Applied Mathematics and Informatics In Drug Discovery (2025)

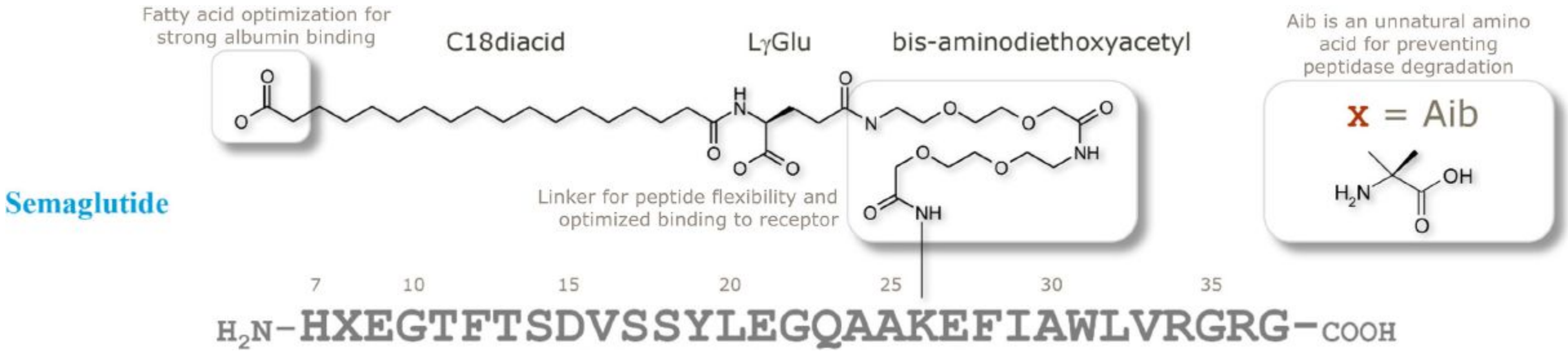


Figure from Knudsen *et al.*, 2019

Dr. Jitao David Zhang, Computational Biologist

[1] Computational Sciences Center of Excellence (CS CoE), Roche Innovation Center Basel, F. Hoffmann-La Roche;
[2] Department of Mathematics and Computer Sciences, University of Basel

Outline

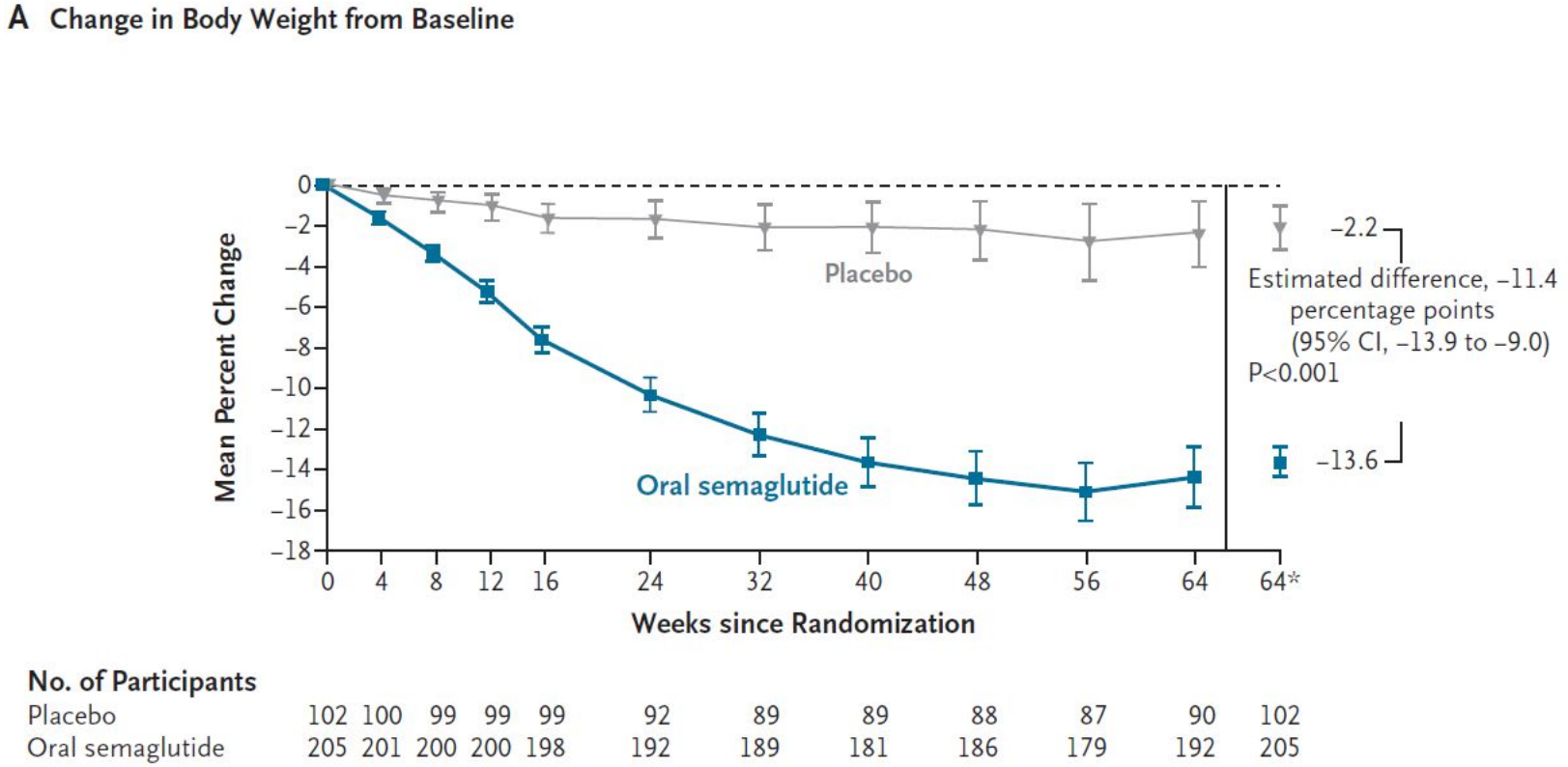
1. Learning drug discovery from an example
2. Learning drug discovery backwards
3. About the course

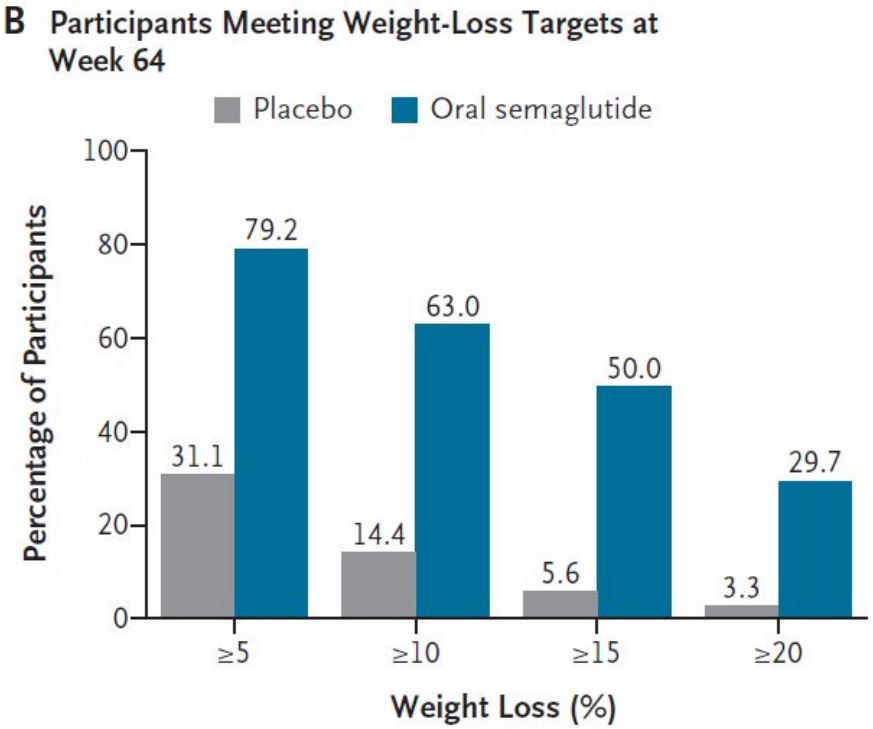
Oral Semaglutide in Adults with Overweight or Obesity

For participants with overweight or obesity, the efficacy and safety of oral semaglutide at a dose of 25 mg once daily for weight management are unclear. New research findings are summarized in a short video, available at NEJM (published on September 18, 2025)

Q1: What is semaglutide?
Q2: What are the proven benefits of semaglutide for patients with obesity?
Q3: What is the dose, the dosing frequency, and the route of administration that has been shown to show a benefit?
Q4: What is the goal of the current clinical study?
Q5: How many patients participated in the trial?
Q6: Which patients participated in the trial?
Q7: What were the coprimary outcomes of the trial?
Q8: What was the most common adverse event? How many patients experienced that?
Q9: What was the conclusion of the authors?
Q10: What questions do you have?

Efficacy and Safety of Oral Semaglutide 25 mg Once Daily in Adults With Overweight or Obesity (The OASIS4 study)





Panel A shows mean percent change in body weight from baseline over time; I bars indicate 95% CIs, numbers below show participants, and asterisks mark estimated means. Panel B shows percentages of participants with ≥5%, ≥10%, ≥15%, and ≥20% weight loss at week 64.

Primary endpoints (not complete)

Table 2. Primary, Confirmatory Secondary, and Selected Exploratory End Points.*

End Point	Oral Semaglutide (N=205)	Placebo (N=102)	Difference (95% CI)†
Primary end points			
Percent change in body weight from baseline to week 64	−13.6	−2.2	−11.4 (−13.9 to −9.0)
Body-weight reduction of ≥5% at week 64 — no./total no. (%)‡	152/192 (79.2)	28/90 (31.1)	7.3 (4.2 to 12.8)
Confirmatory secondary end points			
Body-weight reduction of each target — no./total no. (%)‡			
≥10% at week 64	121/192 (63.0)	13/90 (14.4)	9.1 (4.7 to 17.3)
≥15% at week 64	96/192 (50.0)	5/90 (5.6)	15.7 (6.2 to 40.2)
≥20% at week 64	57/192 (29.7)	3/90 (3.3)	12.2 (3.7 to 40.3)
Change in IWQOL-Lite-CT Physical Function score from baseline to week 64 — points§	16.2	8.4	7.7 (3.3 to 12.2)
Supportive secondary end points¶			
Change in IWQOL-Lite-CT Physical Function score ≥14.6 at week 64 — no./total no. (%)‡	104/188 (55.3)	31/89 (34.8)	2.4 (1.4 to 4.1)
Change in cardiometabolic risk factors from baseline to week 64			
Body weight — kg	−14.2	−2.16	−12.0 (−14.6 to −9.5)
BMI	−5.1	−0.8	−4.3 (−5.2 to −3.4)

CI: confidence interval

IWQOL: A five-item subscore of the Impact of Weight on Quality of Life–Lite Clinical Trials Version (IWQOL-Lite-CT), in which scores range from 0 to 100, with higher scores indicating better level of function. It considers physical function, self-esteem, sexual life, public distress, and work.

BMI: Body-mass Index, the weight in kilograms divided by the square of the height in meters

Safety outcome, i.e. Adverse events

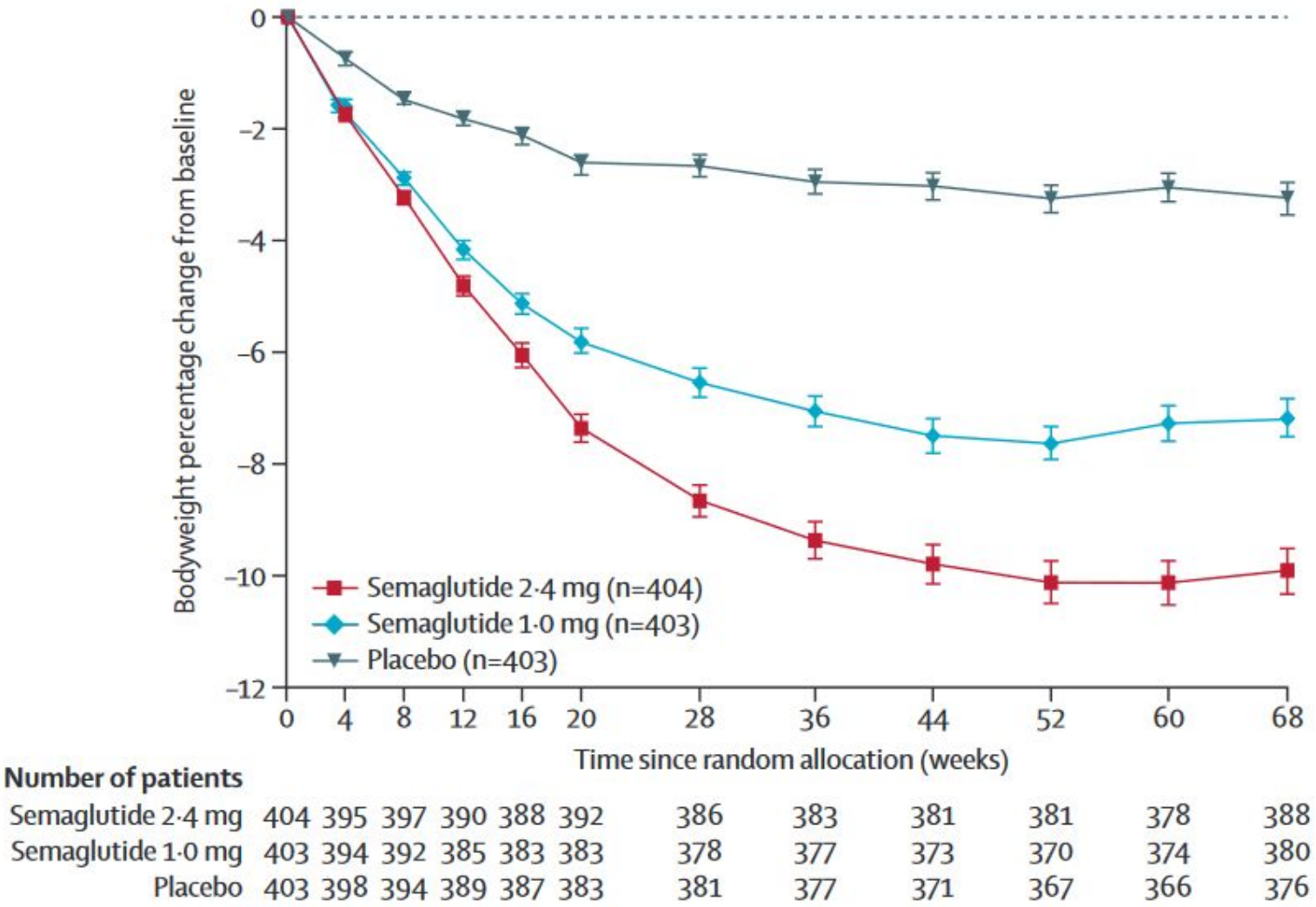
Included are all adverse events that occurred in the safety analysis population, which include all the participants who underwent randomization and were exposed to at least one dose of semaglutide or placebo.

Adverse events were classified by severity as *mild* (causing minimal discomfort and not interfering with everyday activities), *moderate* (causing sufficient discomfort to interfere with normal everyday activities), or *severe* (preventing normal everyday activities).

Table 3. Adverse Events.*

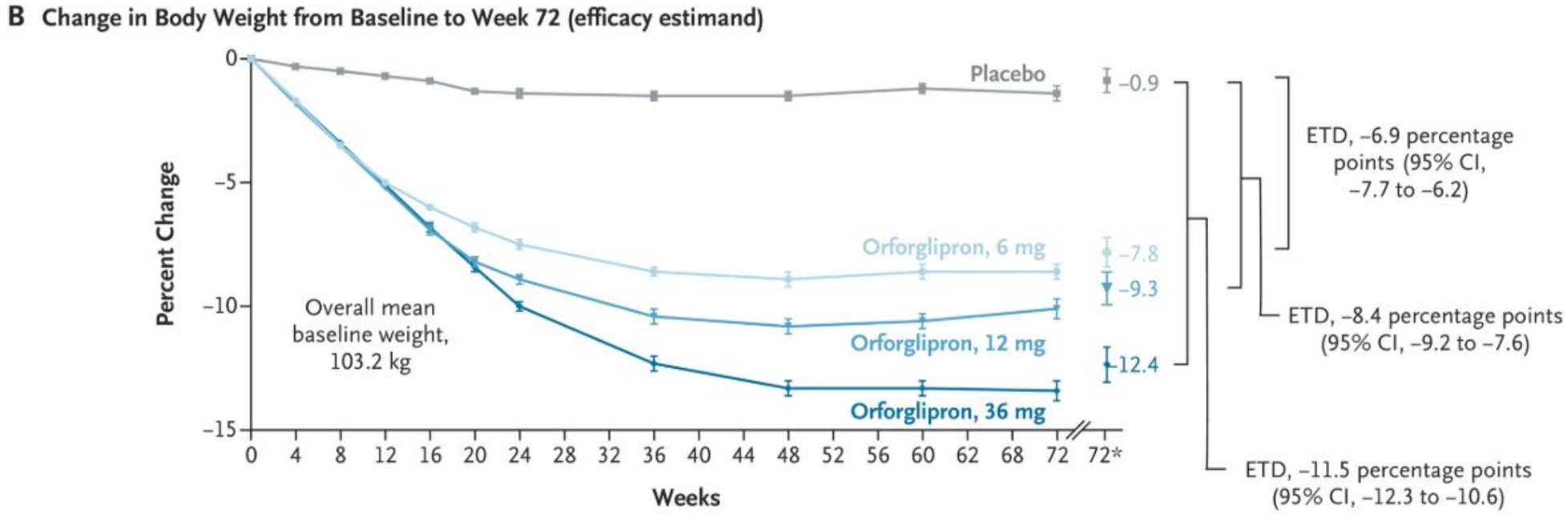
Event	Oral Semaglutide (N=204)			Placebo (N=102)		
	no. of participants (%)	*no. of events*	*events per 100 participant-yr of exposure*	*no. of participants (%)*	*no. of events*	*events per 100 participant-yr of exposure*
Any adverse event	190 (93.1)	1239	493.5	87 (85.3)	432	355.9
Serious adverse events	8 (3.9)	17	6.8	9 (8.8)	13	10.7
Adverse events leading to discontinuation of semaglutide or placebo	14 (6.9)	14	5.6	6 (5.9)	6	4.9
Gastrointestinal disorders	7 (3.4)	7	2.8	2 (2.0)	2	1.6
Fatal events	0	0	0	0	0	0
Adverse events reported in ≥10% of participants						
Nausea	95 (46.6)	157	62.5	19 (18.6)	27	22.2
Vomiting	63 (30.9)	105	41.8	6 (5.9)	6	4.9
Nasopharyngitis	43 (21.1)	59	23.5	27 (26.5)	40	33.0
Coronavirus disease 2019	42 (20.6)	46	18.3	18 (17.6)	19	15.7
Constipation	41 (20.1)	59	23.5	10 (9.8)	11	9.1
Dyspepsia	37 (18.1)	50	19.9	9 (8.8)	11	9.1
Diarrhea	36 (17.6)	61	24.3	9 (8.8)	10	8.2
Headache	24 (11.8)	35	13.9	9 (8.8)	10	8.2
Eructation	21 (10.3)	23	9.2	2 (2.0)	2	1.6

STEP2: a clinical trial for Semaglutide 2.4mg once a week for overweight, obesity, and type-2 diabetes



Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial, Davies *et al.*, 2021

ATTAIN-1: A Study of Orforglipron (LY3502970) in Adult Participants With Obesity or Overweight With Weight-Related Comorbidities

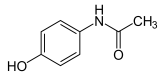


No. of Patients

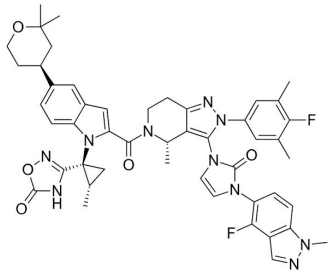
Placebo	949	937	923	910	875	847	817	766	716	688	654	949
Orforglipron, 6 mg	723	713	702	690	675	664	652	630	601	578	559	723
Orforglipron, 12 mg	725	719	695	687	672	652	648	624	602	582	559	725
Orforglipron, 36 mg	730	715	704	689	670	662	644	617	583	573	549	730

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment, Wharton *et al.*, 2025

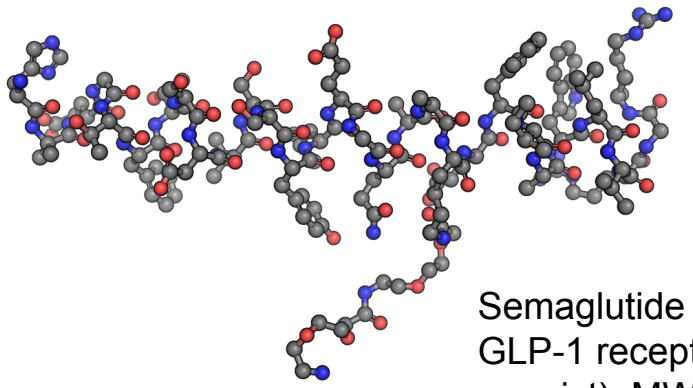
Small molecule, peptide, and antibody



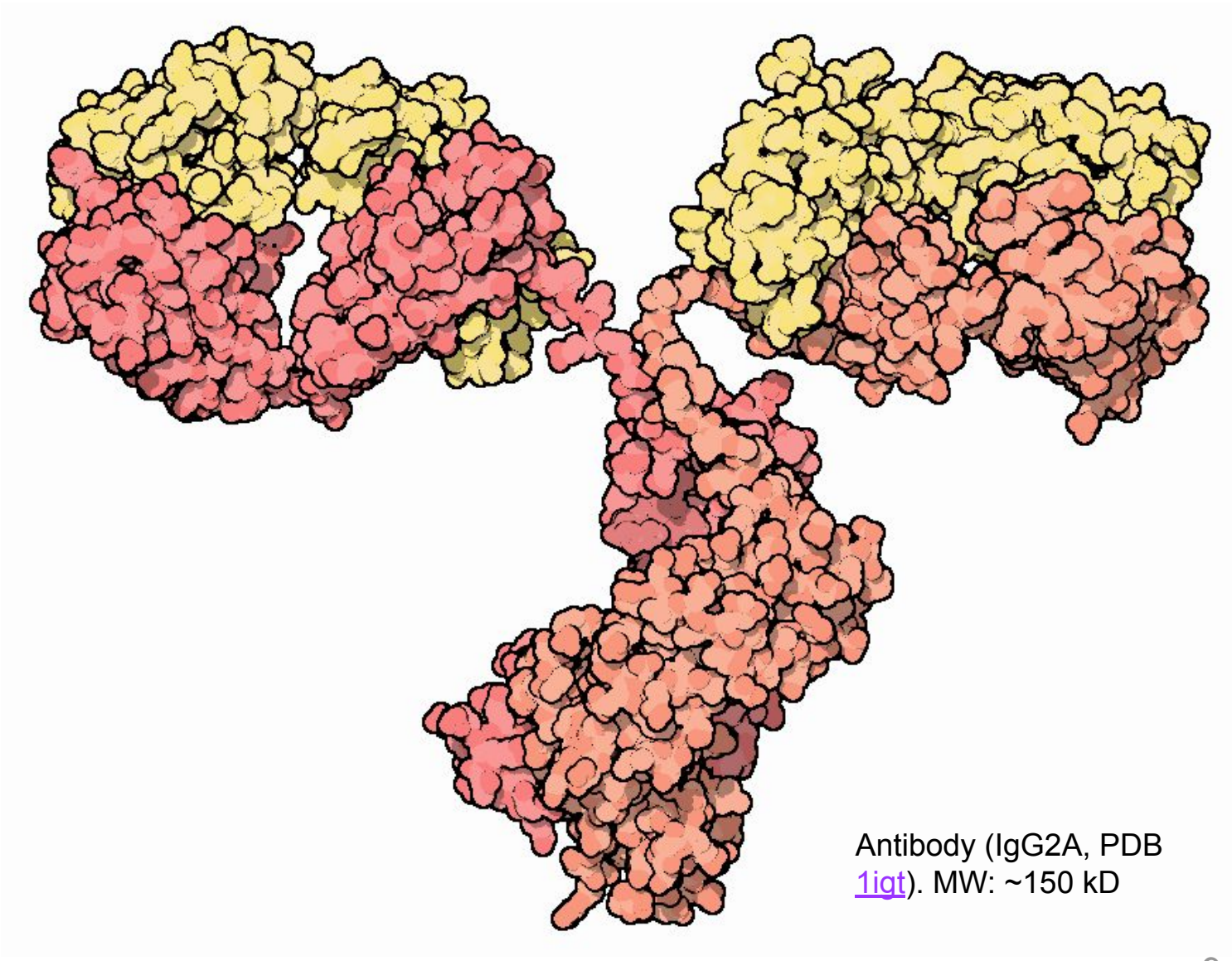
Paracetamol (oral, non-opioid analgesic and antipyretic). Molecular Weight (MW): 151 Dalton (g/Mol)



Orforglipron (oral, non-peptide, small molecule GLP-1 receptor agonist). MW: 883 Dalton.

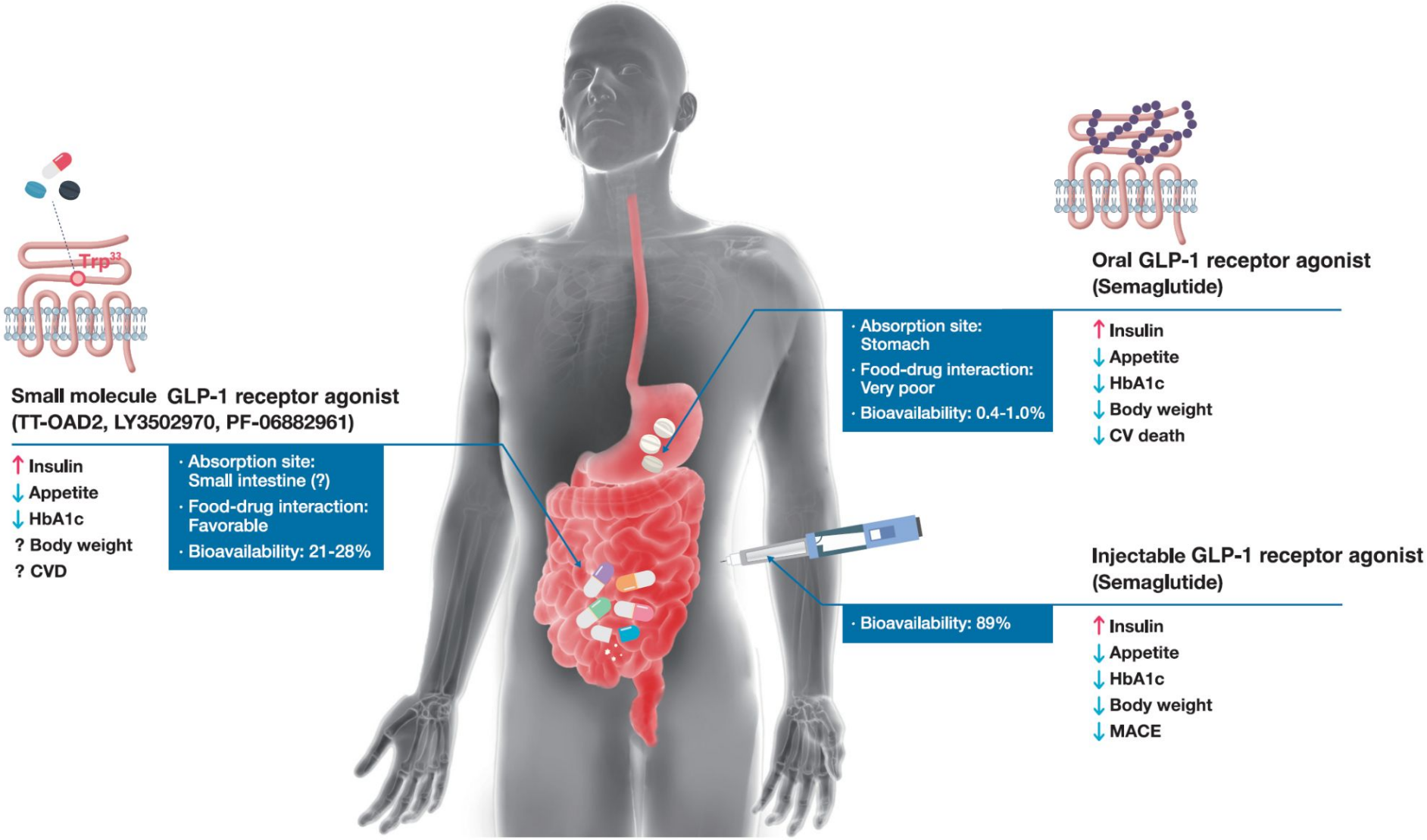


Semaglutide (peptide GLP-1 receptor agonist). MW: ~4000 Dalton (~4 kD)



Antibody (IgG2A, PDB 1igt). MW: ~150 kD

Comparing injectable semaglutide, oral semaglutide, and small-molecule GLP1R agonist



HbA1c: Hemoglobin A1c, hemoglobin chemically linked to a sugar. A HbA1c test shows your average level of blood glucose, i.e. blood sugar, over the past two to three months. HbA1c is there a *biomarker* of blood sugar.

CVD: Cardiovascular disease.

MACE: Major adverse cardiovascular event.

Choe, Hun Jee, and Young Min Cho. 2021. "Peptidyl and Non-Peptidyl Oral Glucagon-Like Peptide-1 Receptor Agonists." Endocrinology and Metabolism 36 (1): 22–29. https://doi.org/10.3803/EnM.2021.102.

Glucagon-like peptide 1 (GLP-1)

GLP-1 is a 30- or 31-amino acid long peptide. It derived from a protein encoded by the gene GCG in human.

Endogenous GLP-1 has a half-life of about 2 minutes, making the natural form a poor drug candidate due to its pharmacokinetic (PK) behaviour.

Synthesized agonists have similar sequences but much longer half-life due to chemical modifications. Examples include:

- Semaglutide (right top panels, approved)
- Taspoglutide (right middle panel, tested, not approved)

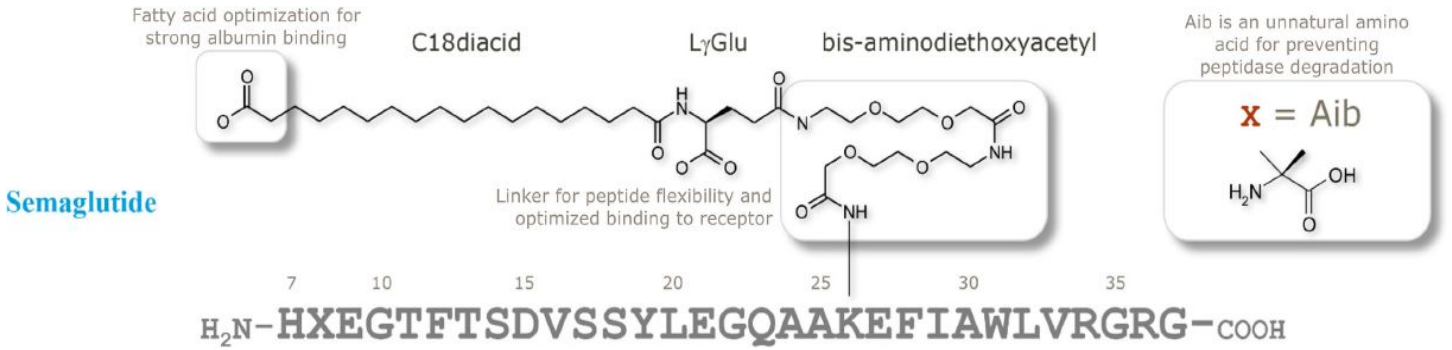


Figure from Knudsen *et al.*, 2019

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SEMAGLUTIDE     1 HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG  31
                  |||||||||||||||||||||||||||:|||
GLP-1           1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG  31

TASPOGLUTIDE    1 HXEGTFTSDVSSYLEGQAAKEFIAWLVKXR  30
                  |||||||||||||||||||||||||||| |
GLP-1           1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR  30
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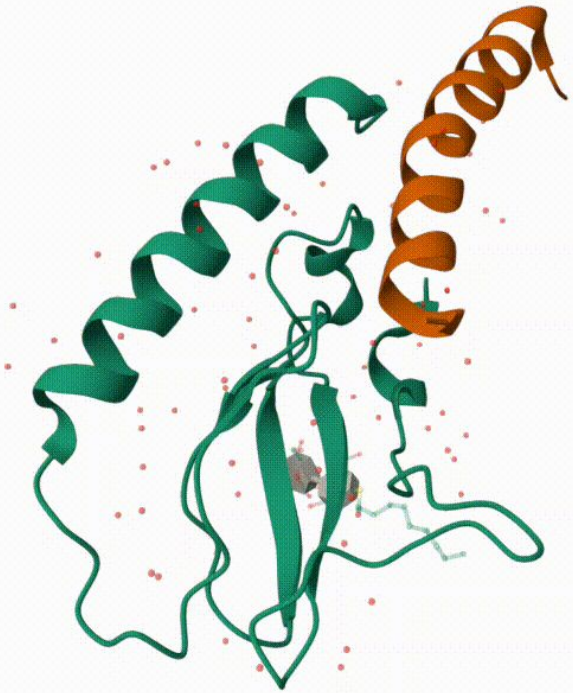
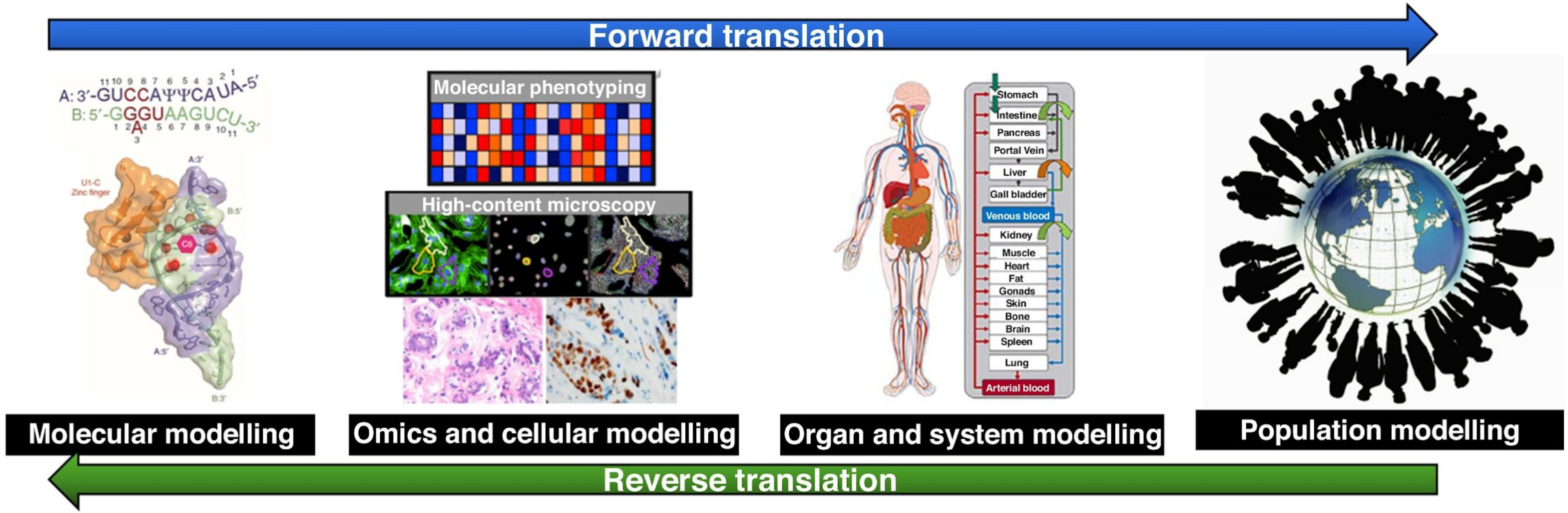
GLP1R, a receptor of GLP-1

GLP1R is a GPCR receptor found on beta cells of the pancreas and on neurons of the brain. It is involved in the regulation of blood sugar level by enhancing insulin secretion (*incretin signaling).*

Right: crystal structure of GLP-1 (orange) bound to a fragment of GLP-1R (green) (PDB: 3IOL)

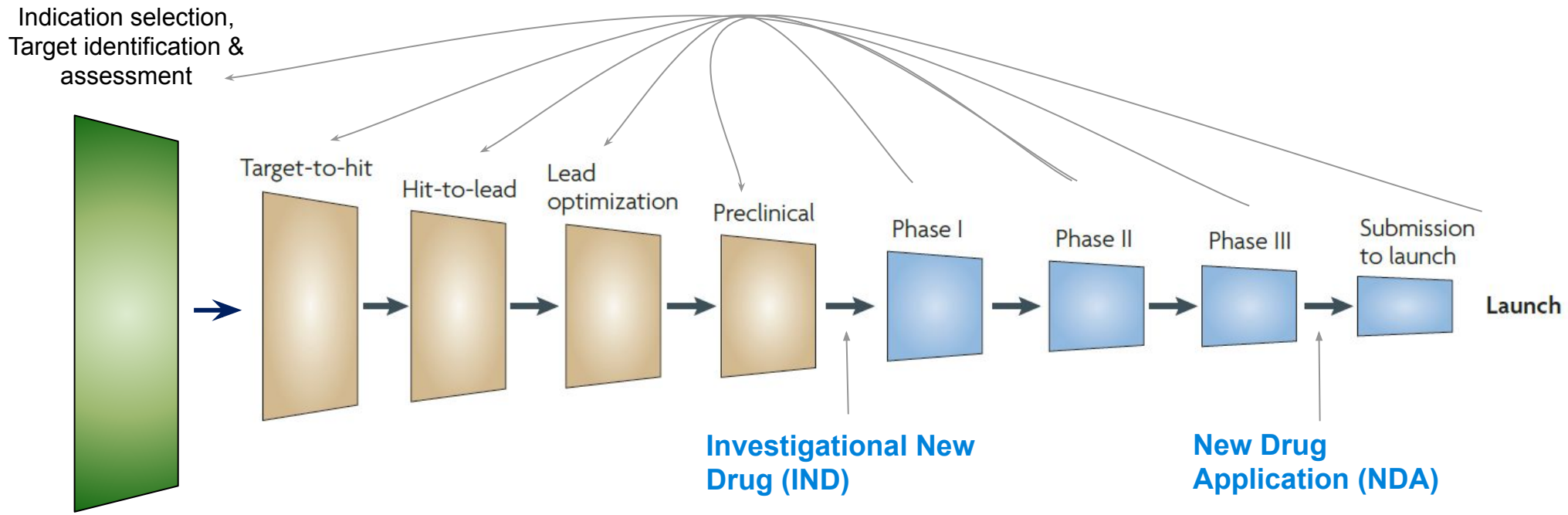


The multiscale modelling view of drug discovery



Zhang, Jitao David, Lisa Sach-Peltason, Christian Kramer, Ken Wang, and Martin Ebeling. 2020. “Multiscale Modelling of Drug Mechanism and Safety.” Drug Discovery Today 25 (3): 519–34. https://doi.org/10.1016/j.drudis.2019.12.009.

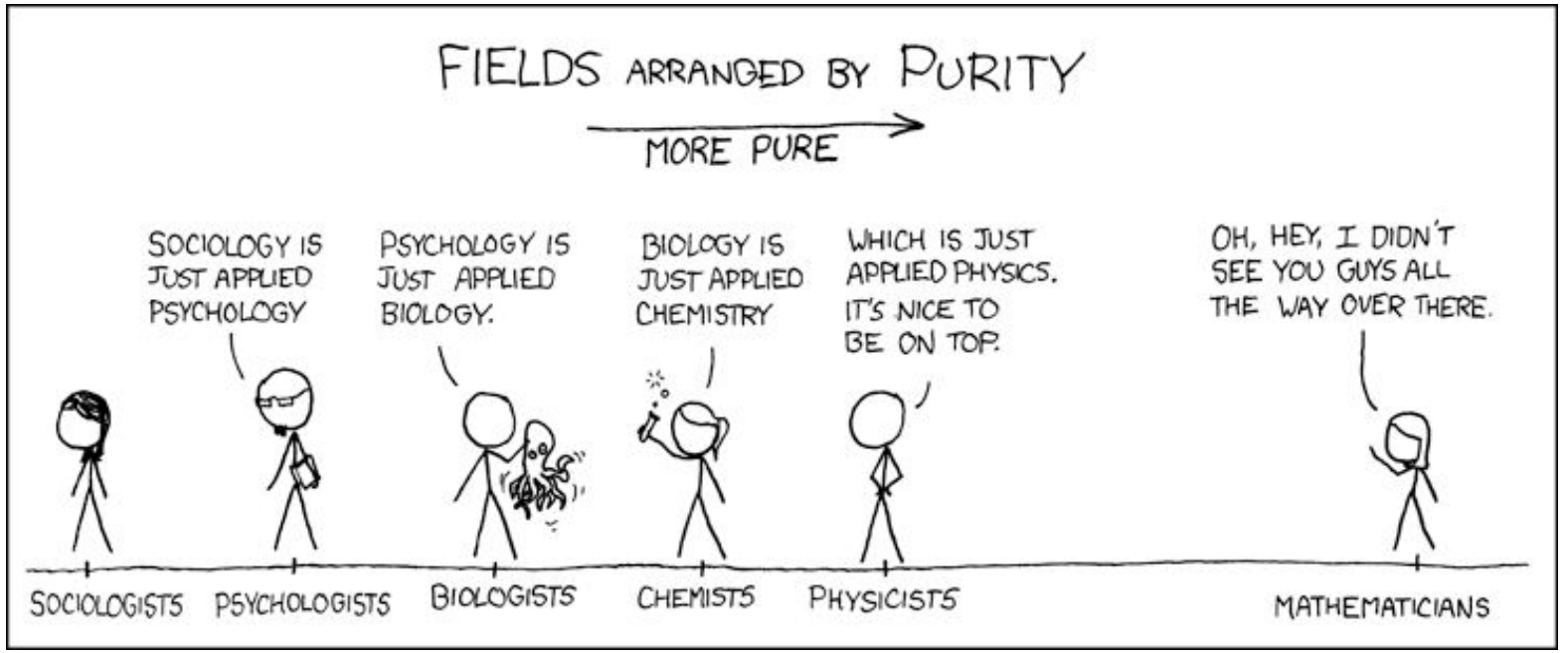
The linear view of drug discovery



Adapted from Paul *et al.* "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery, 2010

Purity

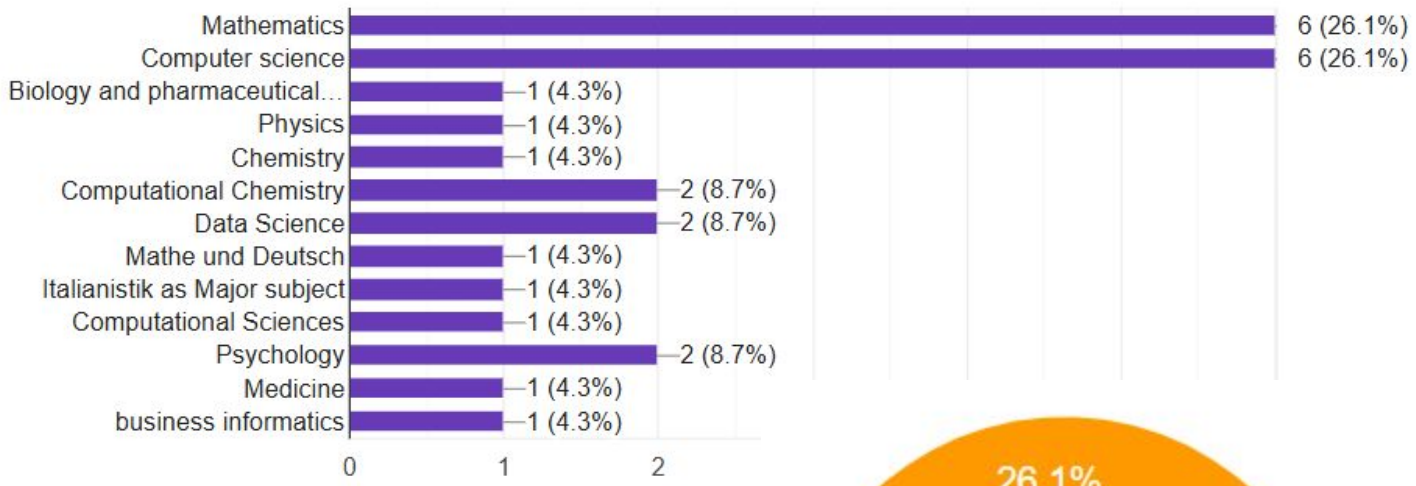
https://xkcd.com/435/



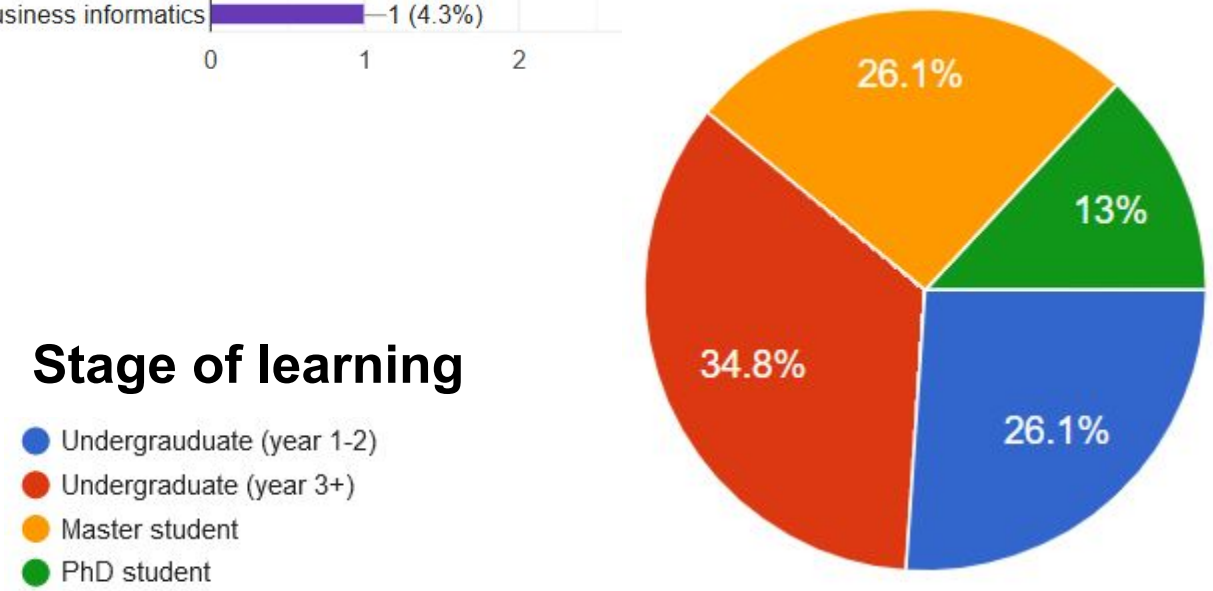
This course aims to bring people together and to promote interdisciplinary research

Our strength: we have a diverse classroom!

Background



Stage of learning



Selected motivations and expectations

- Better understanding in general
- Learn more about other disciplines
- Interested in maths and biology
- how applied mathematics and computational tools drive innovation in drug discovery
- To broaden my knowledge in usage of math and ML in description of living systems, particularly in drug design
- Mandatory for me as Mathematician
- Was a year in Pharma and want to combine it a little with Maths now
- I took the MCBDD course in fall and liked it.
- Do something more practical than just theoretical mathematics
- Pure curiosity

Course information for AMIDD 2025

- Lecturer: Jitao David Zhang (jitao-david.zhang@unibas.ch)
- Website: AMIDD.ch
- Thirteen lectures this semester
  - Introduction (1 session)
  - Mechanistic, statistical, and causal models (2 sessions)
  - Molecular level modelling (2 sessions)
  - Omics- & cellular models (2 sessions)
  - Organ- and system models (2 sessions)
  - Population modelling (2 sessions)
  - Invited guest speakers (1 session)
  - A collaboration challenge (1 session)

- Fridays 12:15-14:00
- Slides, exercises, pre-reading and post-reading articles are shared on the course's website http://www.amidd.ch. We do not provide recordings.
- The final note is given by participation including quizzes (30%), offline activities (40%), and a collaboration challenge in the final session (30%). The topic of collaboration challenge will be announced in the second to last session.
- **Questions**?

I look forward to sharing my experience in drug discovery and learning from you!

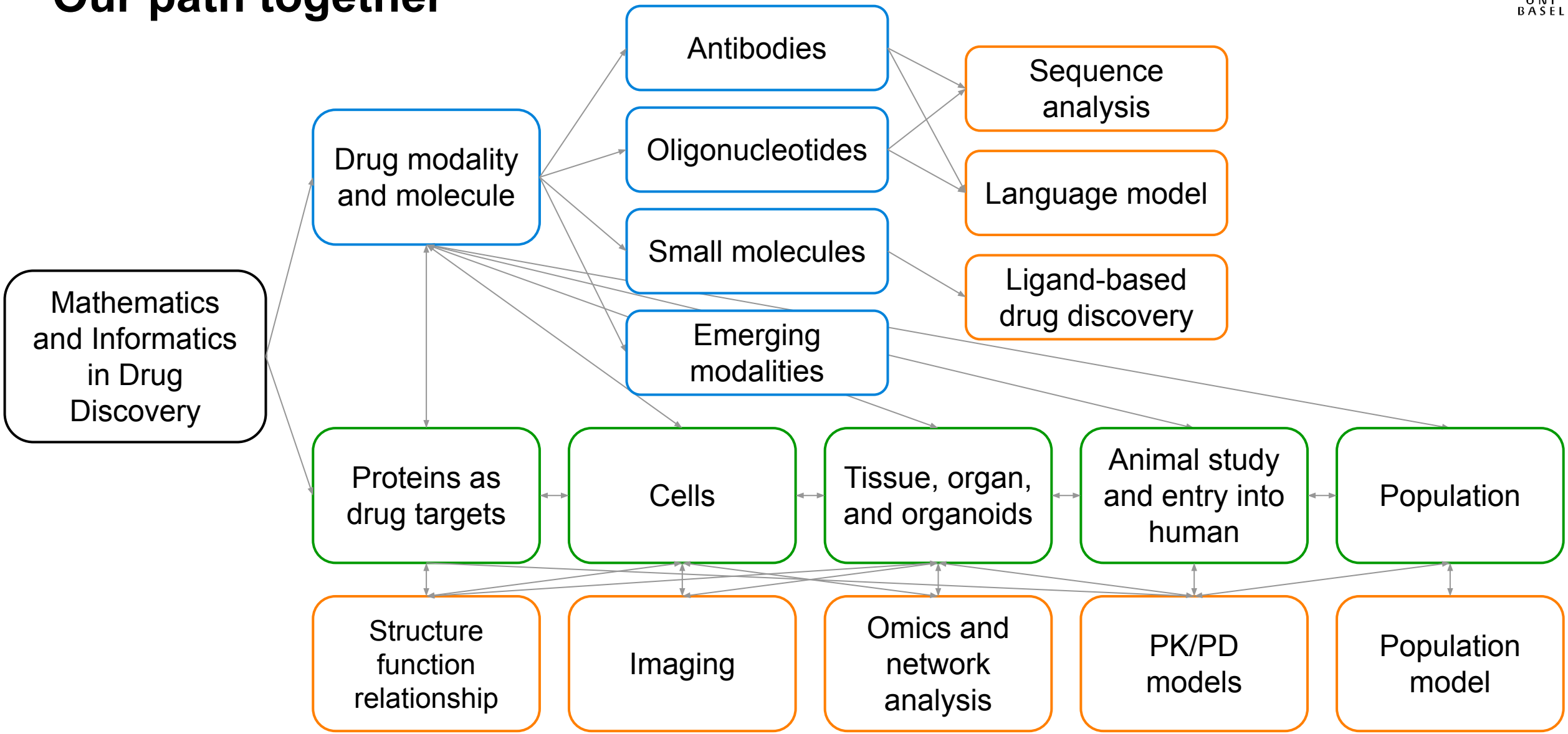
Disclaimer

Teaching is my personal engagement. My opinions and views do not necessarily reflect those by F. Hoffmann-La Roche, my employer.

Please be aware of my biases and limitations.

- I am a computational biologist working in drug discovery, with limited understanding of mathematics, computer science, biology, chemistry, pharmacology, toxicology, and medicine.
- I see my task is to share with you the mathematical concepts and computational approaches used in drug discovery that I find beautiful and useful.
- I look forward to learning from you mathematics and other expertise that I did not know.

Our path together



How does GLP1R agonists affect cells and organs?

Offline activity:

1. Watch the video made by Harvard Medical School Continuing Education (https://www.youtube.com/watch?v=P6gt4A_3Whs).
2. What other possibilities do we have to control weight and improve health? What are the pros and cons compared with pharmaceutical inventions? What would *you* do?

Contact the author