Applied Mathematics and Informatics In Drug Discovery (2024)

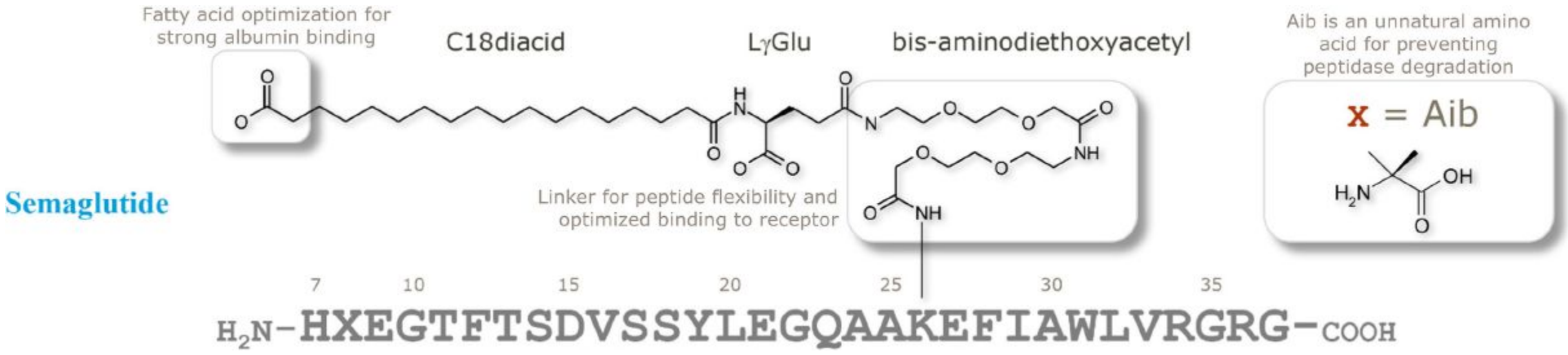

Figure from Knudsen *et al.*, 2019

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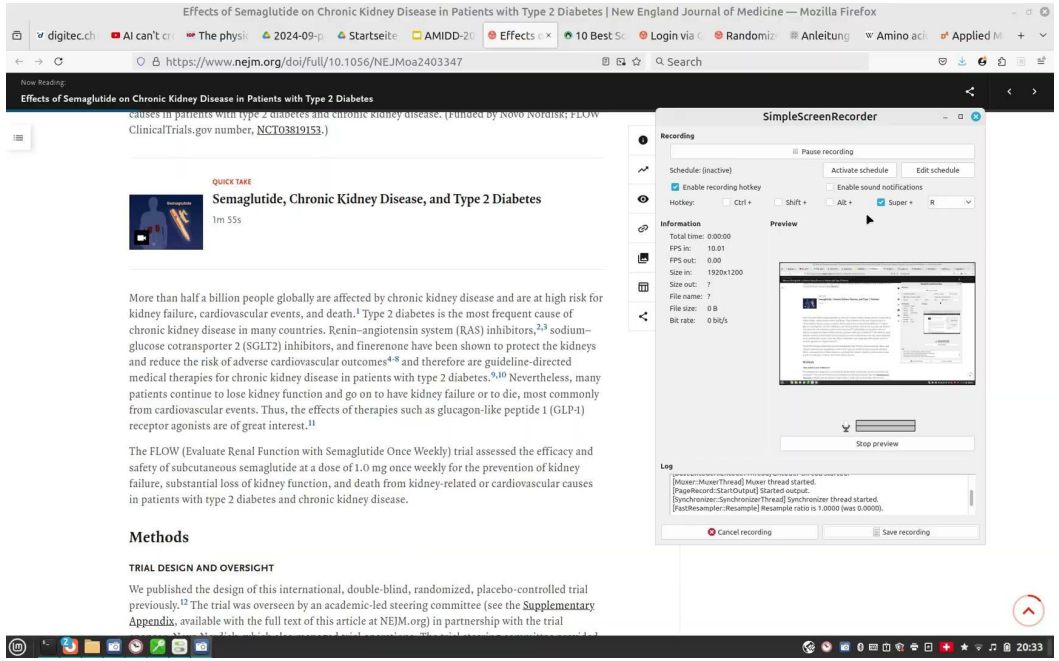
Outline

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

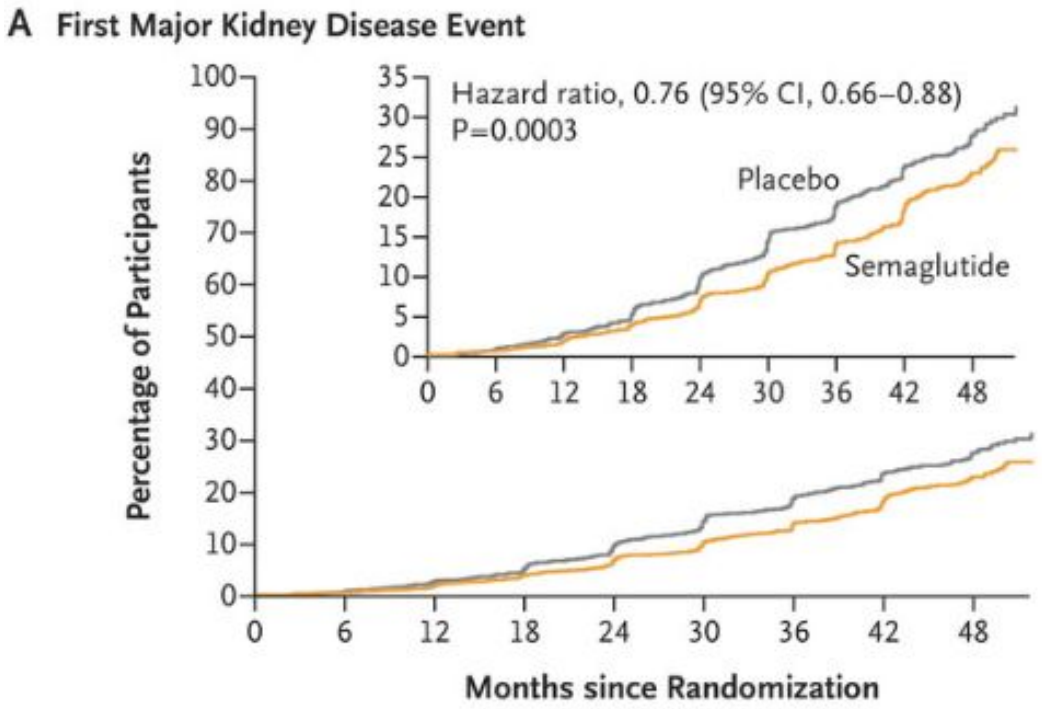
FLOW: a Phase 3 clinical trial for Semaglutide 1.0 mg once a week for people with type 2 diabetes and chronic kidney disease

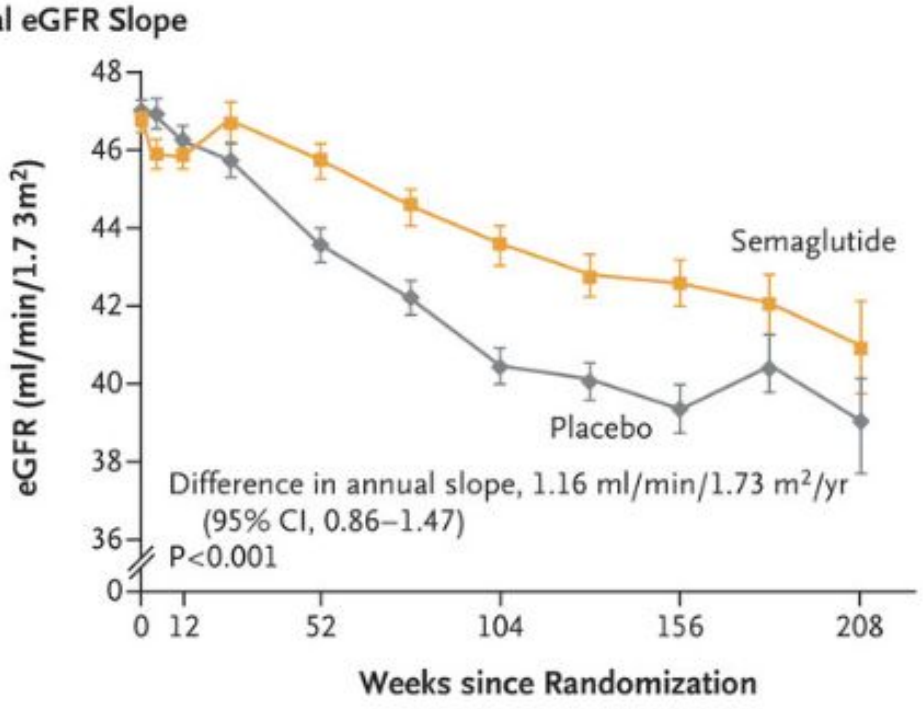


Q1: What is semaglutide?
Q2: What are the proven benefits of semaglutide for patients with Type II diabetes?
Q3: Why was the clinical trial conducted?
Q4: How many patients participated in the trial?
Q5: What was the primary outcome of the trial?
Q6: How many patients experienced serious adverse effects?
Q7: What was the conclusion of the authors?

Perkovic, V. et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. New England Journal of Medicine 391, 109–121 (2024). ClinicalTrials.gov: NCT03819153

The primary outcome (major kidney disease events) and one confirmatory secondary outcome (reduction of the estimated glomerular filtration rate, or eGFR) of the FLOW trial

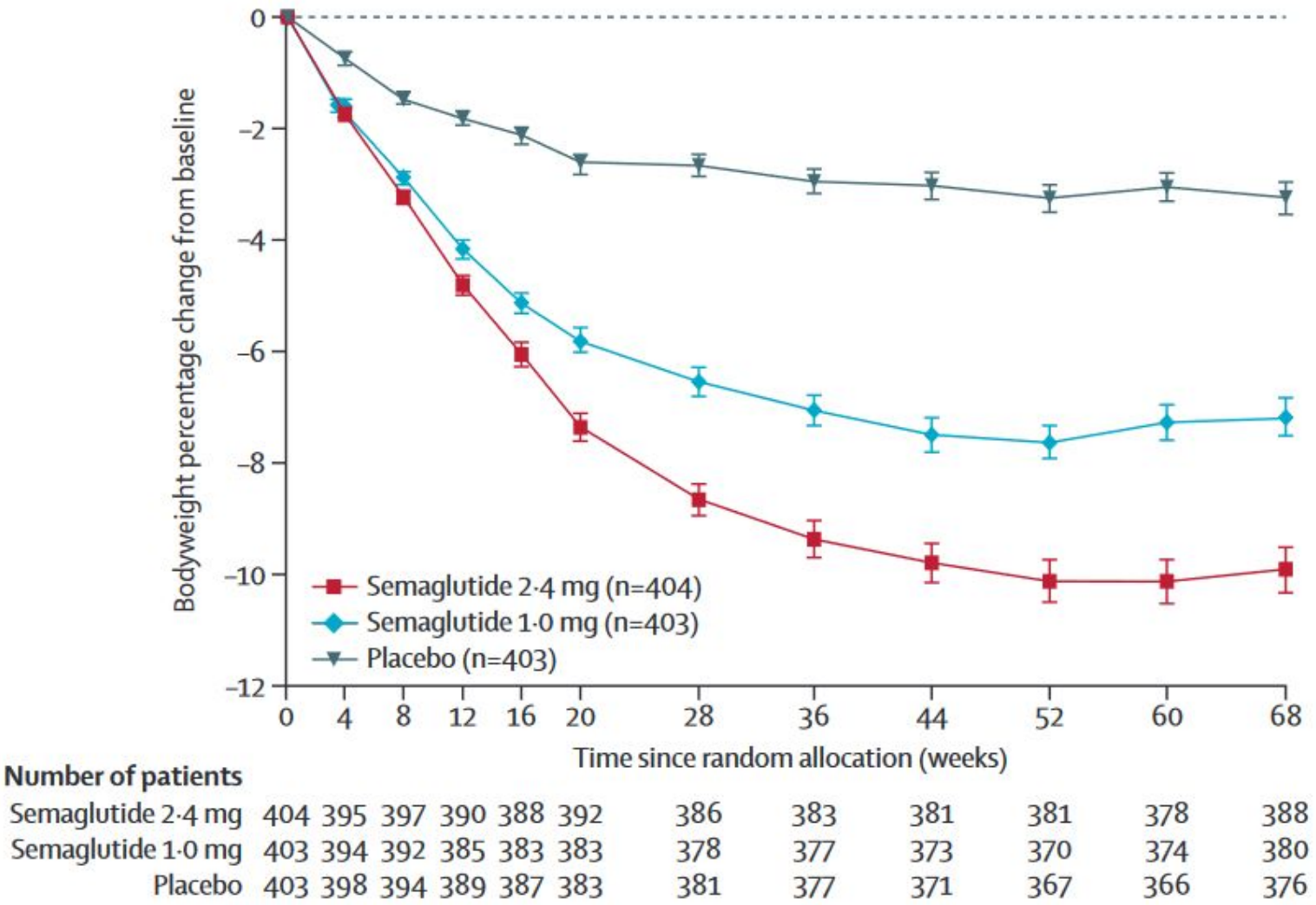




Safety outcome (partially shown)

Adverse Event	Semaglutide (N=1767)	Placebo (N=1766)
	no. of participants (%)	
Serious adverse event	877 (49.6)	950 (53.8)
Adverse event leading to permanent discontinuation of semaglutide or placebo	233 (13.2)	211 (11.9)
Prespecified adverse events of special interest		
Diabetic retinopathy*	402 (22.8)	398 (22.5)
Covid-19–related disorder	358 (20.3)	404 (22.9)
Serious adverse event: cardiovascular disorder	273 (15.4)	319 (18.1)
Heart failure*	133 (7.5)	175 (9.9)
Acute kidney failure*	172 (9.7)	182 (10.3)
Malignant tumor*	120 (6.8)	104 (5.9)

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

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)

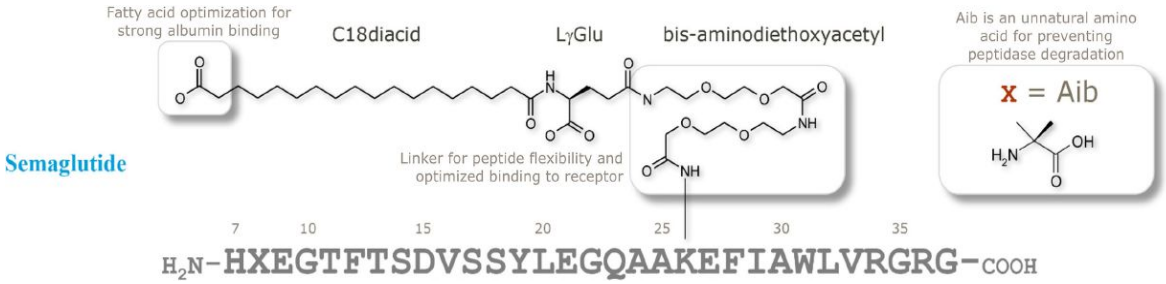


Figure from Knudsen *et al.*, 2019

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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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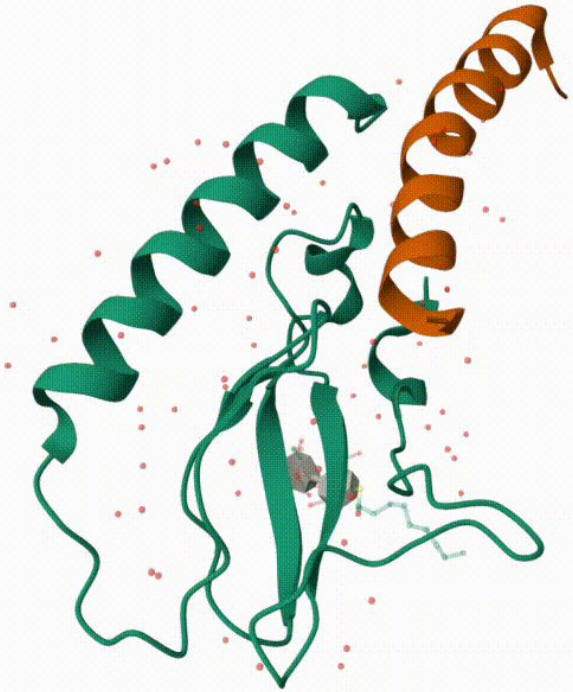
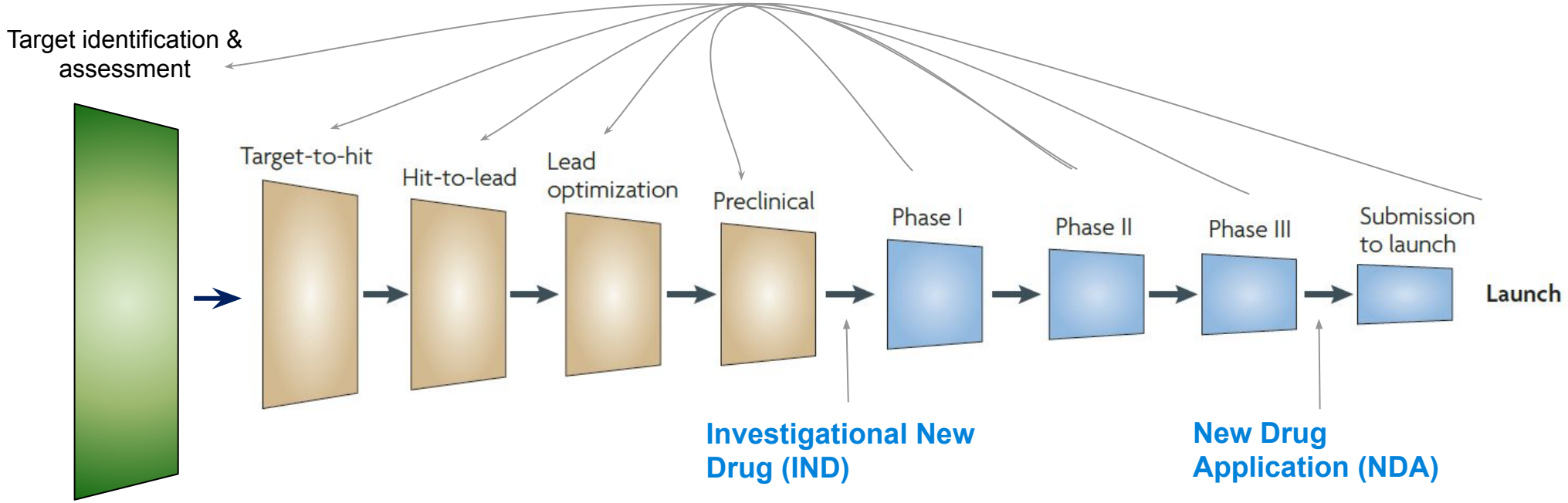
GLP1R, a receptor of GLP-1

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



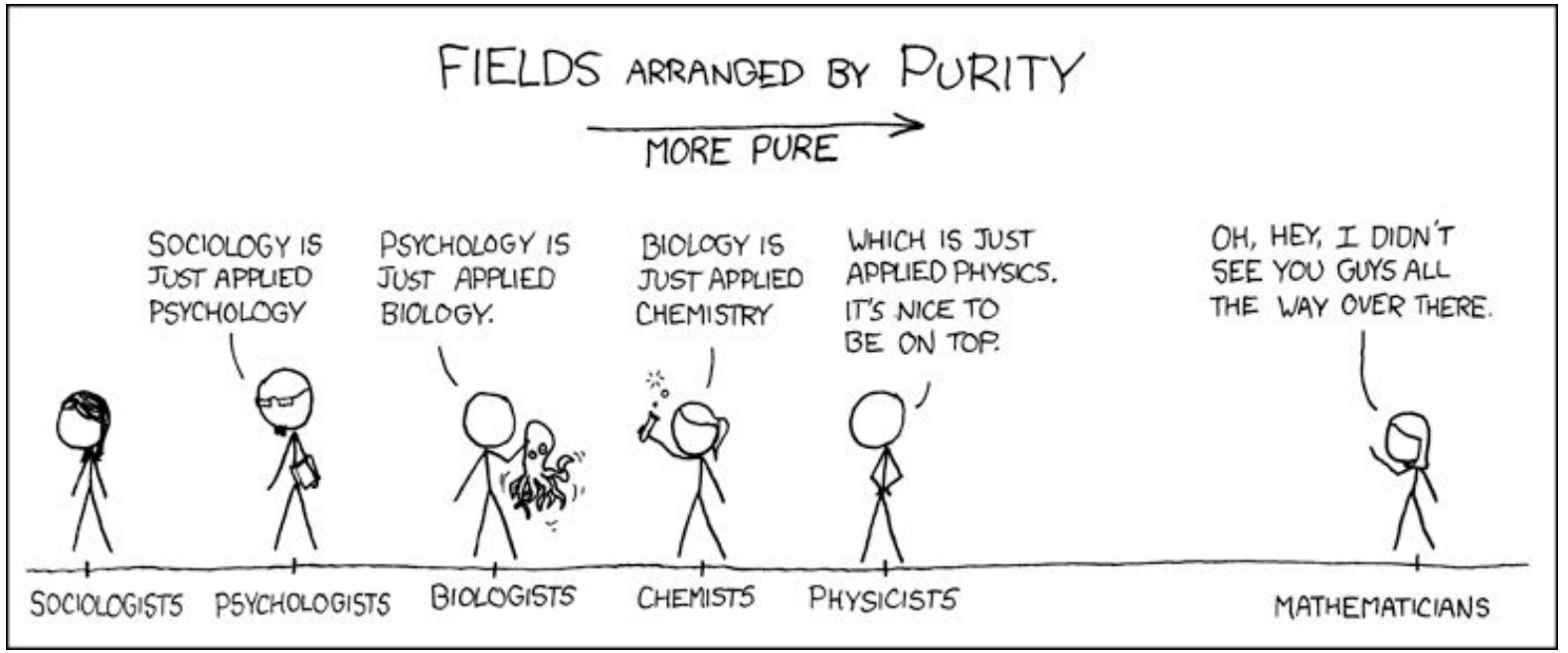
The linear view of drug discovery



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

Purity

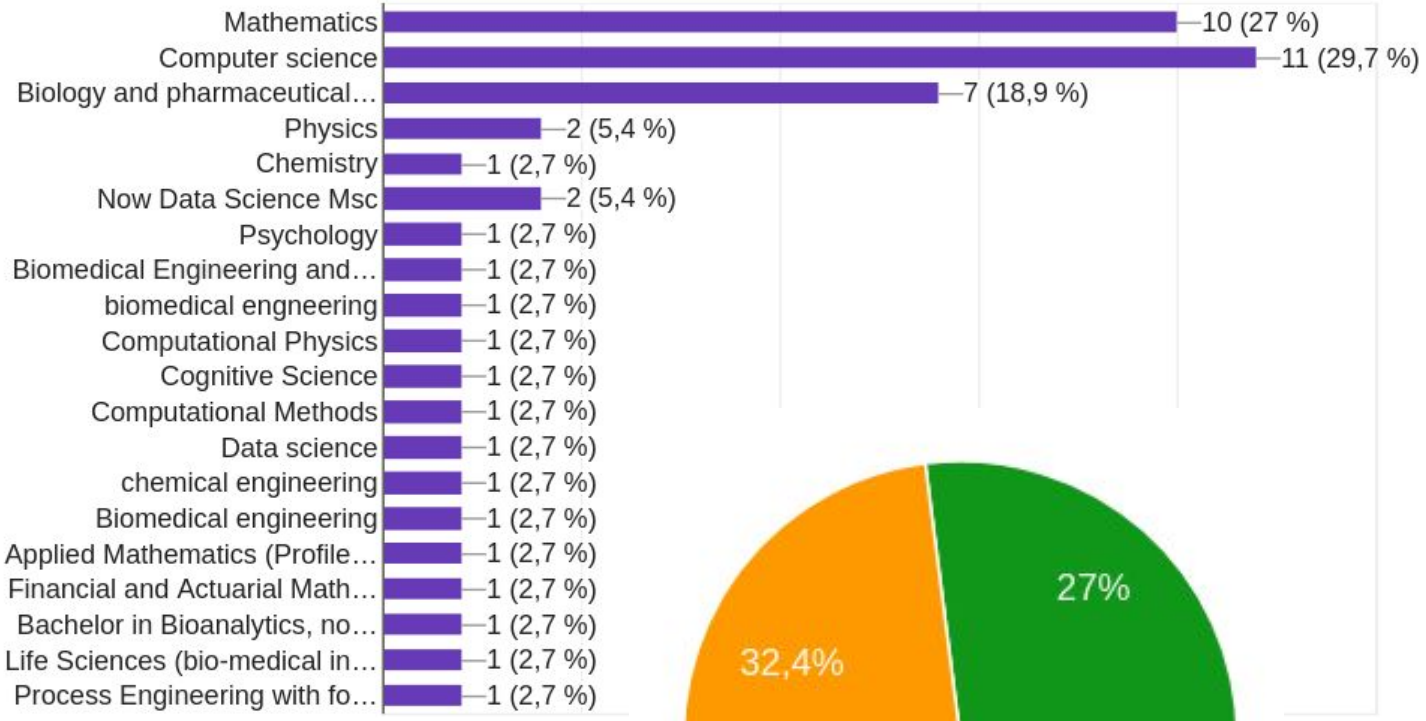
https://xkcd.com/435/



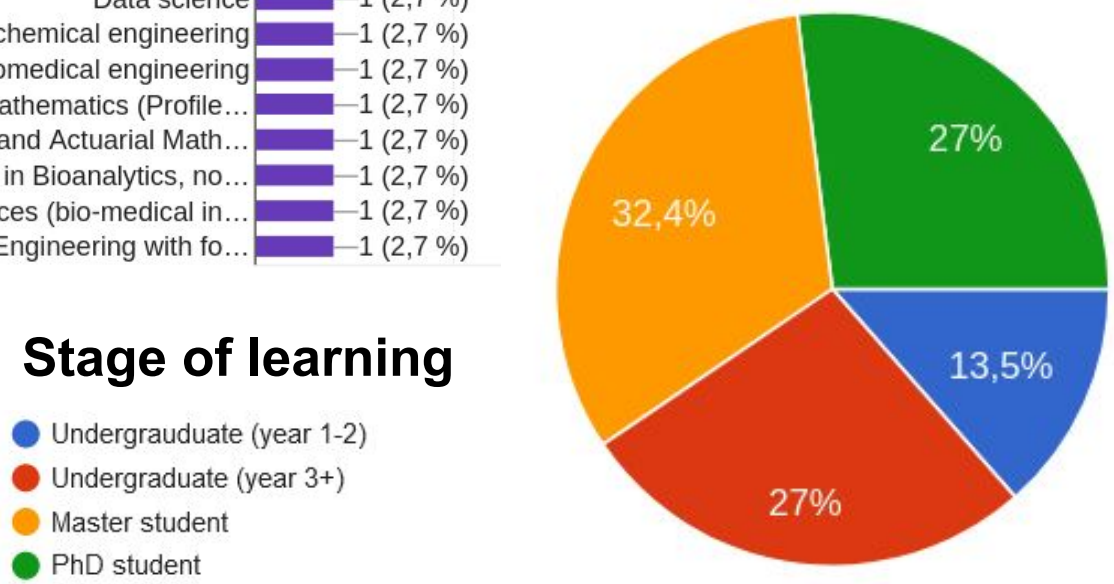
This course aims to bring people together and to promote interdisciplinary research

Our strength: we have a diverse classroom!

Background



Stage of learning



Selected Motivations

- How mathematics can be applied to different research fields.
- I would like to shape my career towards drug discovery
- As biologist, most of the time I work with a trial-and-error approach. I am curious to get to know how mathematics and informatics can guide a more informed approach to drug discovery/design.
- Interesting and different course that gives credits
- State of the art, prevalence in industry
- To learn something new
- learn about advanced computational methods AND their application

Course information for AMIDD 2024

- 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. Unfortunately 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 last session.
- **Questions**?

I am glad to share my experience in drug discovery, and to learn from you!

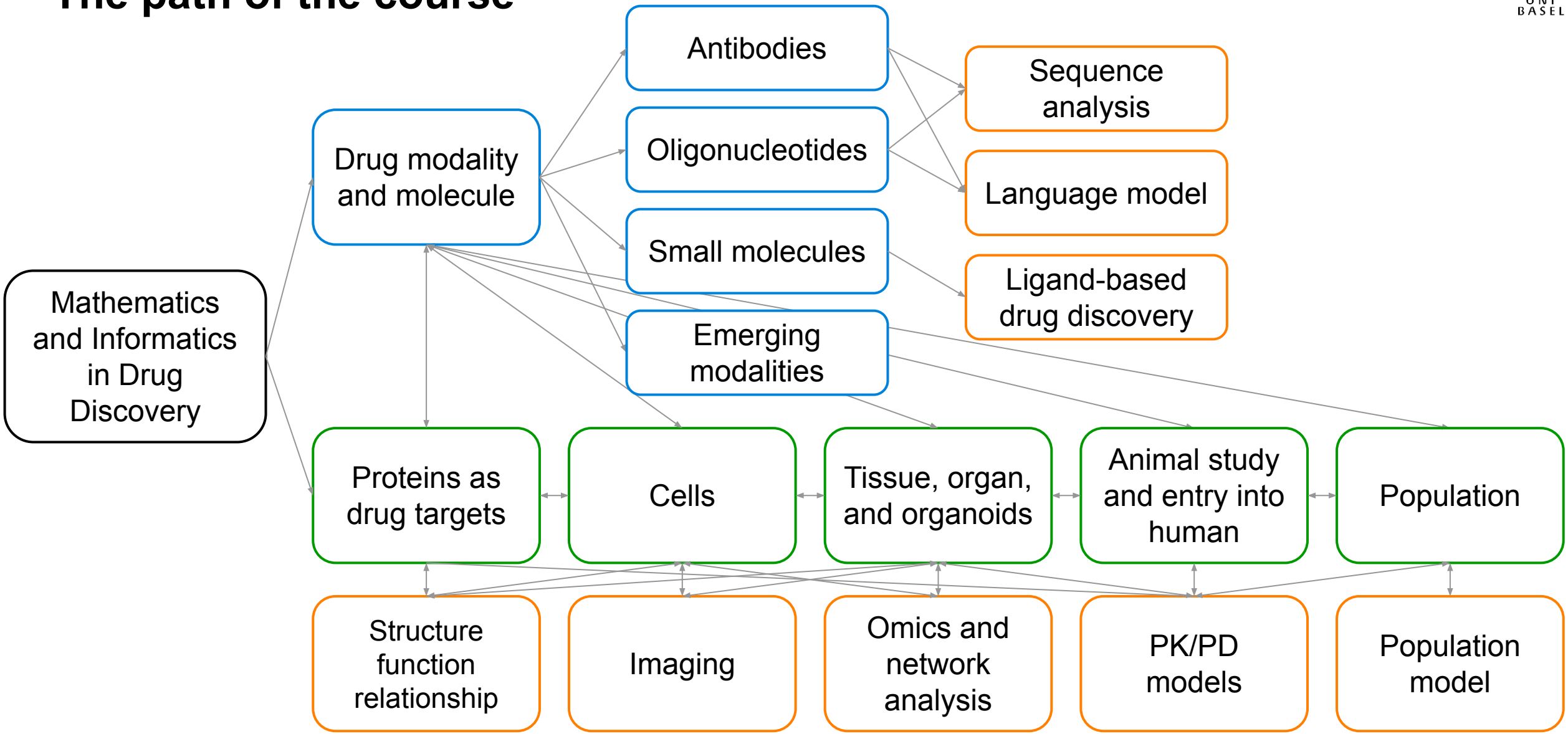
Disclaimer

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.

The path of the course



Contact the author