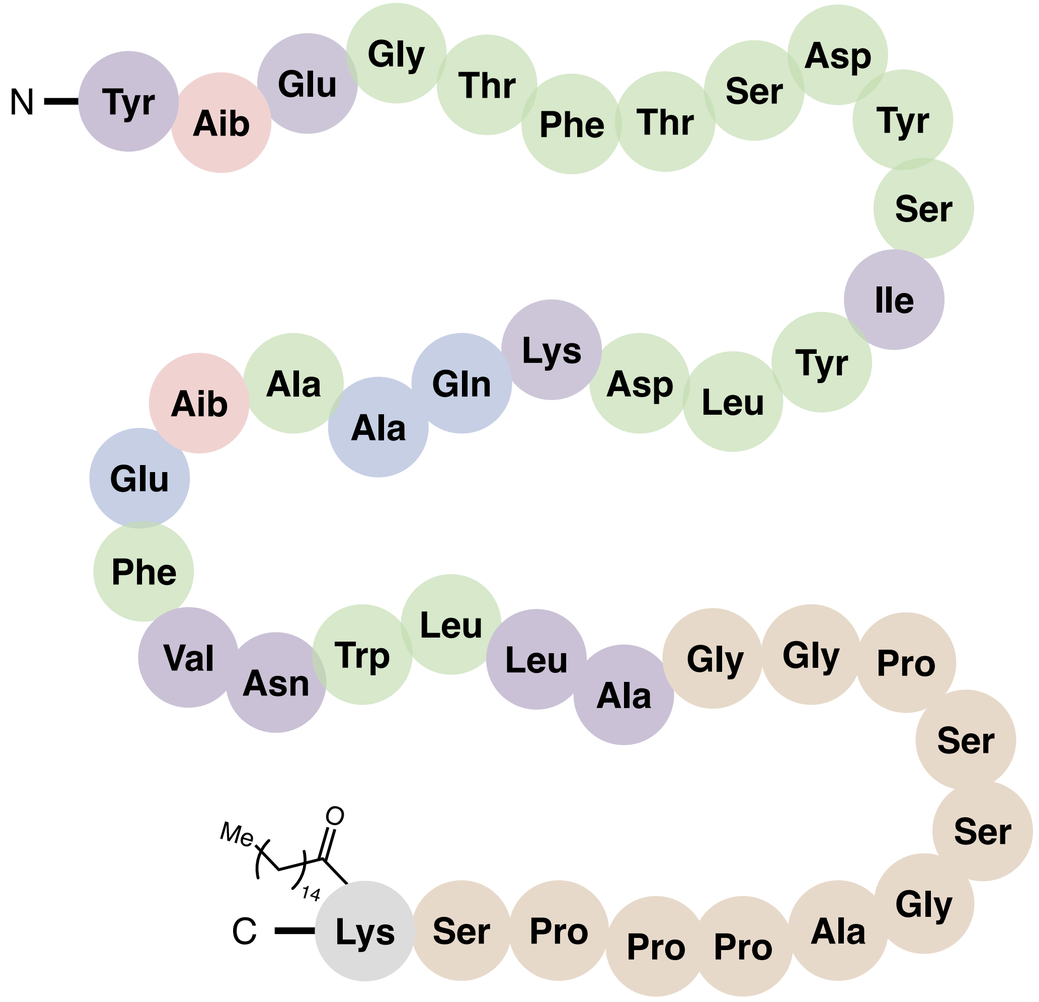
Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03
2	0.02	6.3	0.03
3	0.02	14.6	0.06
4	0.02	0.01	6.9

Substitute amino acids from GIP sequence

Additional changes made for stability/ reduced GCGR affinity

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



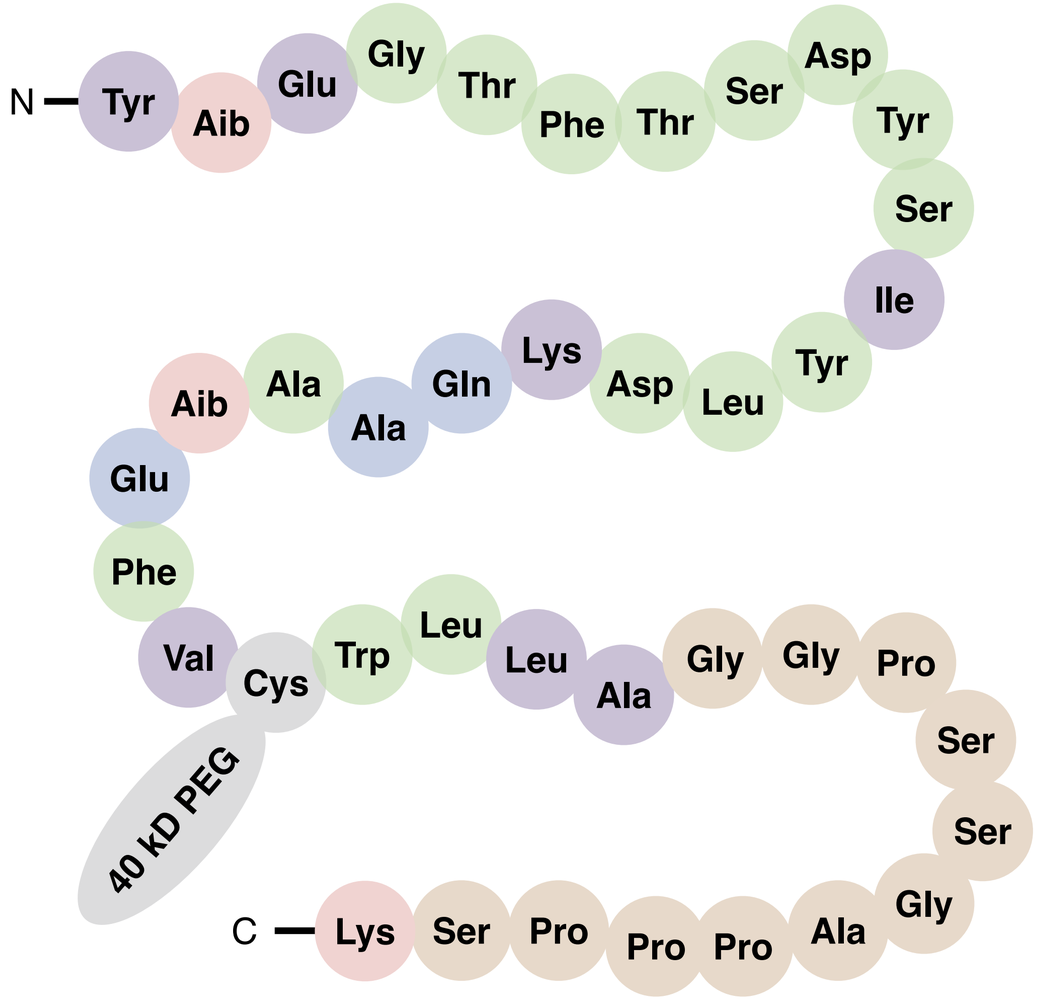
Compound 5

Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03
2	0.02	6.3	0.03
3	0.02	14.6	0.06
4	0.02	0.01	6.9
5	0.005	0.003	1.3

Acylated to improve potency

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

Dual GIP/GLP-1 Receptor Agonists



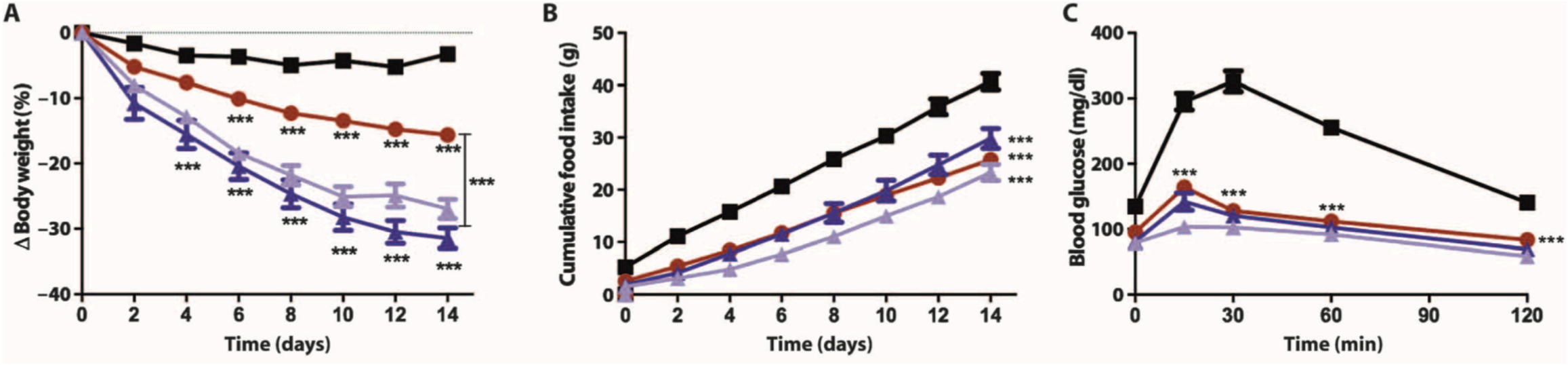
Compound 6

Compound	GLP-1R EC_{50}	GIPR EC_{50}	GCGR EC_{50}
1	3.1	1538	0.03
2	0.02	6.3	0.03
3	0.02	14.6	0.06
4	0.02	0.01	6.9
5	0.005	0.003	1.3
6	0.32	0.19	359

PEGylated to reduce GCGR affinity

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

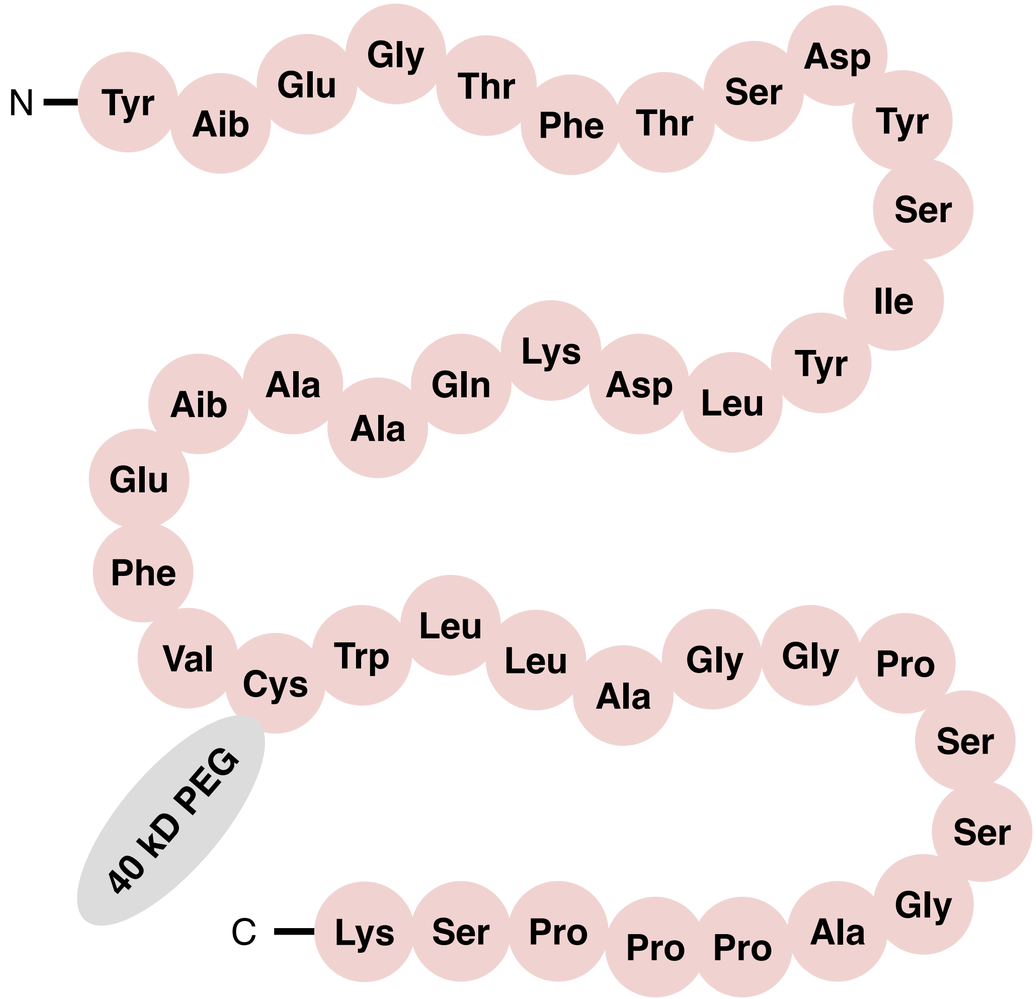
Dual GIP/GLP-1 Receptor Agonists



- Both “designer” dual analogues outperform liraglutide in body weight reduction and glucose regulation in mice
- Acylated derivative (Compound 5) outperforms PEDylated derivative (Compound 6) in vivo

Finan, B. *et. al. Sci. Trans. Med.* **2013**, *5,* 1.

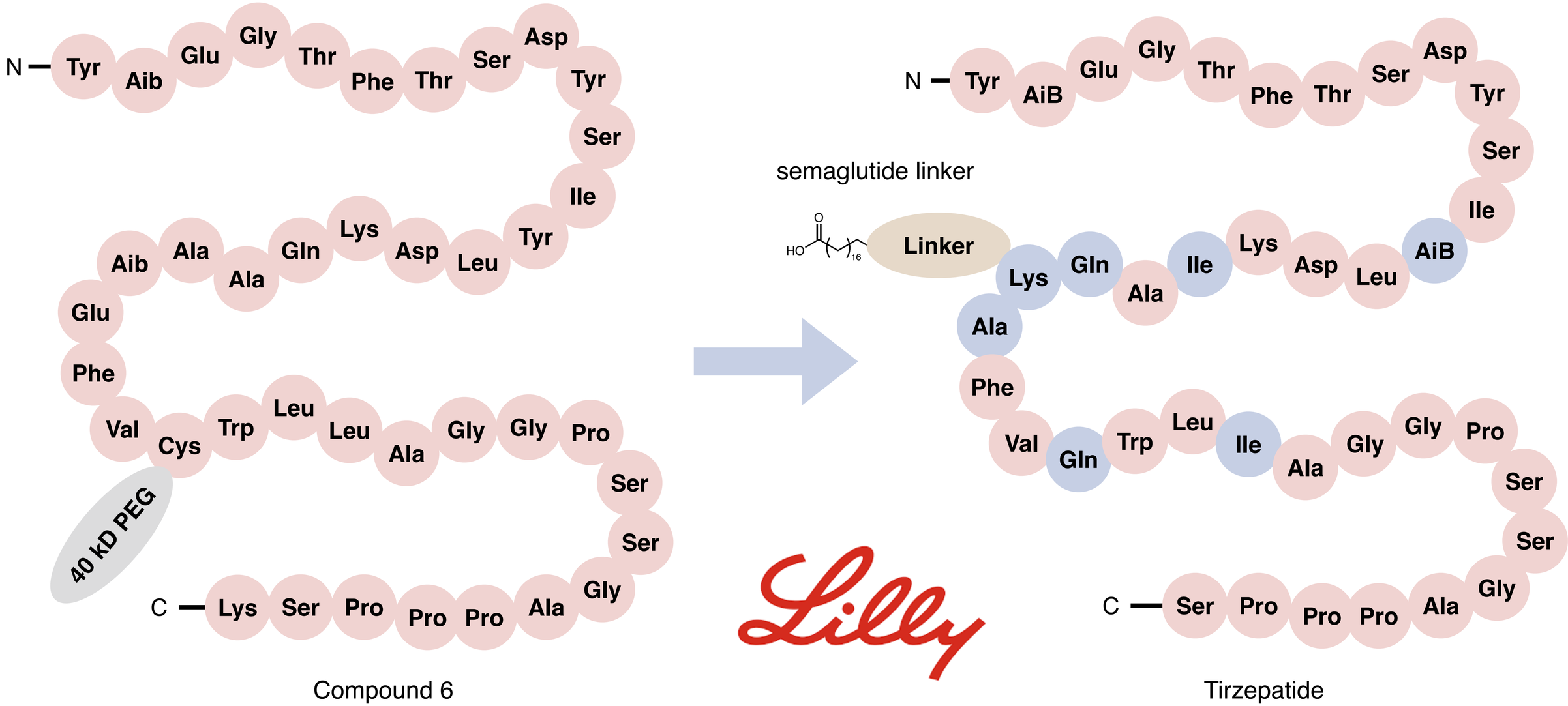
Tirzepatide Development



Compound 6

Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

Tirzepatide Development

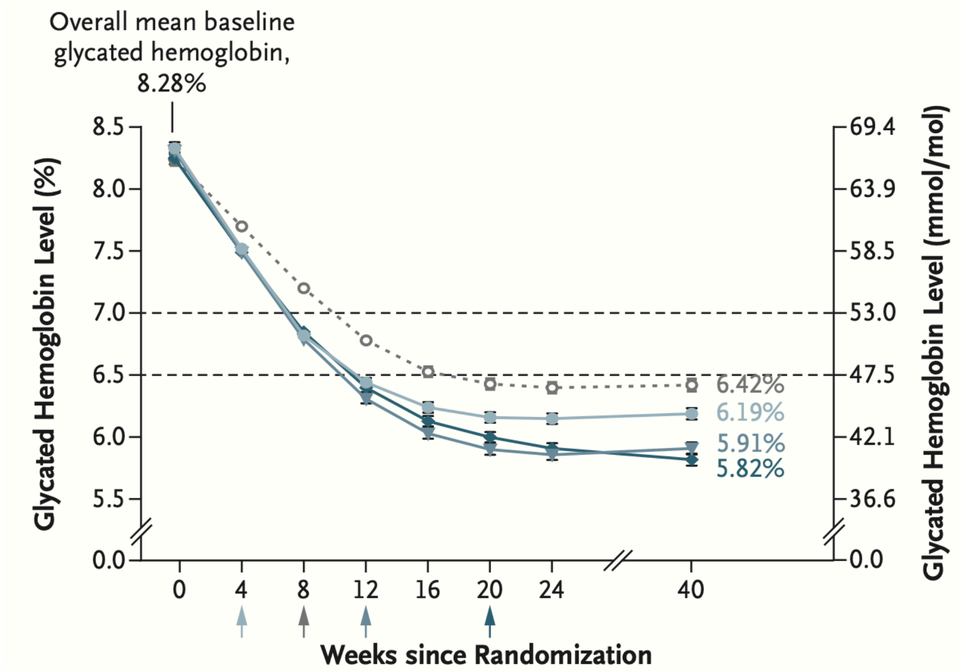


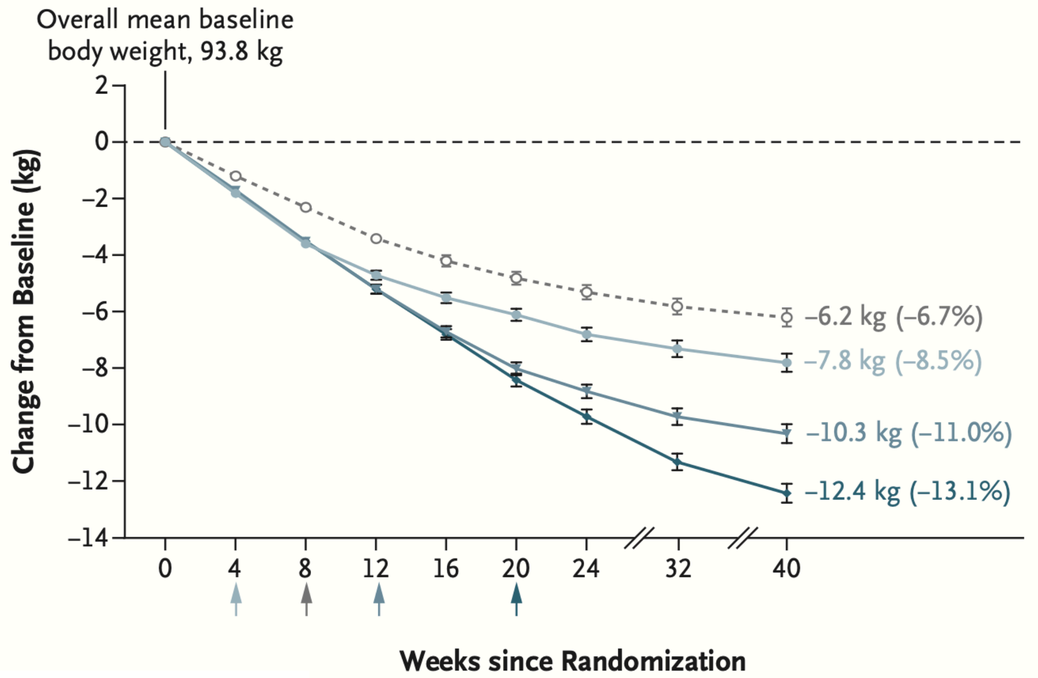
Compound 6

Tirzepatide

Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

Tirzepatide Phase 3 Trials



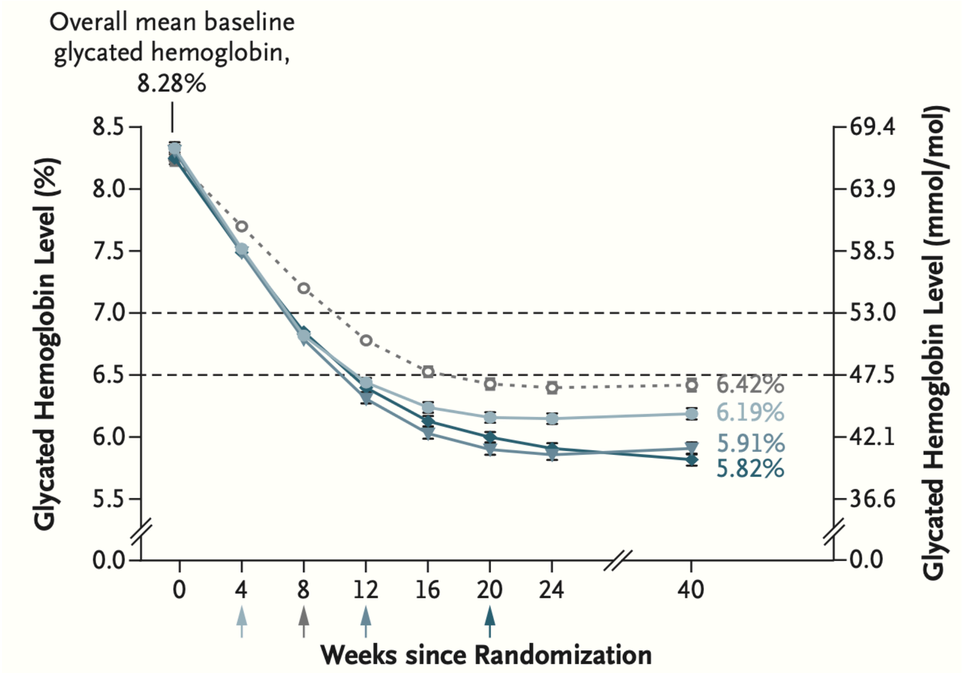


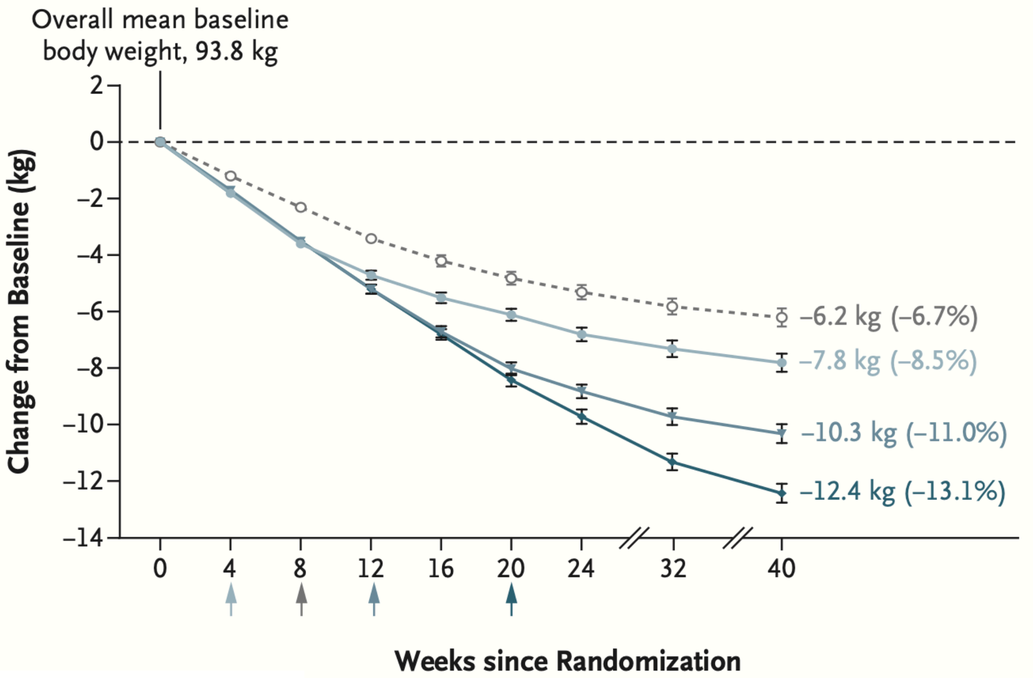
Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Semaglutide, 1 mg

- Patients get tirzepatide or semaglutide once weekly
- A1C values decreased by 2.3% at the highest dose of tirzepatide (past the 7% threshold for diabetes)

Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

Tirzepatide Phase 3 Trials



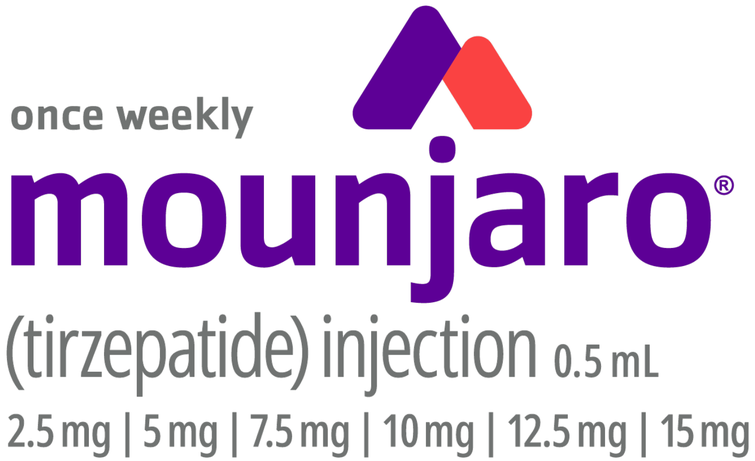


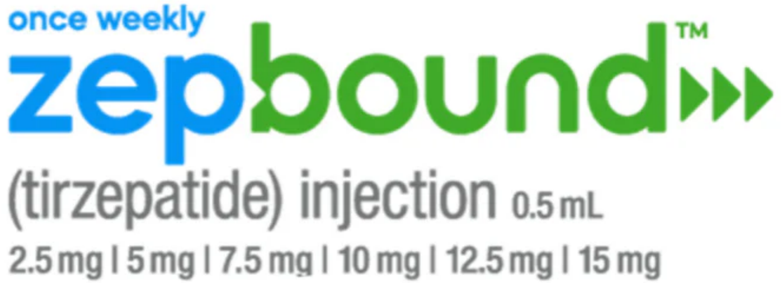
Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Semaglutide, 1 mg

- Patients get tirzepatide or semaglutide once weekly
- A1C values decreased by 2.3% at the highest dose of tirzepatide (past the 7% threshold for diabetes)
- Patients lose >12 kg at the highest dose of tirzepatide (2x as effective as semaglutide)
- GI side effects similar for both drugs

Coskun, T. *et. al. Mol. Metab.* **2018**, *18,* 3.

Tirzepatide Becomes FDA Approved





FDA approves Lilly's Mounjaro™ (tirzepatide) injection, the first and only GIP and GLP-1 receptor agonist for the treatment of adults with type 2 diabetes

May 13, 2022

FDA NEWS RELEASE

FDA Approves New Medication for Chronic Weight Management

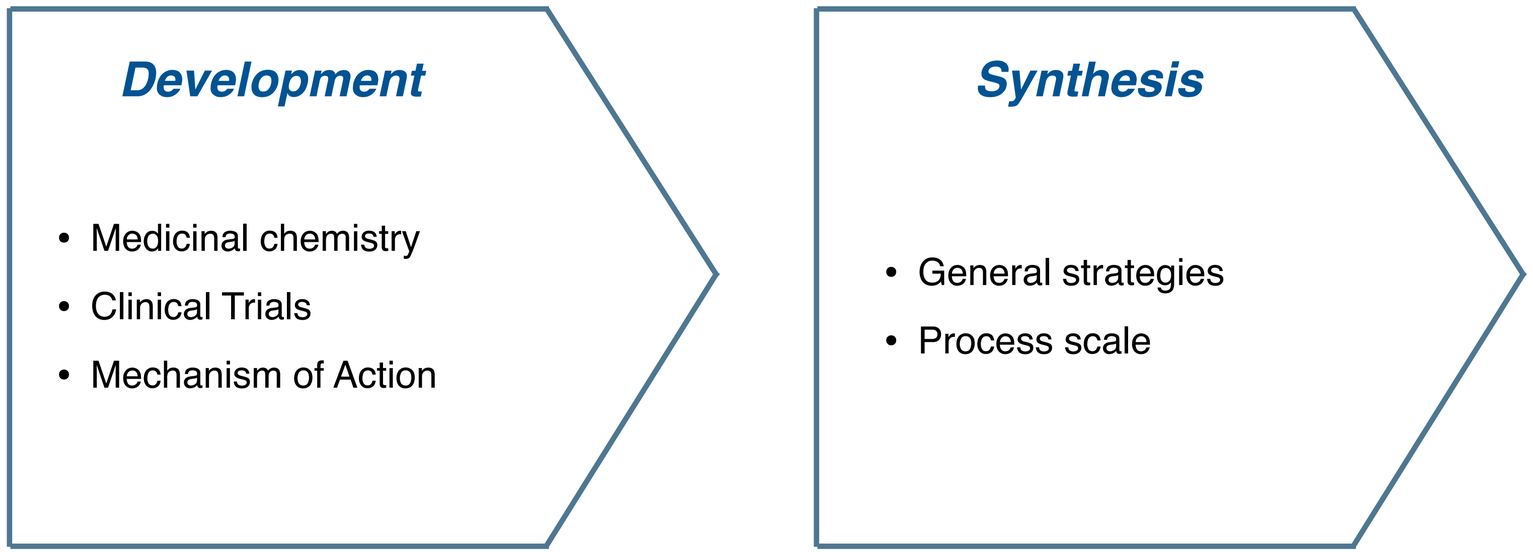
For Immediate Release: November 08, 2023

GLP-1 Receptor Agonists: Design and Development

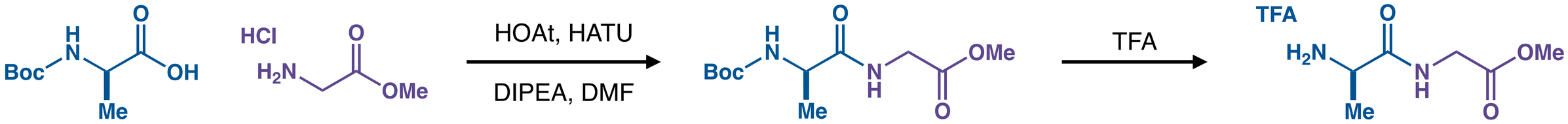
Development

- Medicinal chemistry
- Clinical Trials
- Mechanism of Action

GLP-1 Receptor Agonists: Design and Development



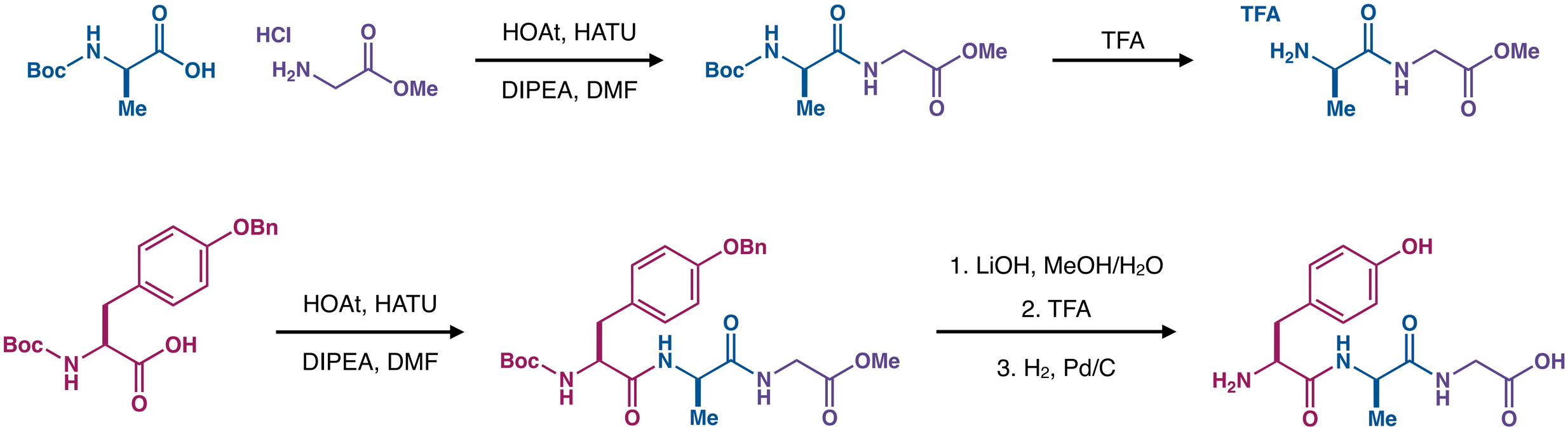
Solution-Phase Peptide Synthesis



- “old school” method of peptide synthesis
- Requires sequential coupling and deprotection steps for each new amino acid
- Outdated except for small peptides where more advanced methods are not cost effective

Tymecka, D. *et. al. Peptide Synthesis* **2019**, 1-11.

Solution-Phase Peptide Synthesis



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- Requires sequential coupling and deprotection steps for each new amino acid

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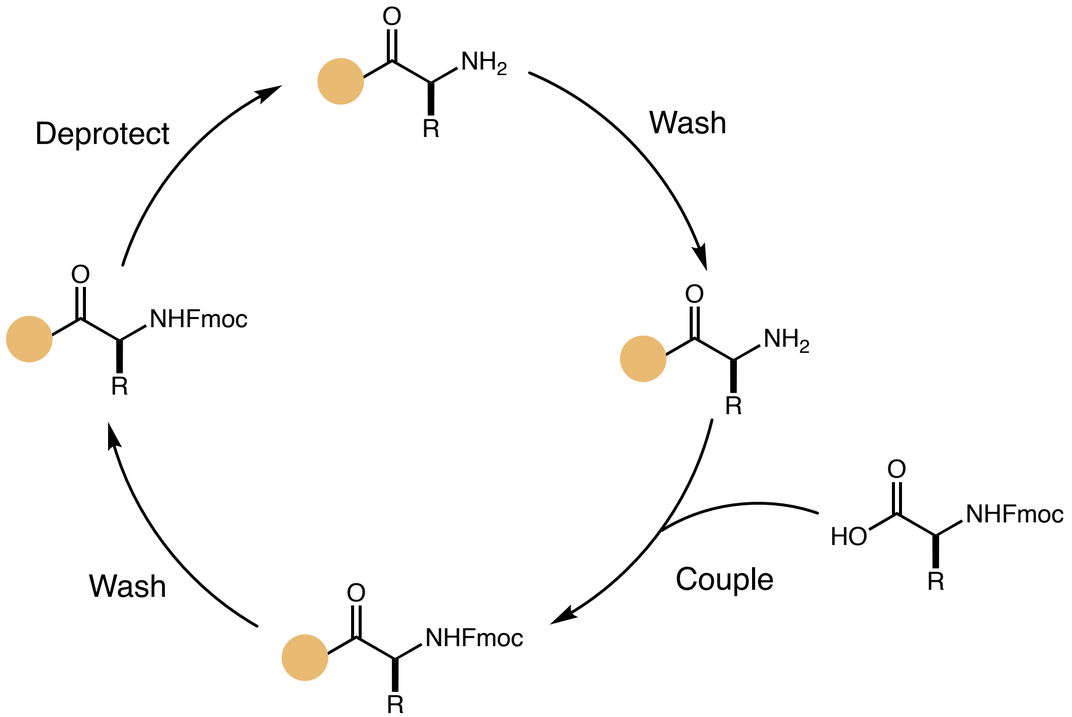
Tymecka, D. *et. al. Peptide Synthesis* **2019**, 1-11.

Solid-Phase Peptide Synthesis



R.B. Merrifield

Nobel Prize 1984

- Growing peptide chain is fused to a solid support
- Still requires sequential coupling and deprotection steps, but wash steps simplify purification
- Once fully synthesized, peptide is cleaved off and fully purified
- Significantly improves synthetic efficiency

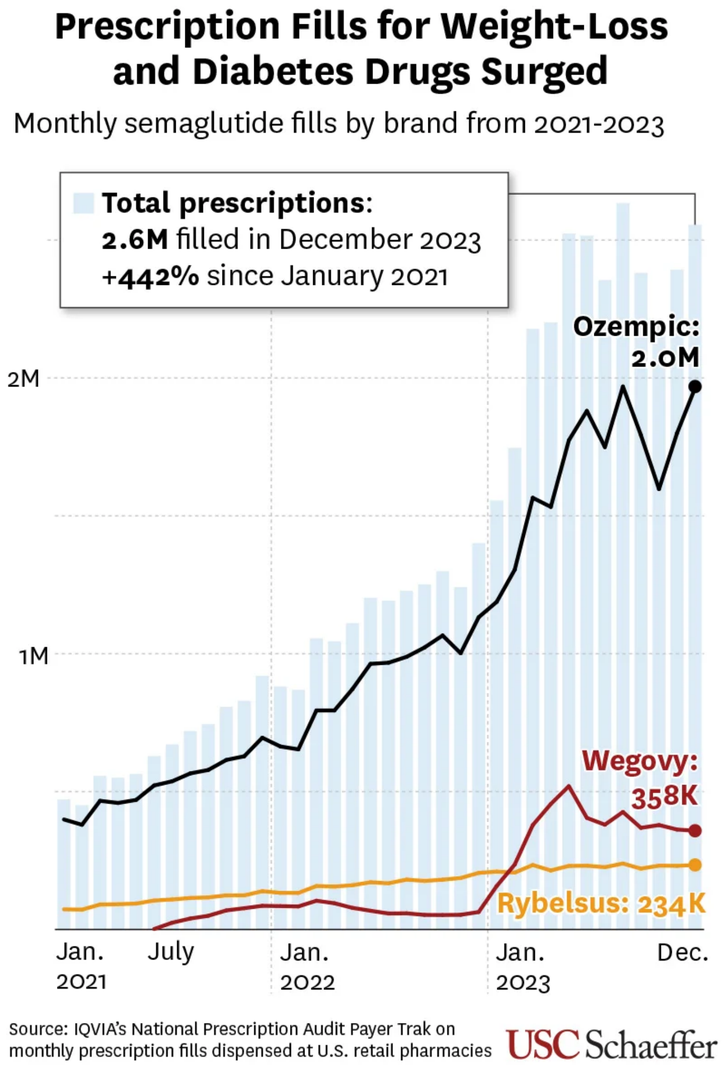
Tymecka, D. *et. al. Peptide Synthesis* **2019**, 1-11.

Automated SPPS

Most academic and industrial labs have

automated peptide synthesizers

Increased Demand for GLP-1 Analogues



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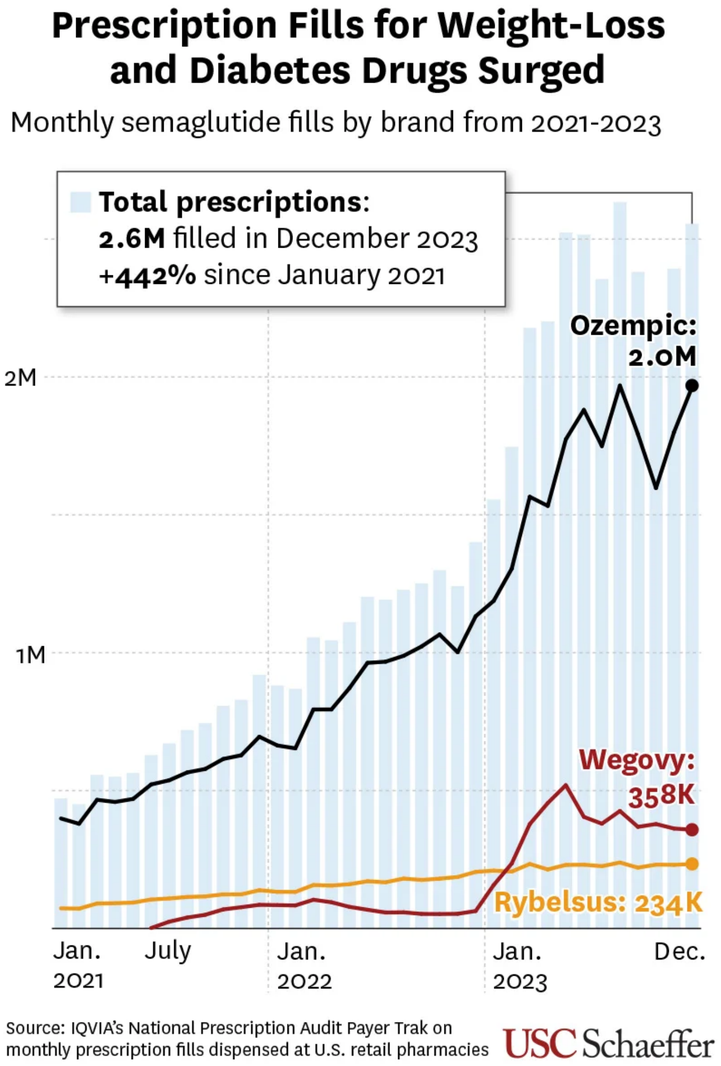

A dramatic surge in prescriptions for GLP-1 analogues, particularly due to off-label use, led to a worldwide shortage in 2022

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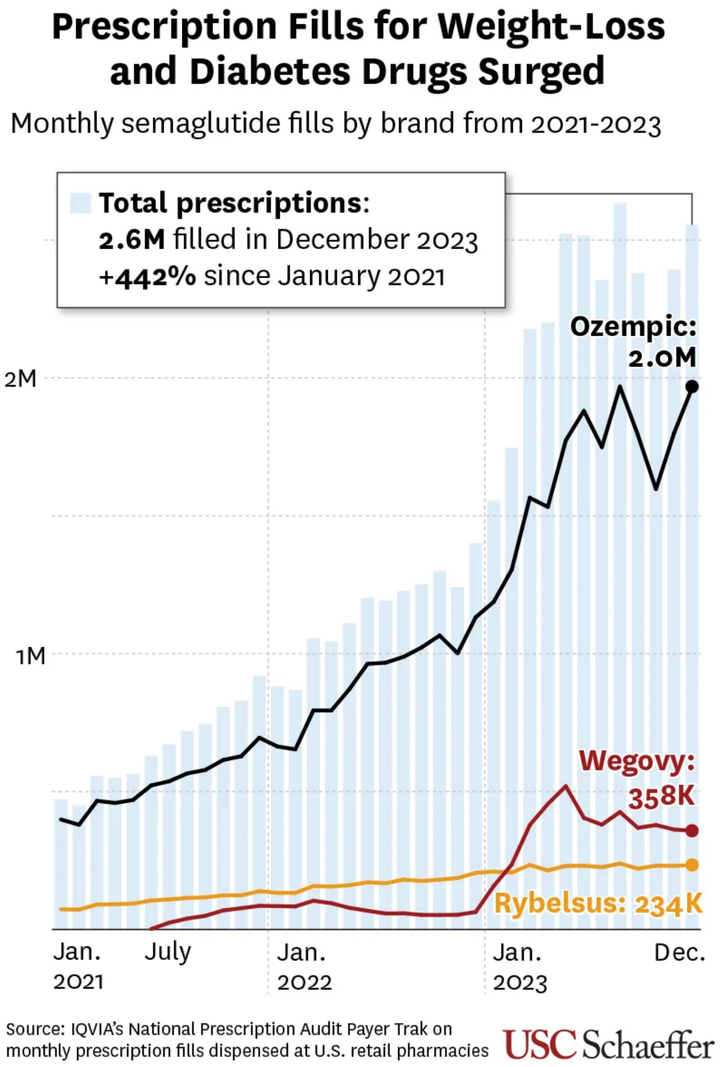

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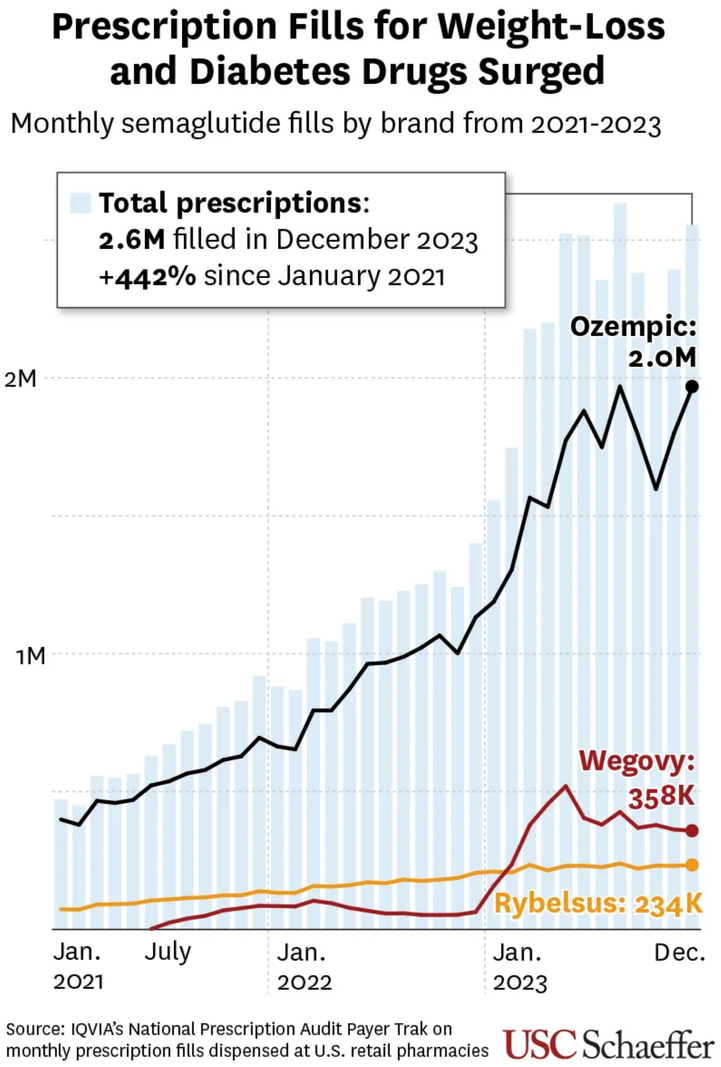

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FDA warns consumers not to use counterfeit Ozempic (semaglutide) found in U.S. drug supply chain

10:01 AM February 21 2025

FDA declares Wegovy® and Ozempic® shortage is over and that Novo Nordisk is fully meeting or exceeding nationwide demand for all doses

SPPS on Process Scale

Example: Exenatide

- Solid phase synthesis has been scaled up to 5000 L
- A membrane at the bottom of the reactor catches resin-bound peptides to facilitate washing
- Difficult coupling regions are often made separately and then coupled to the resin-bound fragment

Pennington, M. *et. al. Med. Drug Discov.* **2021**, *9,* 100071.

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Pros:

- Good for short peptides
- Single reactor setup
- Agnostic towards unnatural AAs

Cons:

- Low yield and purity typically for longer peptides
- Large manufacturing risk (many consecutive steps must be performed without error)

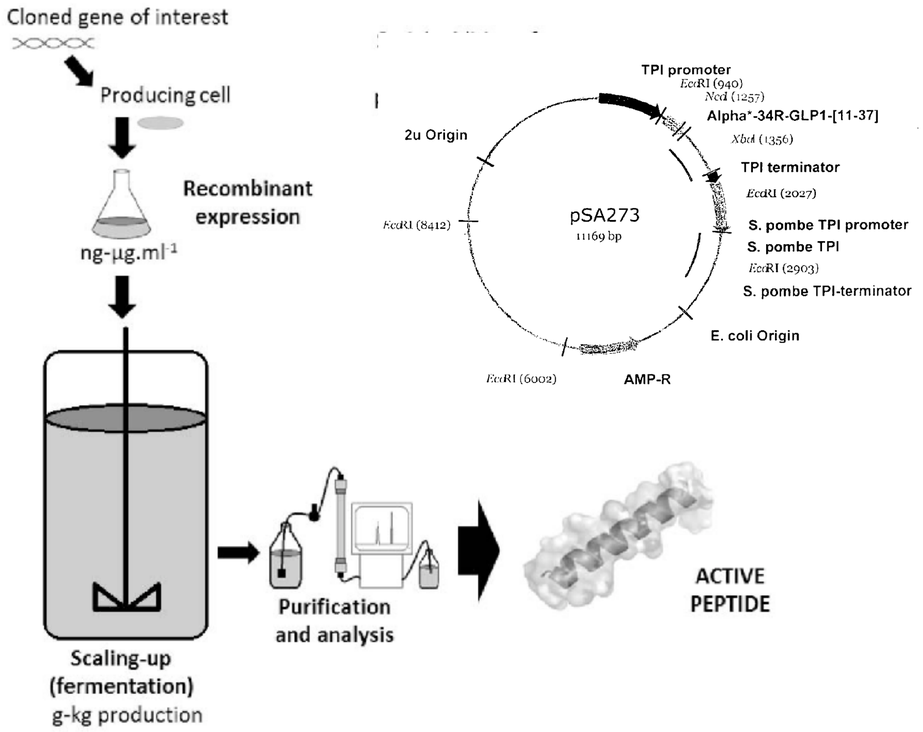
Pennington, M. *et. al. Med. Drug Discov.* **2021**, *9,* 100071.

Peptide Purification on Process Scale

- Typical process purification methods such as precipitation and recrystallization are generally not suitable for peptide APIs
- Reverse phase HPLC with a 60-100 cm column is generally necessary for purification
- Generates a large amount of solvent waste
- Ion exchange chromatography can occasionally be used for purification of charged peptides

Pennington, M. *et. al. Med. Drug Discov.* **2021**, *9,* 100071.

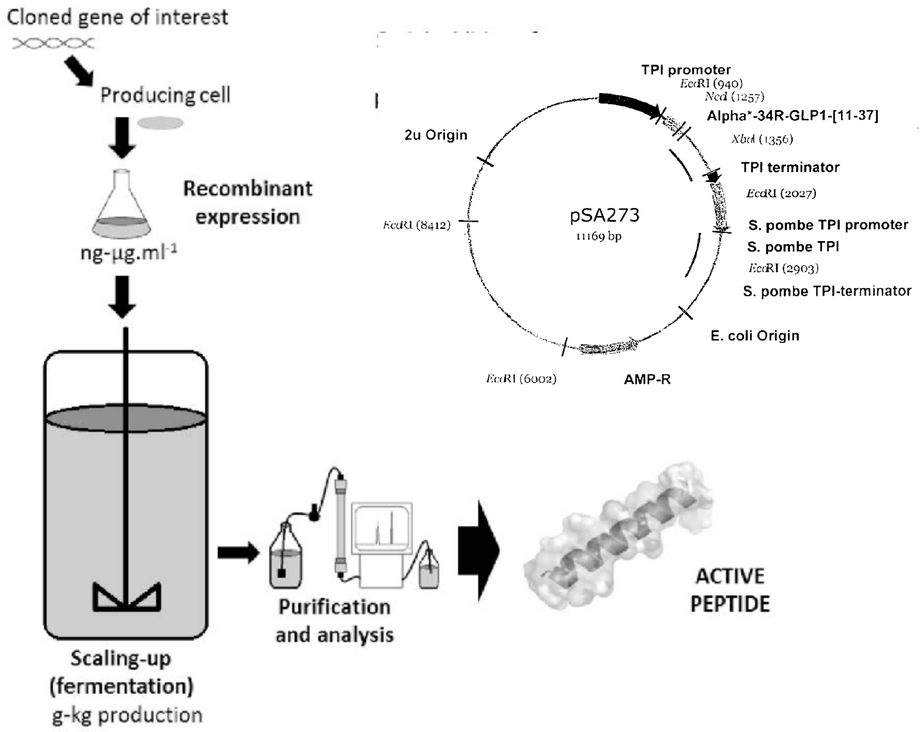
Semi-Recombinant Synthesis of Semiglutide

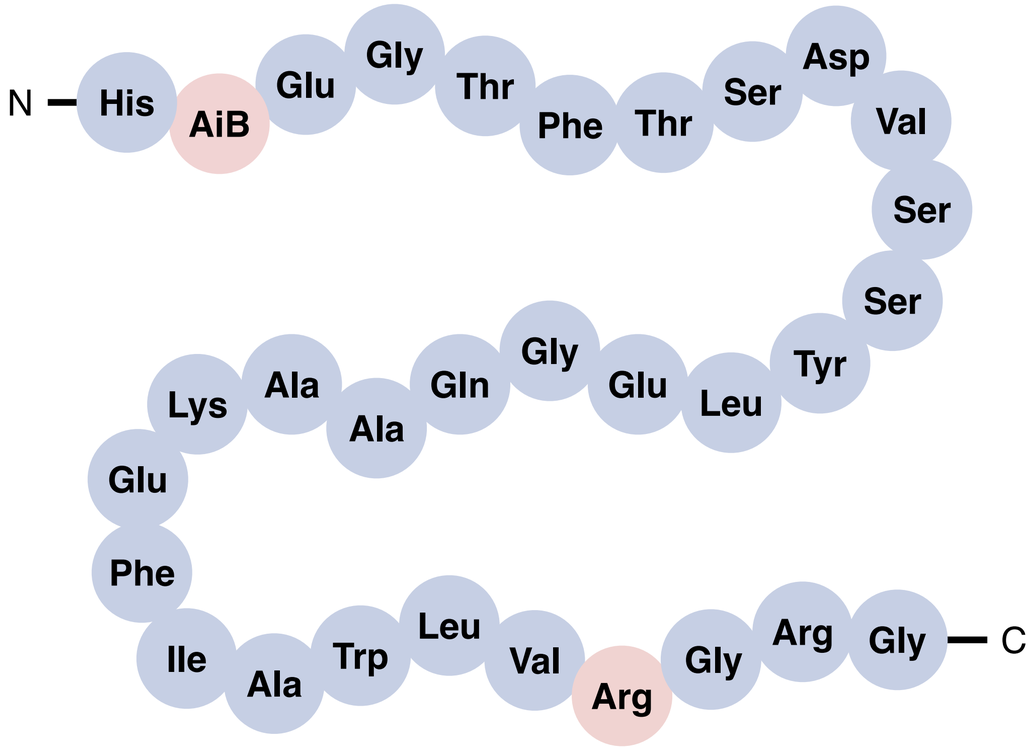


- Plasmid encoded with desired sequence is incorporated into bacteria, which then express the peptide
- Can be performed on process scale to create the semaglutide peptide backbone

US 2010/0317057A1. Mulder, K.C.L. *et. al. Curr. Protein Pep. Synth.* **2013**, *14,* 556.

Semi-Recombinant Synthesis of Semiglutide





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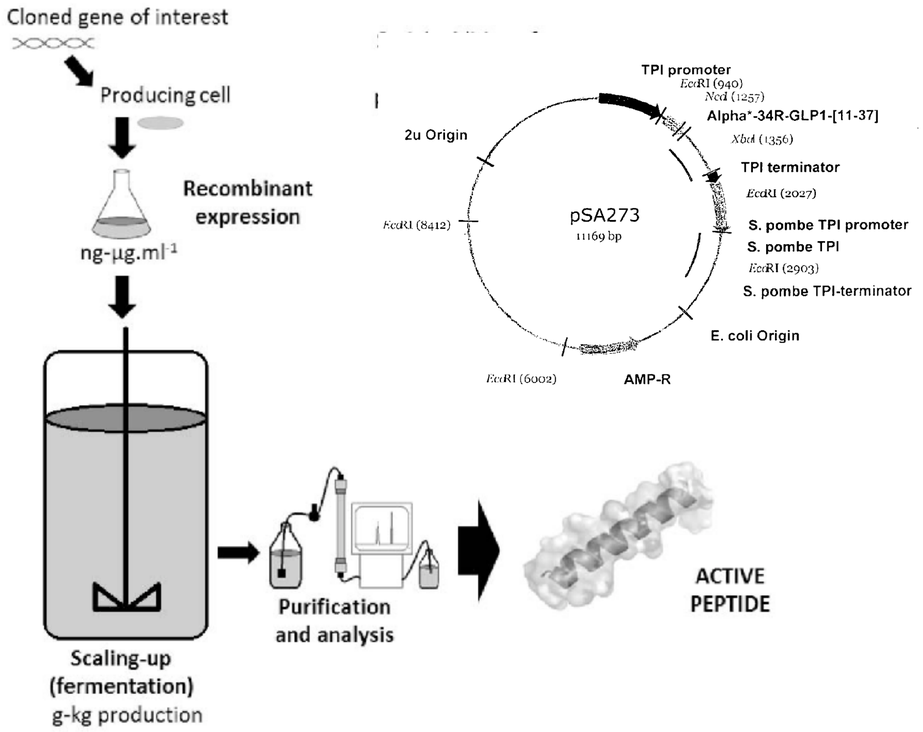

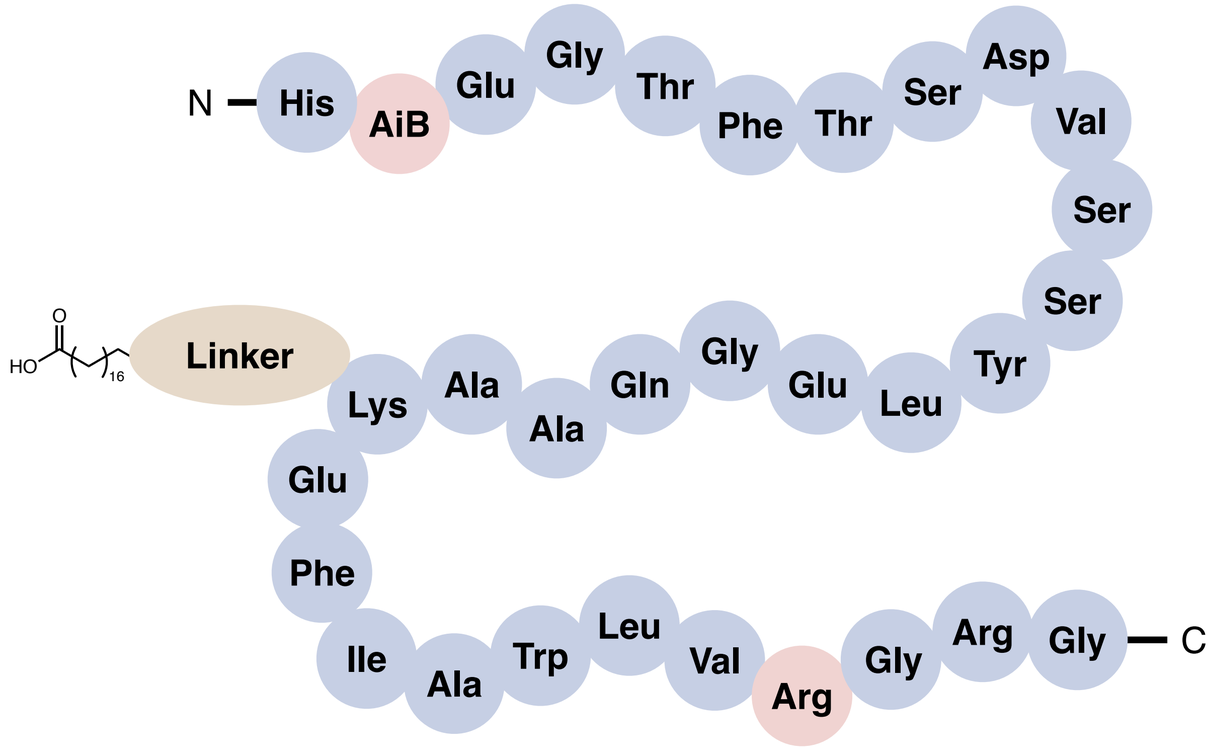

- Plasmid encoded with desired sequence is incorporated into bacteria, which then express the peptide
- Can be performed on process scale to create the semaglutide peptide backbone

- Separate peptide from culture broth, acylate with desired fatty acid chain/linker and perform additional purification

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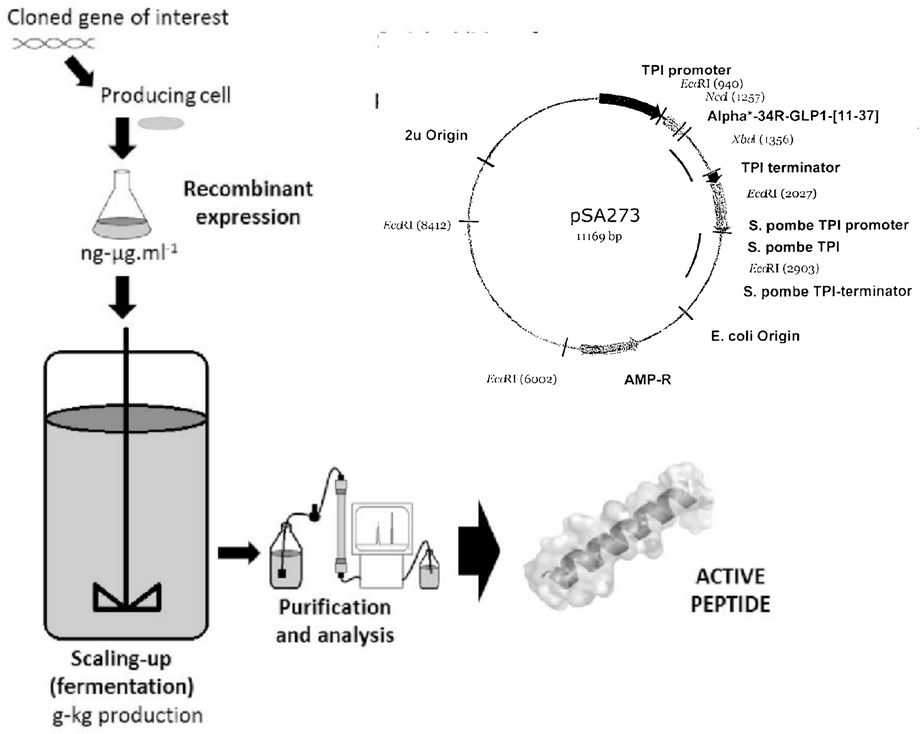

Pros:

- Good for medium/long peptides
- Single reactor setup
- Reduced manufacturing risk

Cons:

- Longer development time
- Challenging for peptides with several unnatural amino acids

US 2010/0317057A1. Mulder, K.C.L. *et. al. Curr. Protein Pep. Synth.* **2013**, *14,* 556.

Kilogram-Scale Tirzepatide Synthesis (Hybrid SPPS/LPPS)

1. Use SPPS to synthesize short peptide fragments
   in high purity and lower manufacturing risk
2. “Soft clevage” of peptide fragments from resin

Frederick, M.O. *et. al. Org. Process Res. Dev.* **2021**, *25,* 1628.

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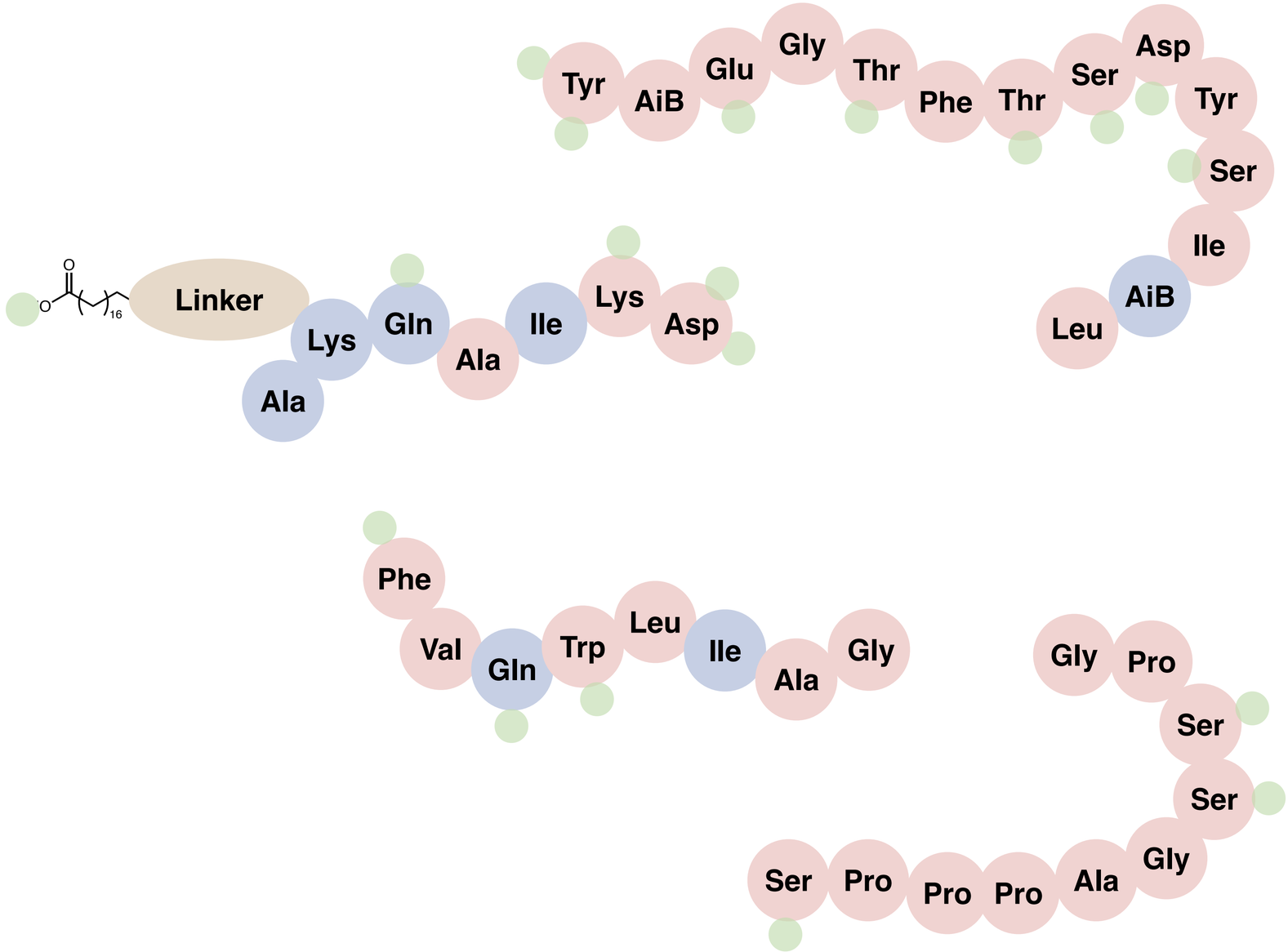

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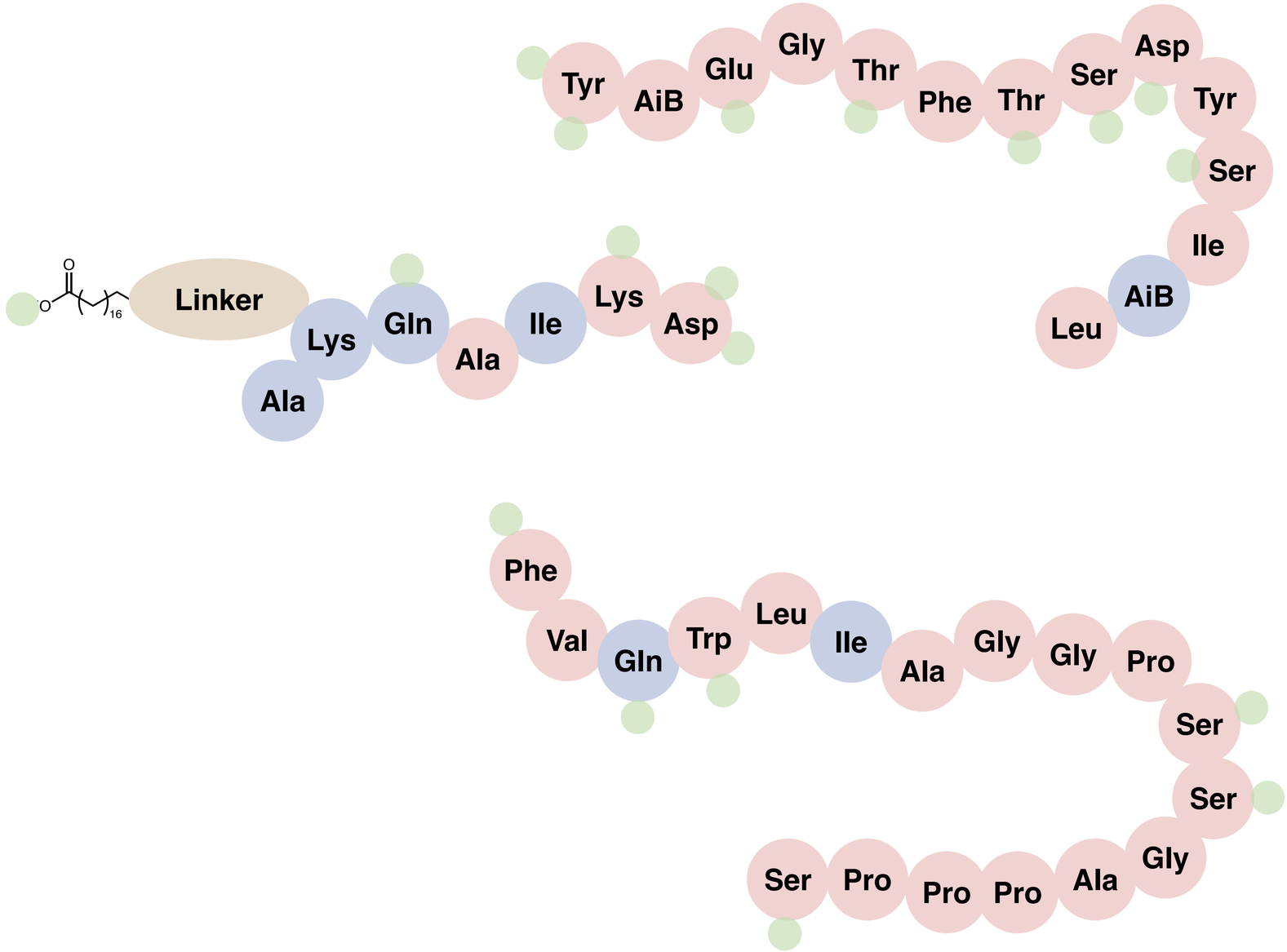

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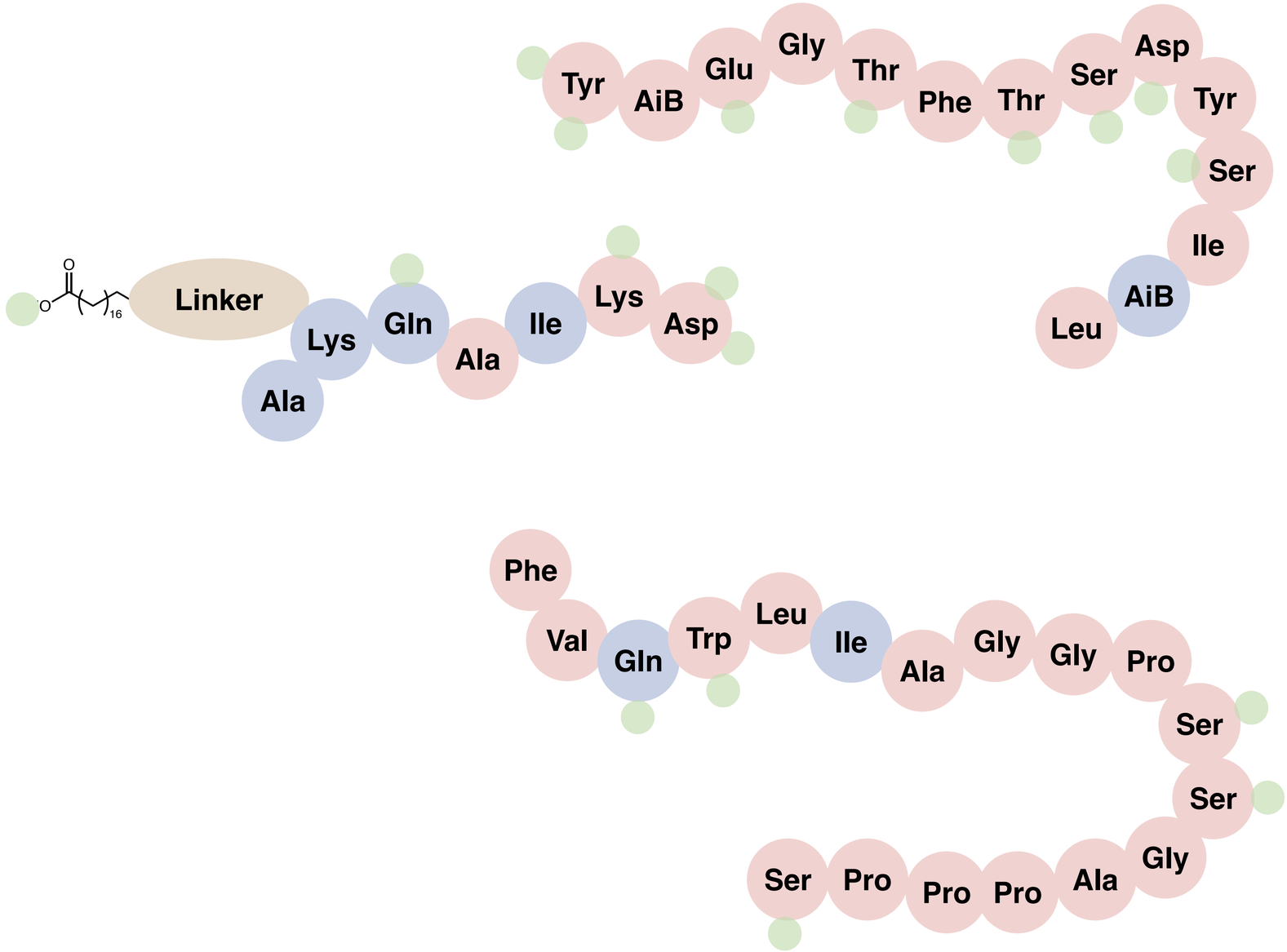

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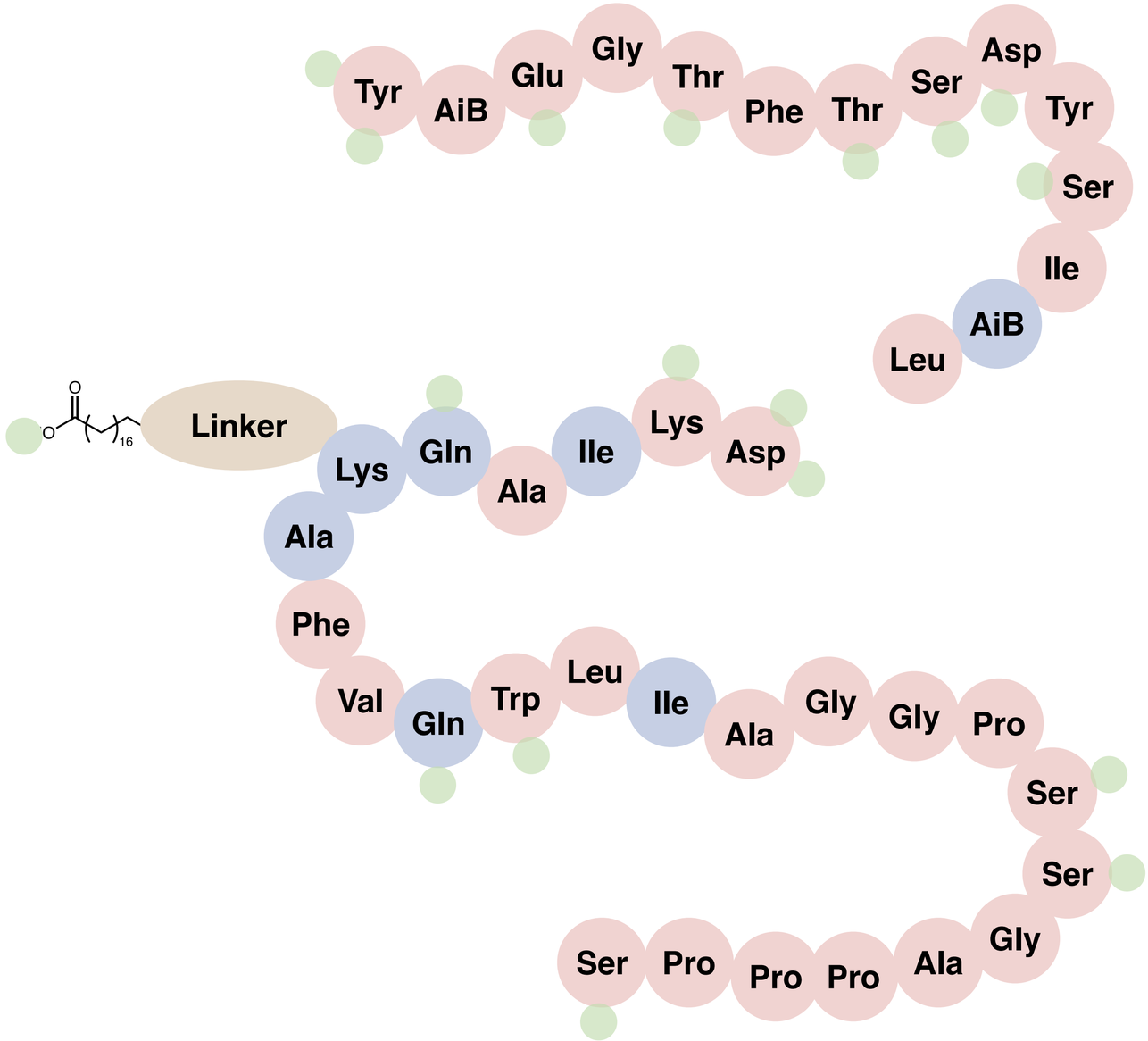

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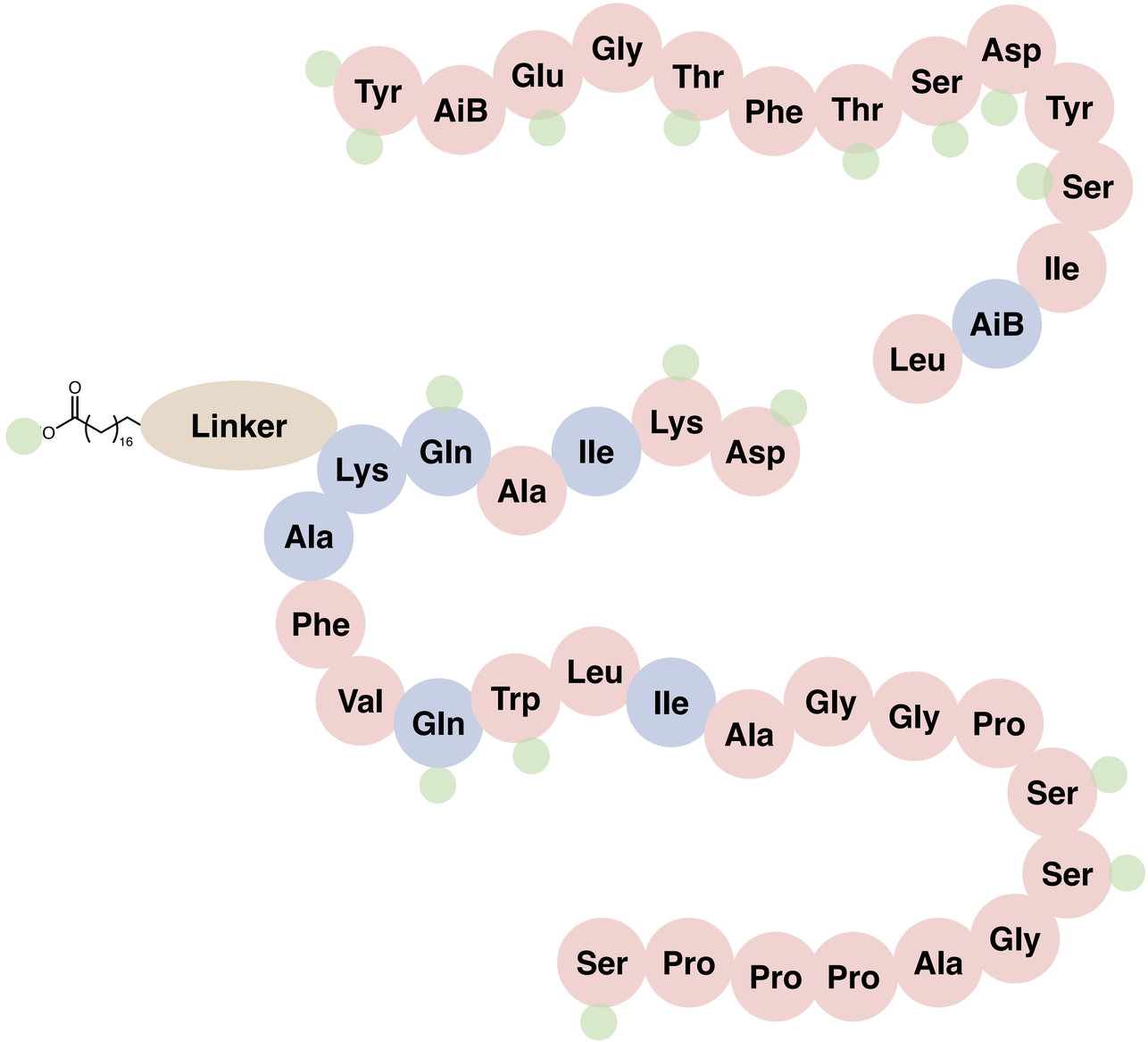

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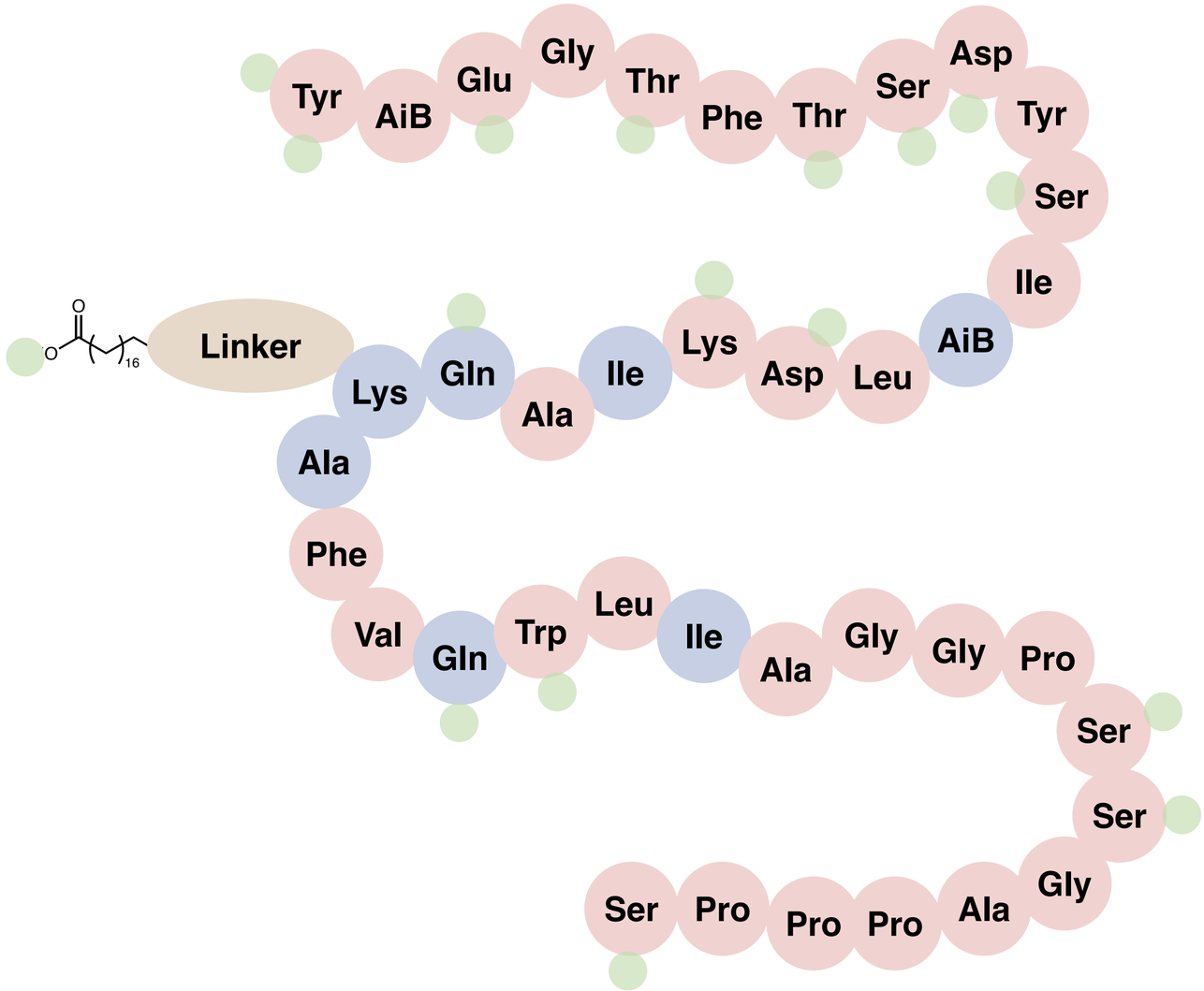

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1. Use SPPS to synthesize short peptide fragments in high purity and lower manufacturing risk
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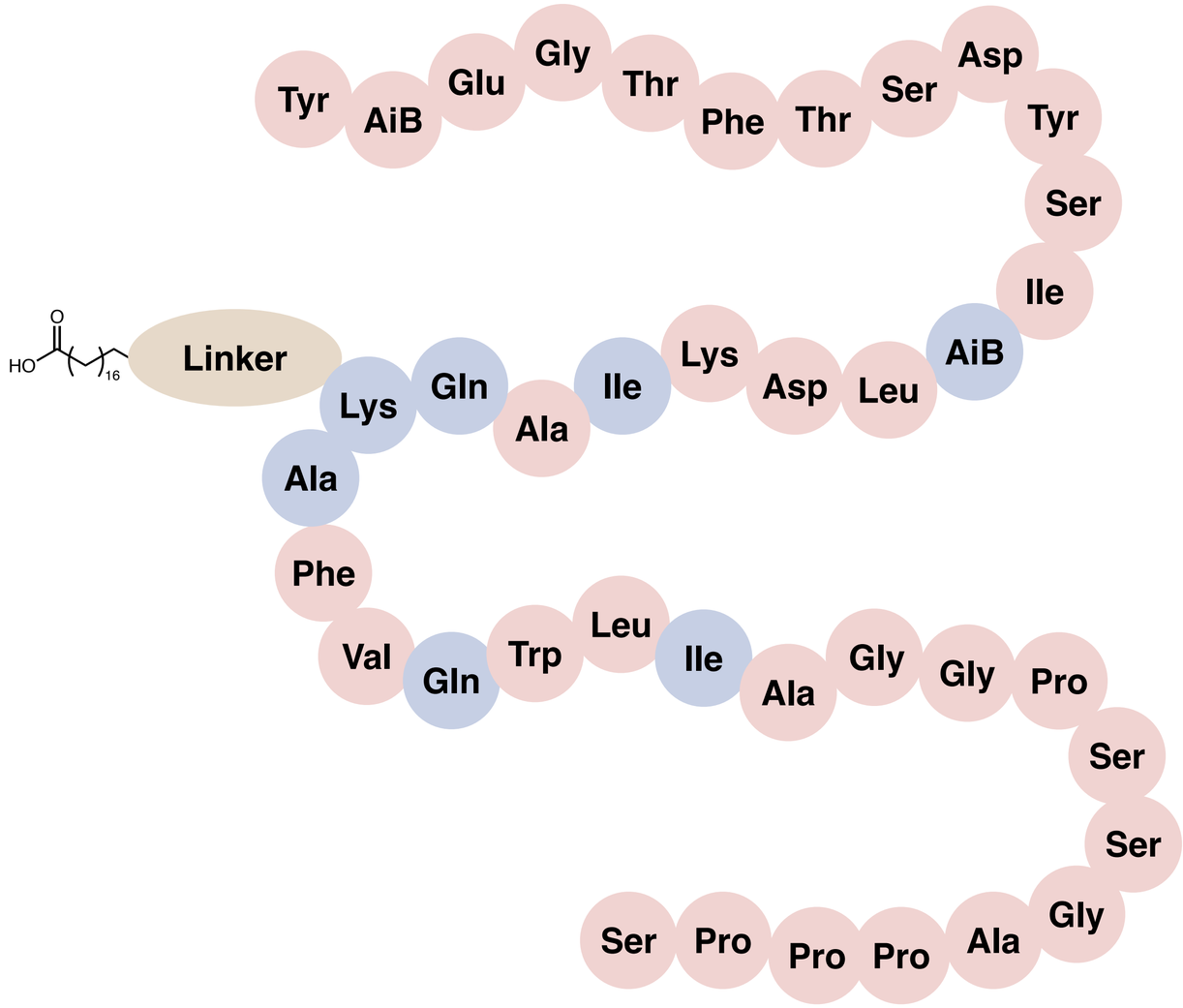
4. Perform a global deprotection



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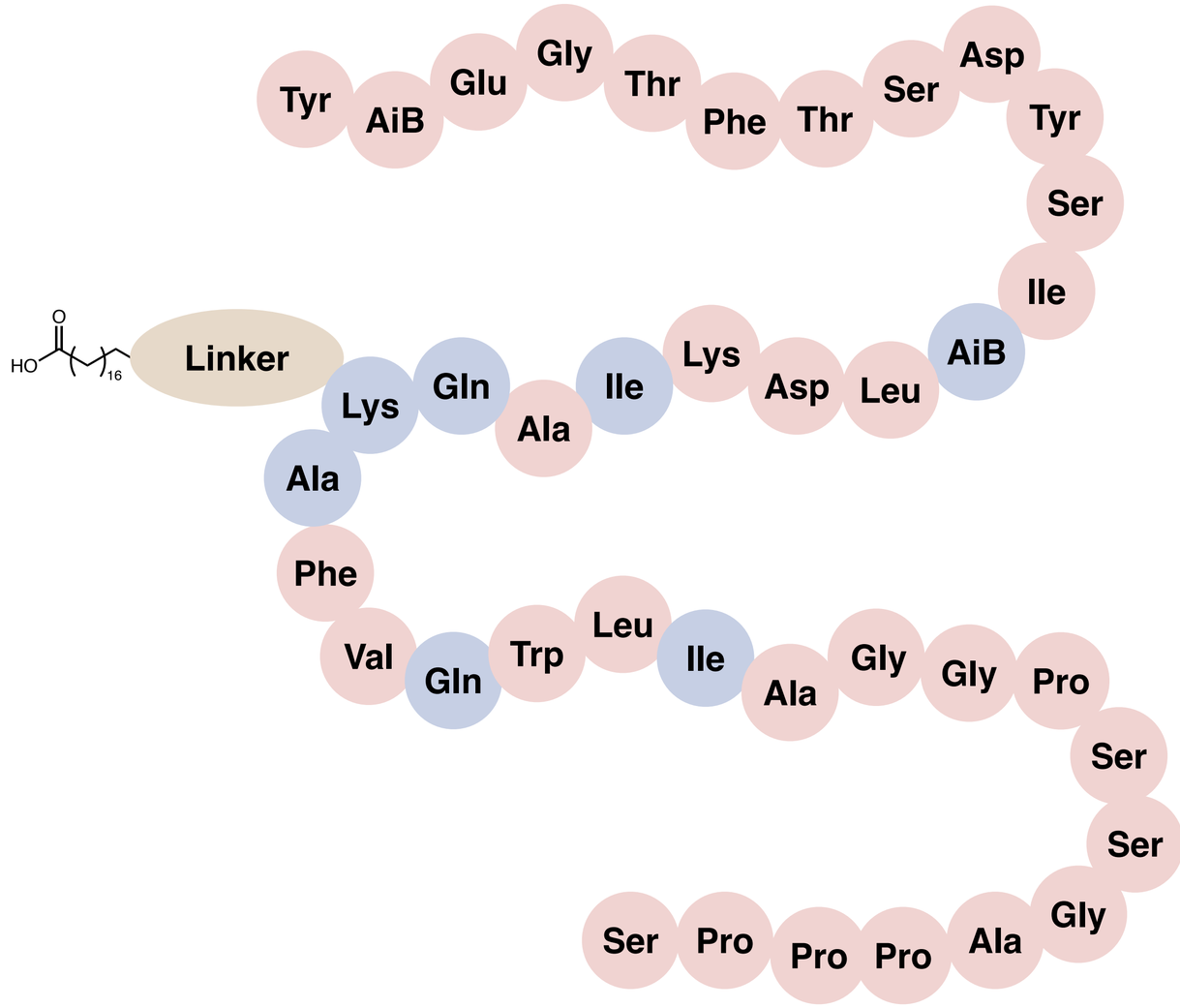
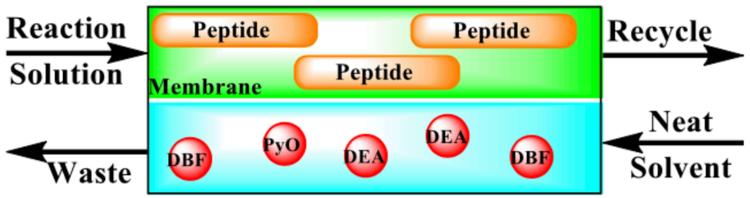


Nanofiltration used for intermediate purification



Reaction mixture is passed through a membrane that separates components based on molecular weight and hydrophobicity

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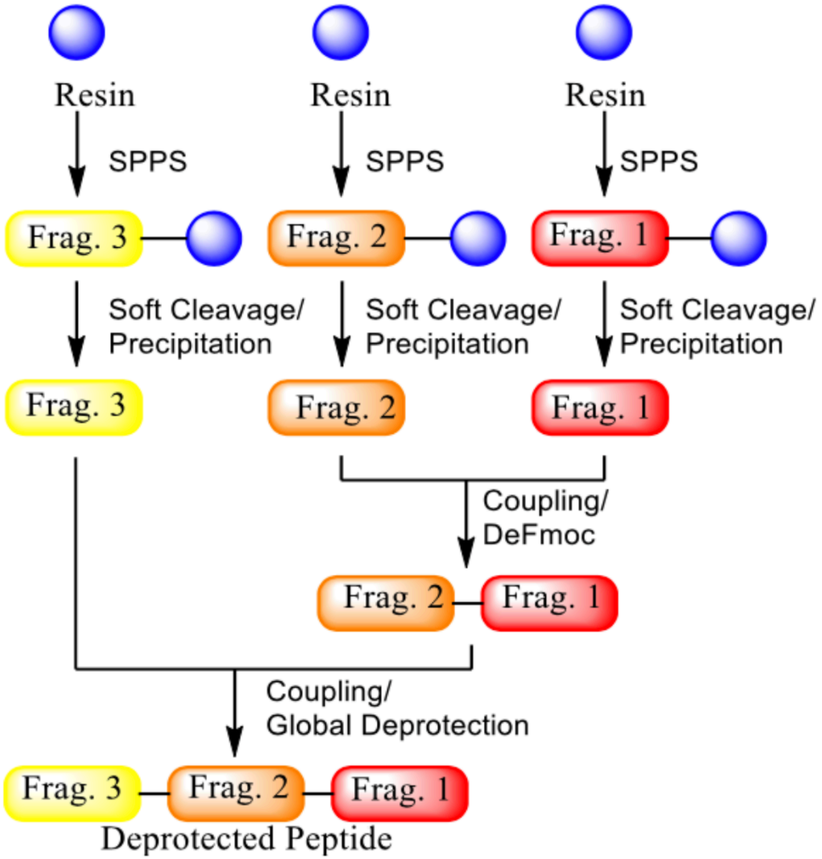

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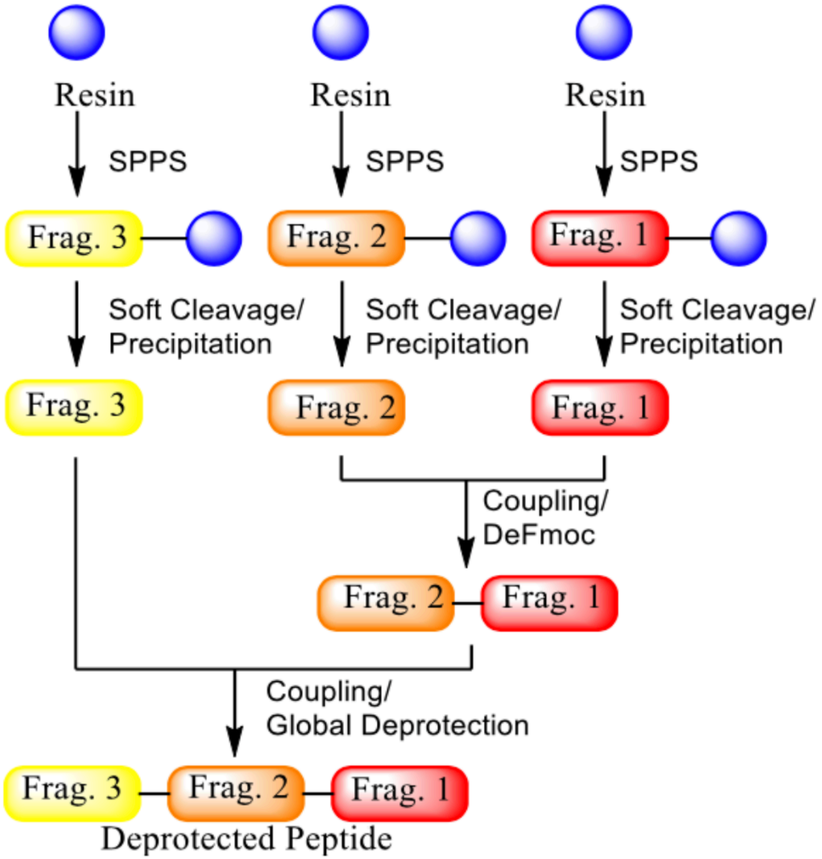


Pros:

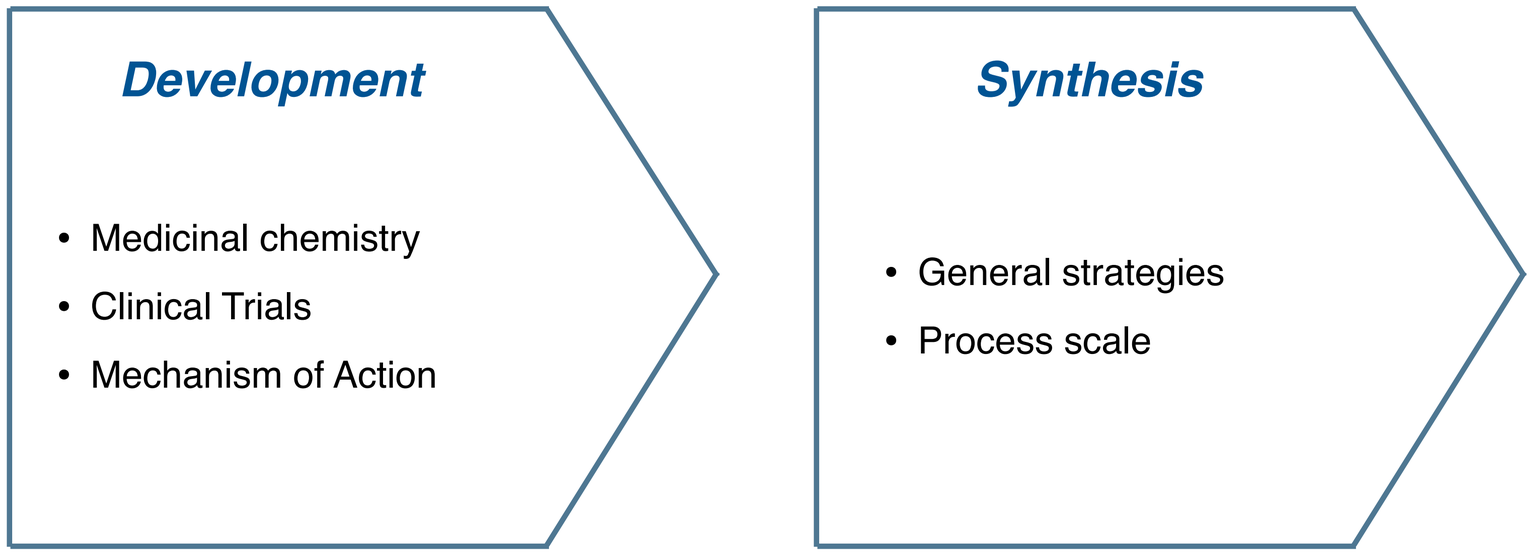
- Good for long peptides
- Agnostic towards unnatural AAs
- Reduced manufacturing risk
- Higher crude API purity

Cons:

- Judicious choice of fragments required to prevent racemization
- More sequential process operations than recombinant approaches

Frederick, M.O. *et. al. Org. Process Res. Dev.* **2021**, *25,* 1628.

GLP-1 Receptor Agonists: Design and Development



GLP-1 Receptor Agonists: Design and Development

Development

- Medicinal chemistry
- Clinical Trials
- Mechanism of Action

Synthesis

- General strategies
- Process scale

State of the Field

- Oral GLP-1R agonists
- Current research
- Future drug development

The Quest for Oral GLP-1 Analogues

- Peptides generally have low oral bioavailability unless they are low molecular weight and a specific hydrophobicity
- Oral semaglutide is highly desired due to patient convenience and treatment compliance

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

The Quest for Oral GLP-1 Analogues

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- Oral semaglutide is highly desired due to patient convenience and treatment compliance

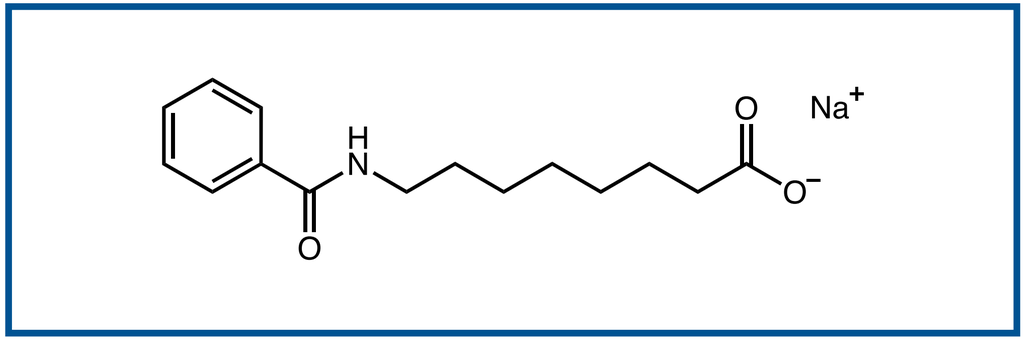
Can we develop an enhancer to improved semaglutide bioavailability?

Enhancer Properties:

1. Pharmaceutically inert small molecule
2. Provide a transient effect of increased semaglutide absorption
3. Absorption is selective for semaglutide and not co-administered drugs

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32.

The Quest for Oral GLP-1 Analogues



SNAC

sodium N-[8-(2-hydroxybenzoyl)amino] caprylate

Small molecule additive developed by Emisphere and generally recognized as safe (GRAS) for food supplements, vitamins, etc by the FDA

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32. Bækdal, T.A. *el. al. CPPD* **2021**, *10,* 453.

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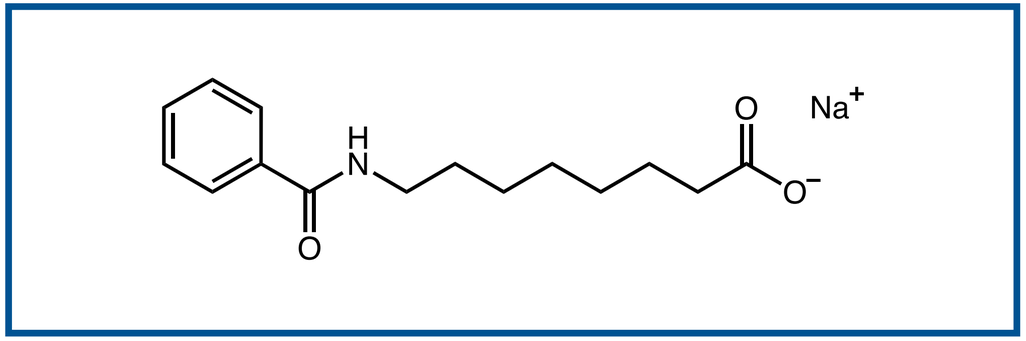

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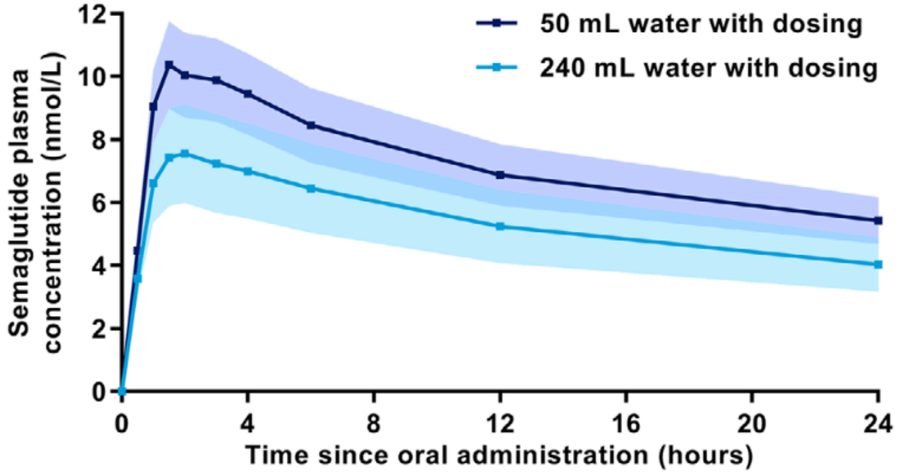
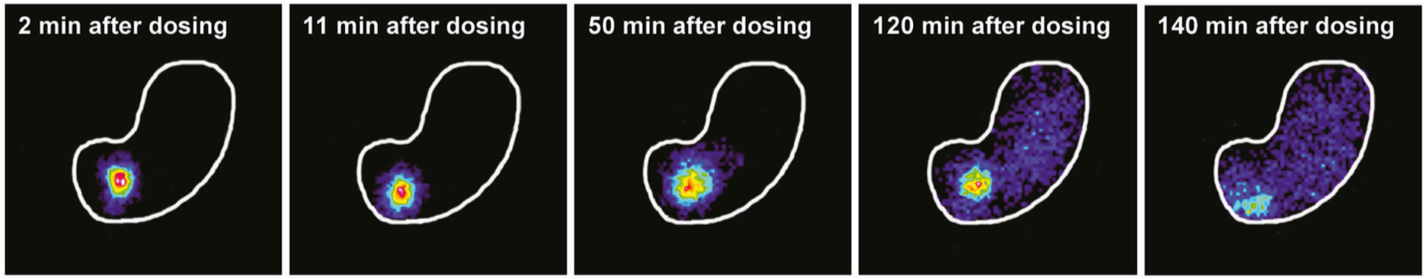


Small molecule additive developed by Emisphere and generally recognized as safe (GRAS) for food supplements, vitamins, etc by the FDA

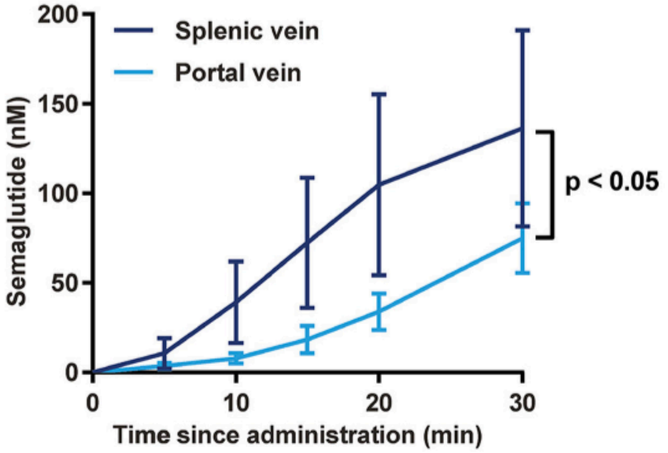
- Improves oral bioavailability, but only to **~1%**
- At high doses of semaglutide, the oral formulation shows similar efficacy to injectables for glycemic control and weight loss

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32. Bækdal, T.A. *el. al. CPPD* **2021**, *10,* 453.

The Quest for Oral GLP-1 Analogues



Tablet absorption in the stomach (white outline)



- Hypothesized to shift peptide absorption from the intestines to the stomach
- Facilitates localized increase in pH that improves semaglutide solubility and slows degradation

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32. Bækdal, T.A. *el. al. CPPD* **2021**, *10,* 453.

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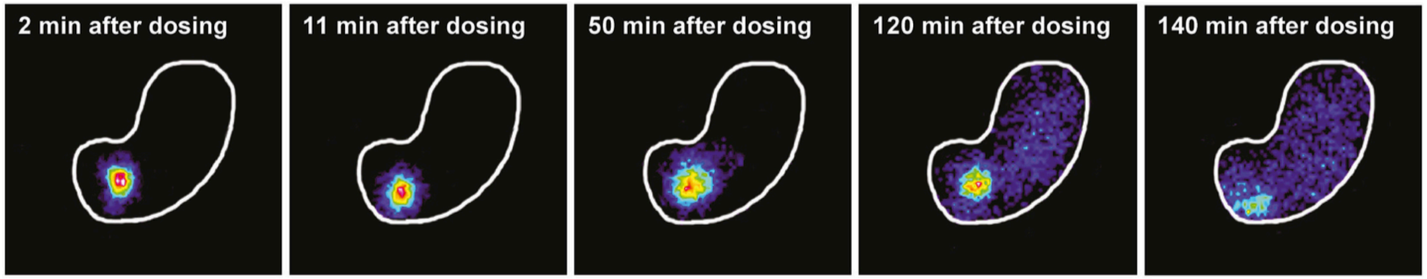

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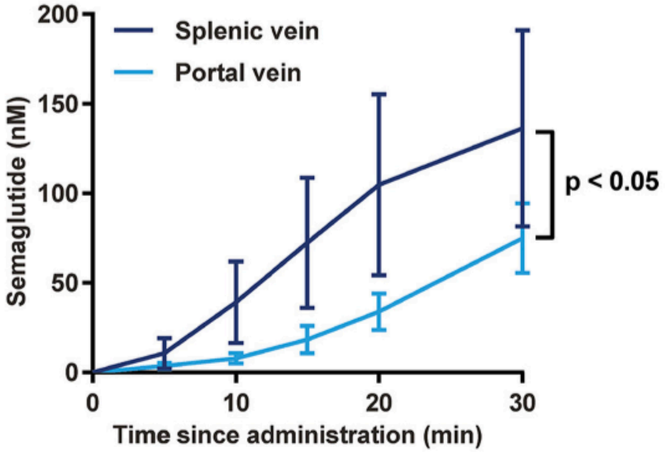


- Hypothesized to shift peptide absorption from the intestines to the stomach
- Facilitates localized increase in pH that improves semaglutide solubility and slows degradation

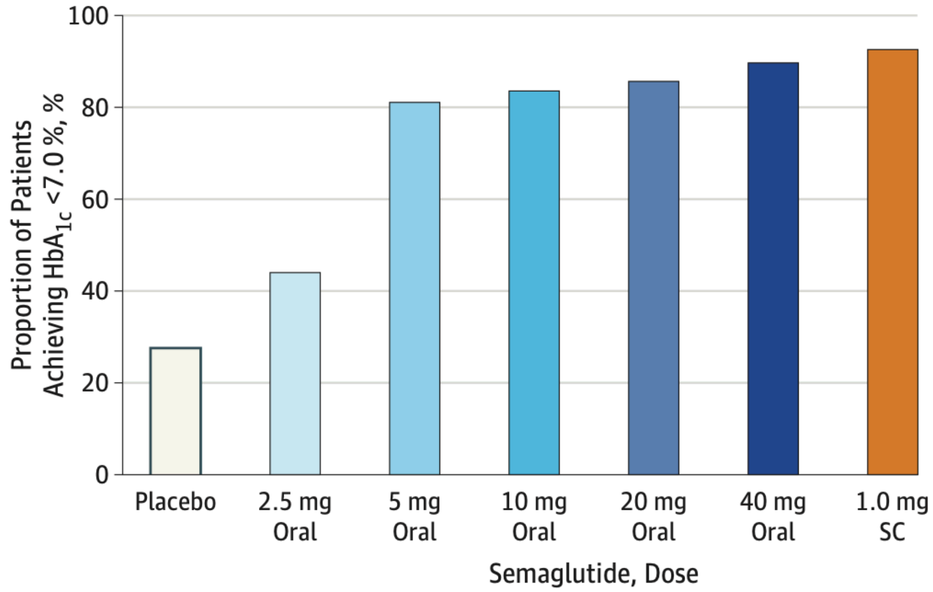
- Provides a transient effect on membrane fluidity, where SNAC partitioning into the cell membrane causes rapid transcellular absorption of both semaglutide and SNAC
- Does not appear to improve absorption of small molecule drugs or other peptides such as liraglutide

Knudsen, L.B.; Lau, J. *Front. Endocrinol.* **2019**, *10* (155), 1-32. Bækdal, T.A. *el. al. CPPD* **2021**, *10,* 453.

The Quest for Oral GLP-1 Analogues

- Phase 2 clinical trial comparing daily oral and weekly injectable doses of semaglutide in patients with T2D
- At the highest dose (40 mg), the oral treatment matches the 1.0 mg injected dose for lowering A1C

B Proportion of patients achieving HbA_{1c} <7.0% after 26 wk of treatment



Davies, M. *et. al. JAMA* **2017**, *318,* 1460.

The Quest for Oral GLP-1 Analogues

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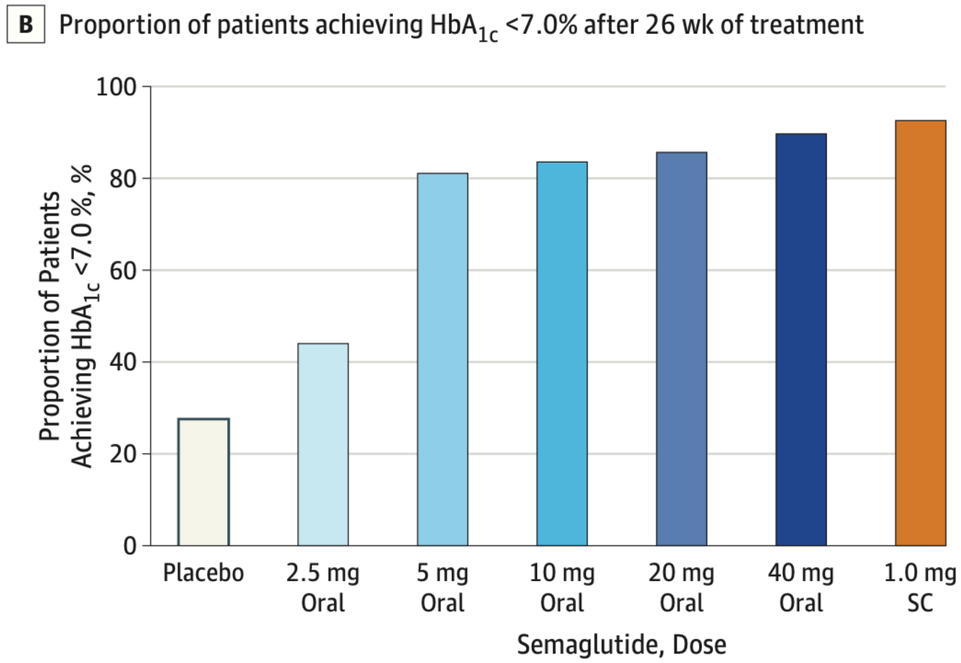
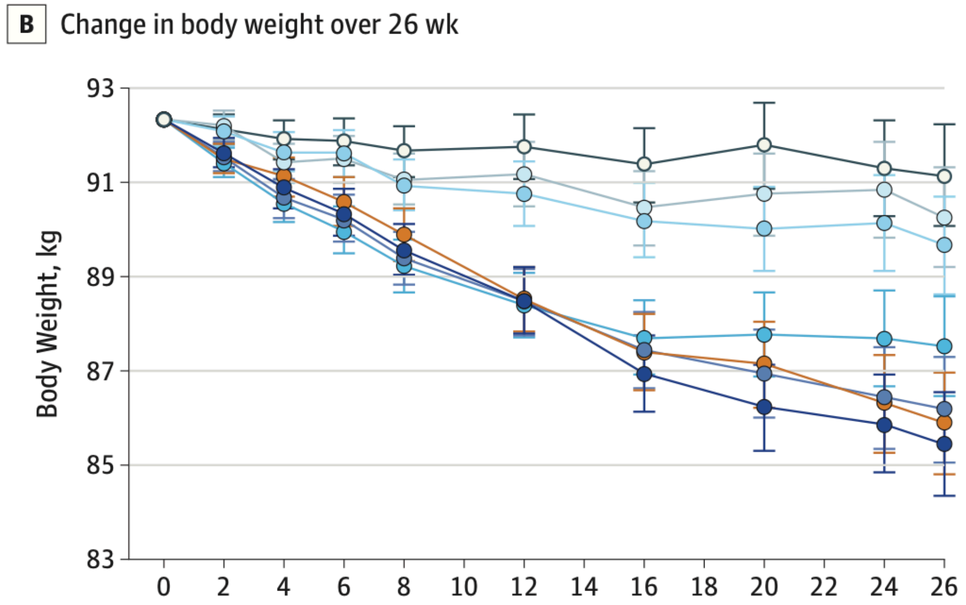
- Oral doses >10 mg led to statistically significant weight loss, with over 5 kg for the 20 and 40 mg oral dose and standard injectable dose





Davies, M. *et. al. JAMA* **2017**, *318,* 1460.

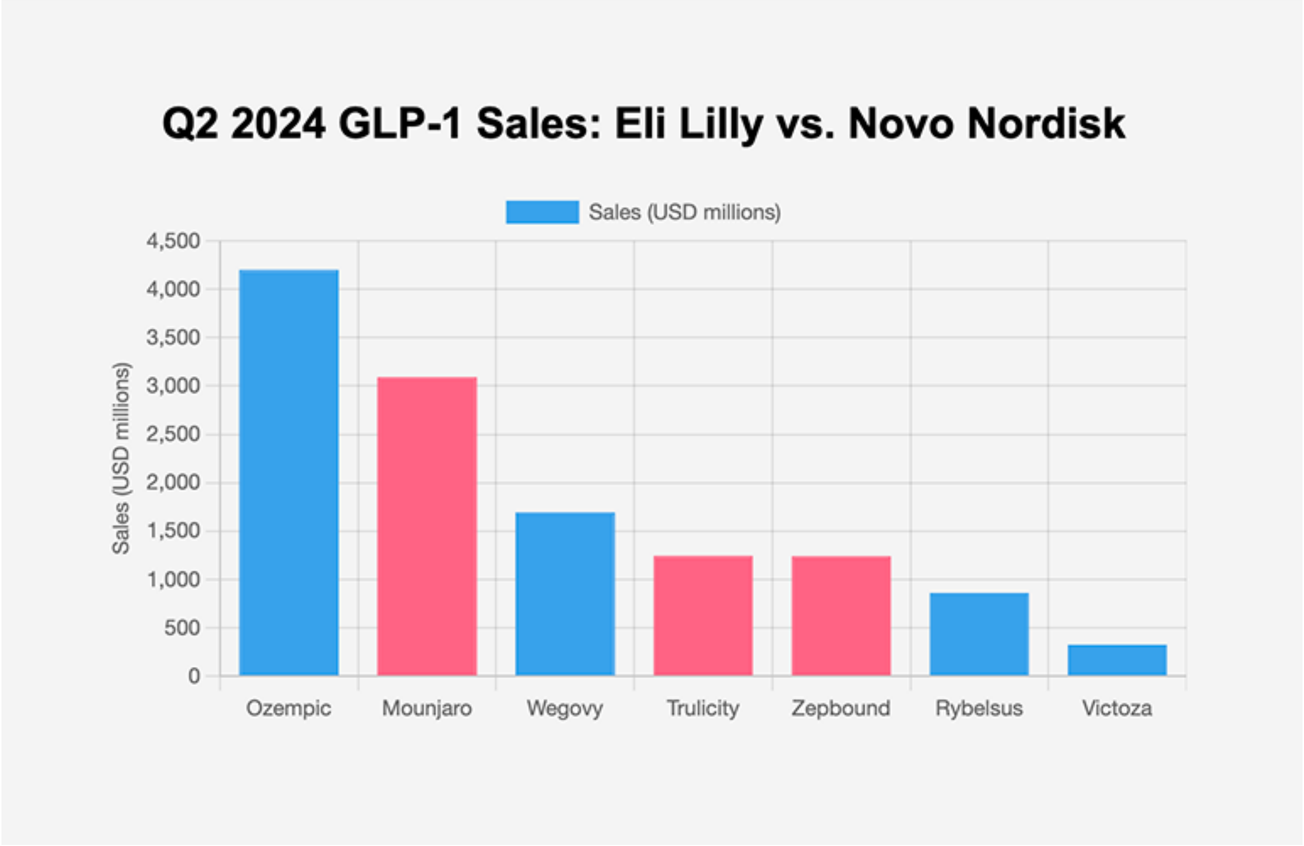
The Quest for Oral GLP-1 Analogues

	Month 1	Month 2	Month 3	Month 4	Month 5+
Rybelsus	3mg/day	7mg/day	7mg/day (14mg if needed)	7mg/day (14mg if needed)	7mg/day (14mg if needed)
	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5+**
Wegovy	0.25mg/week	0.5mg/week	1mg/week	1.7mg/week	2.4mg/week

Rybelsus was FDA approved in 2019 for T2D, but requires much higher doses than injectable semaglutide (Ozempic or Wegovy)

Puddick, R. Second Nature, 2025.

The Quest for Oral GLP-1 Analogues



Rybelsus is currently outsold by most GLP-1 competitors, but demand could go up as supply chain shortages are resolved

Buntz, B. Drug Discovery and Development, 2024.

Beyond T2D and Weight Loss

FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight

For Immediate Release: March 08, 2024

FDA Approves Ozempic for Type 2 Diabetes and Chronic Kidney Disease

February 20, 2025

Beyond T2D and Weight Loss

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For Immediate Release: March 08, 2024

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February 20, 2025

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- Phase 3 trial for **Alzheimer's Disease** ongoing
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- Preclinical studies for **alcohol use disorder** complete
- Phase 2 trial for **non-alcoholic steatohepatitis (NASH)/ non-acoholic fatty liver disease (NAFLD)** are complete with mixed results

GLP-1 Receptor Agonists: Design and Development

Development

- Medicinal chemistry
- Clinical Trials
- Mechanism of Action

Synthesis

- General strategies
- Process scale

State of the Field

- Oral GLP-1R agonists
- Current research
- Future drug development

Questions?