

Applied Mathematics and Informatics In Drug Discovery (2024)

Semaglutide

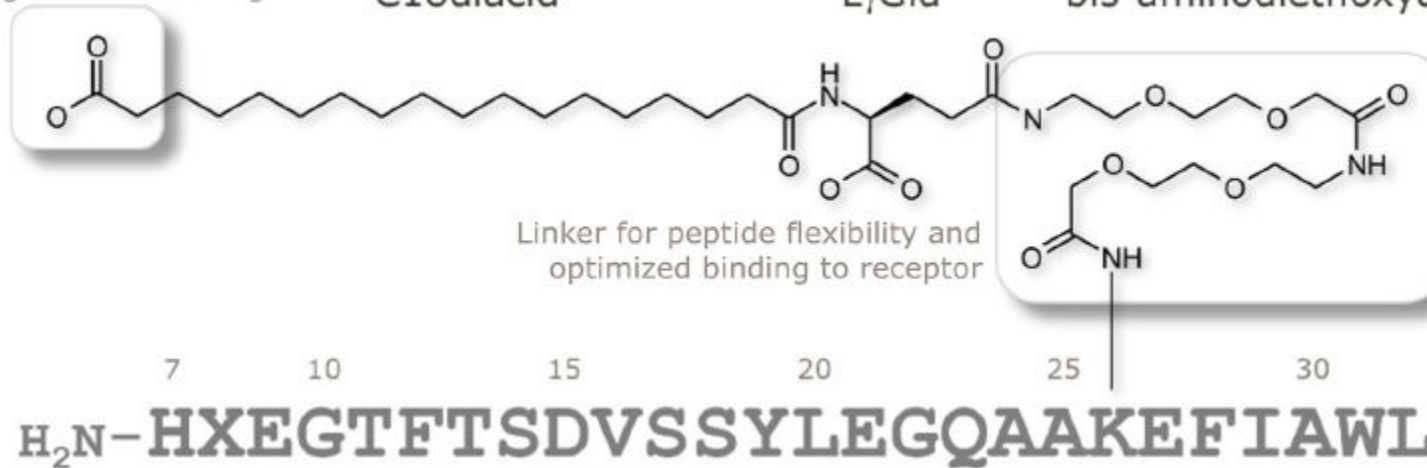
Fatty acid optimization for strong albumin binding

C18diacid

L γ Glu

bis-aminodiethoxyacetyl

Aib is an unnatural amino acid for preventing peptidase degradation



X = Aib

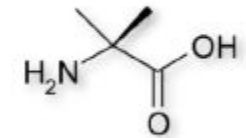


Figure from [Knudsen et al., 2019](#)

Dr. Jitao David Zhang, Computational Biologist

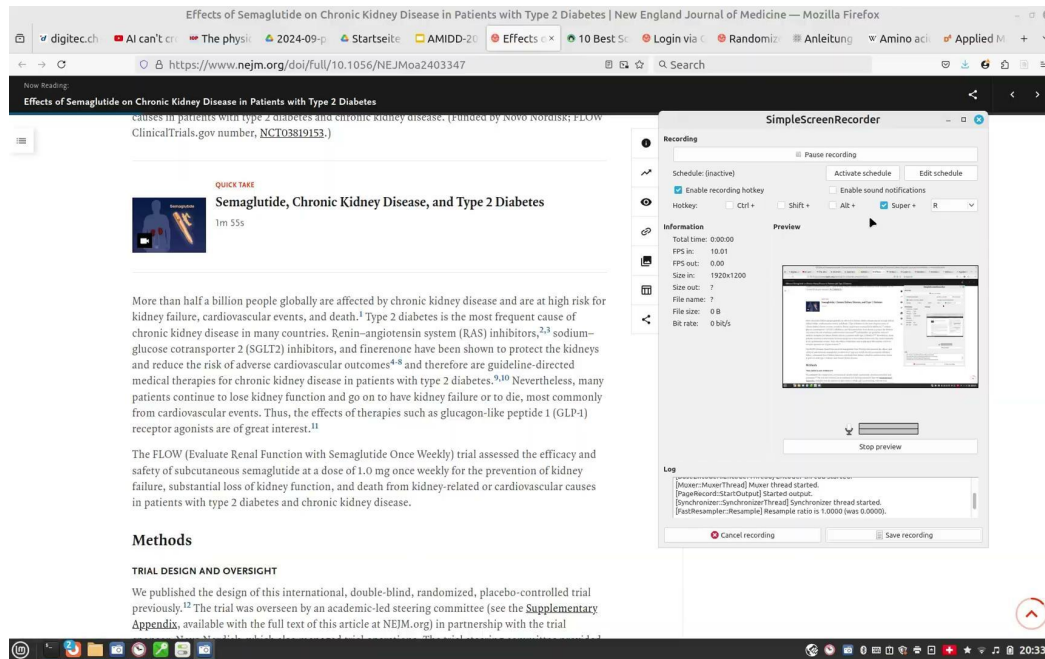
¹ Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche;

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

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?

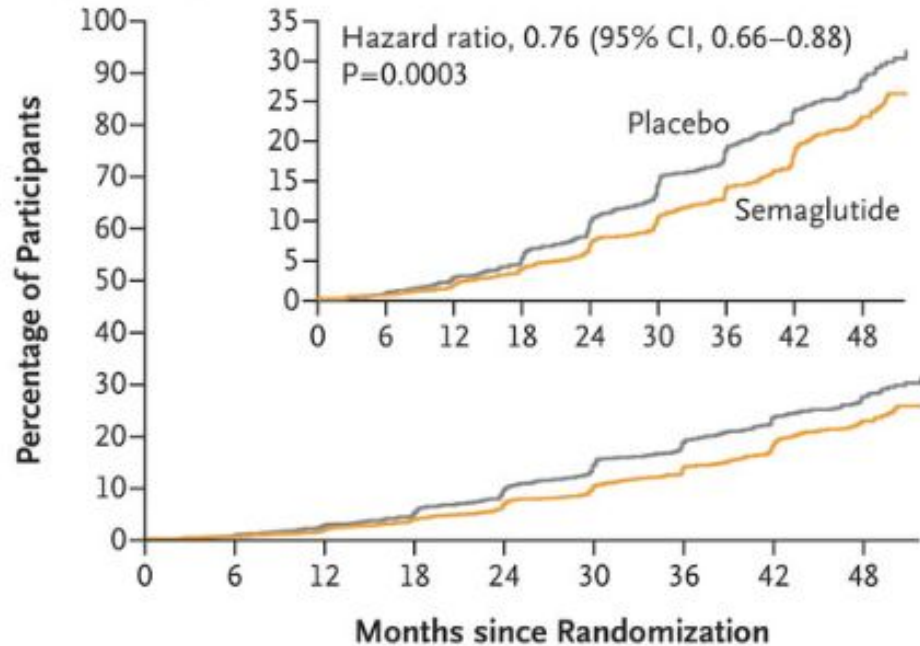
Q6: How many patients experienced serious adverse effects?

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

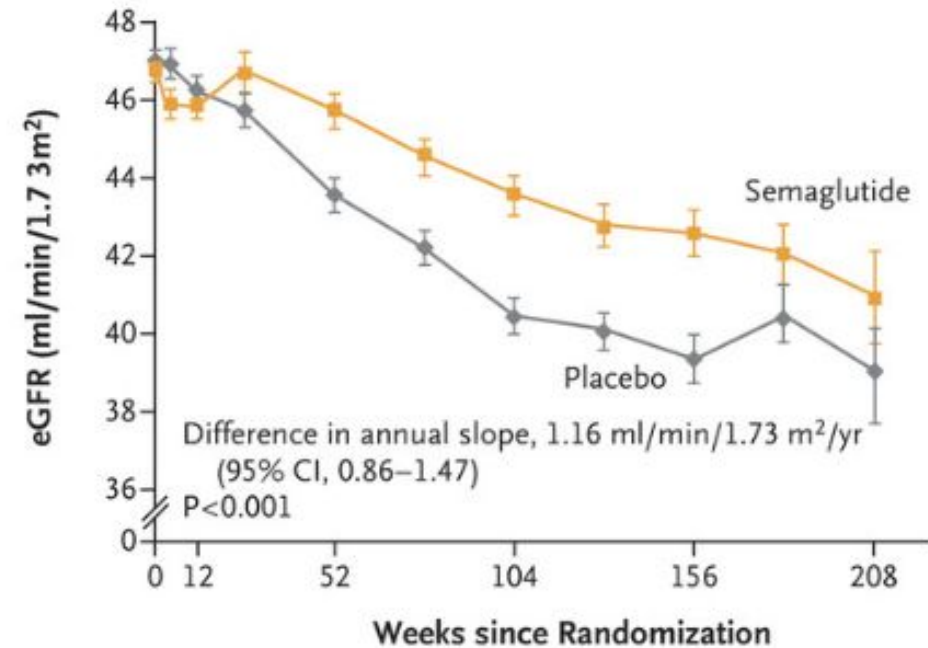
A First Major Kidney Disease Event



No. at Risk

Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

D Total eGFR Slope



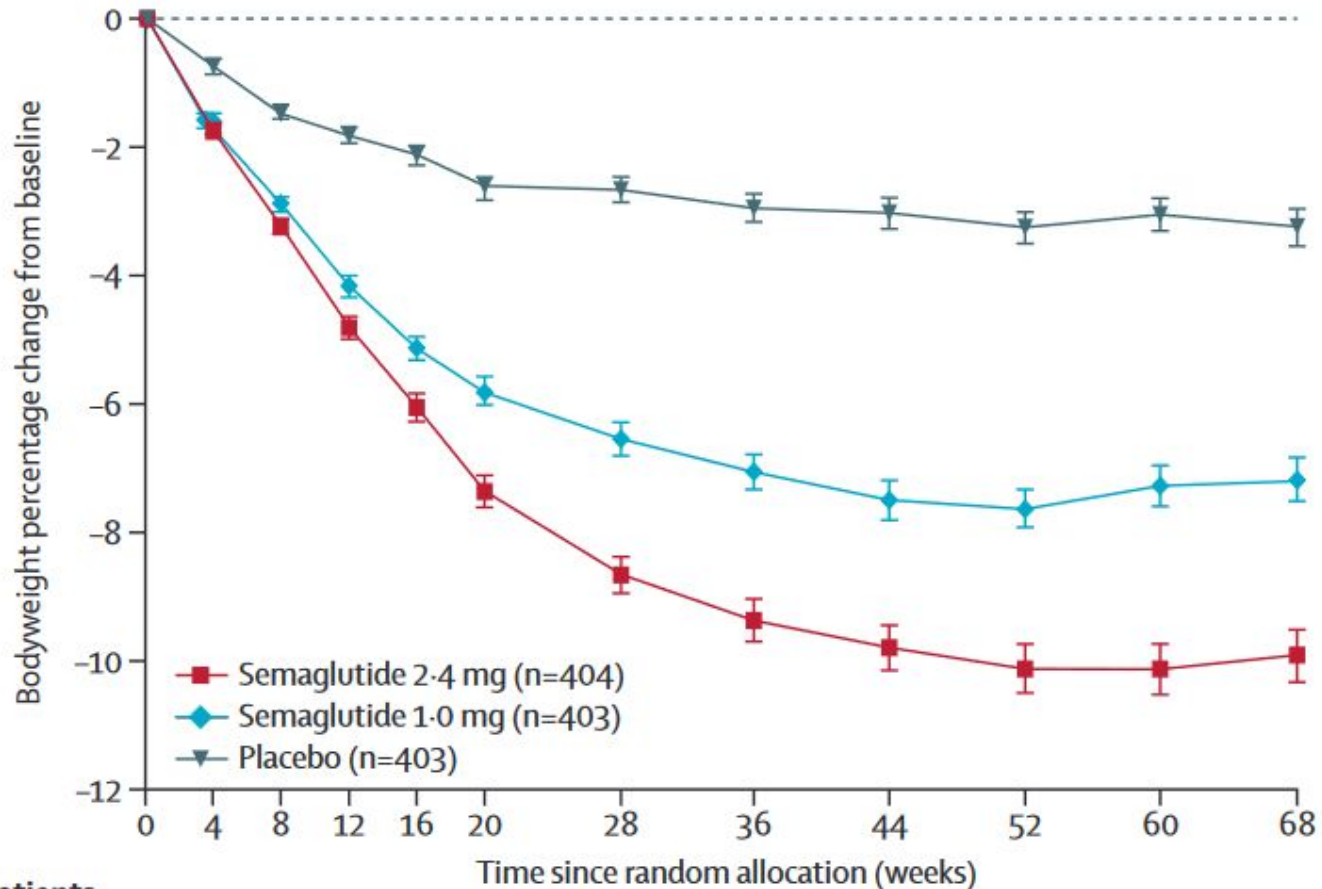
No. at Risk

Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

Safety outcome (partially shown)

Adverse Event	Semaglutide (N=1767)	Placebo (N=1766)
	<i>no. of participants (%)</i>	
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

Number of patients

Semaglutide 2.4 mg	404	395	397	390	388	392	386	383	381	381	378	388
Semaglutide 1.0 mg	403	394	392	385	383	383	378	377	373	370	374	380
Placebo	403	398	394	389	387	383	381	377	371	367	366	376

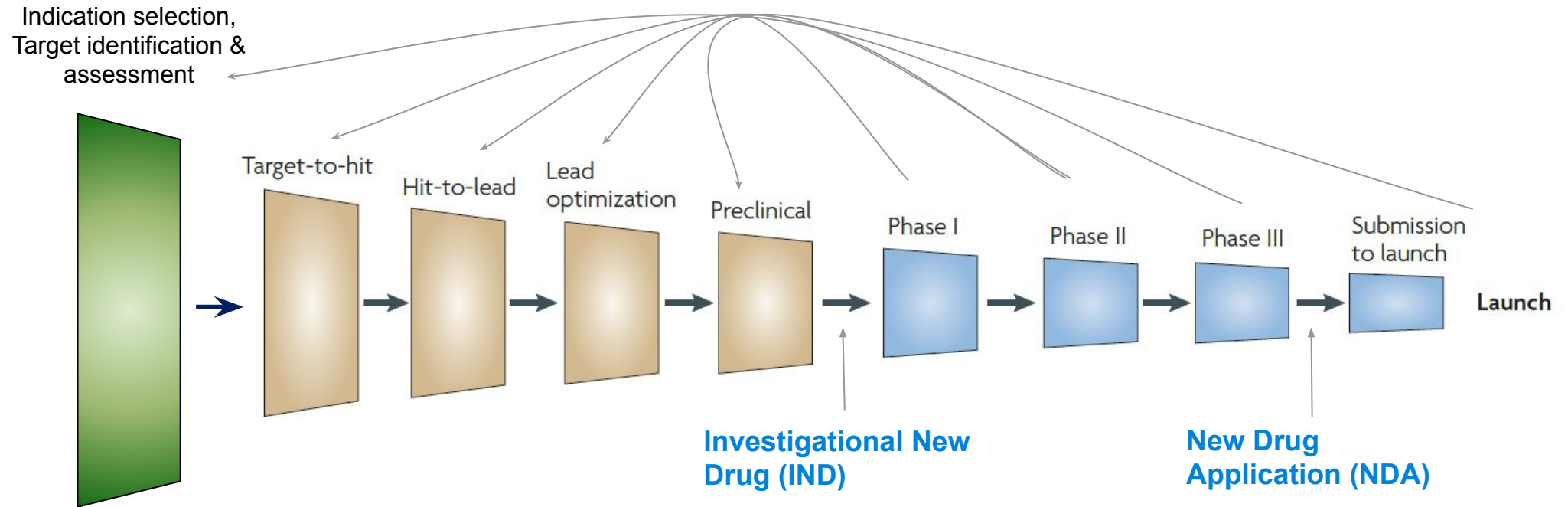
GLP1R, a receptor of GLP-1

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](https://www.rcsb.org/structure/3IOL))



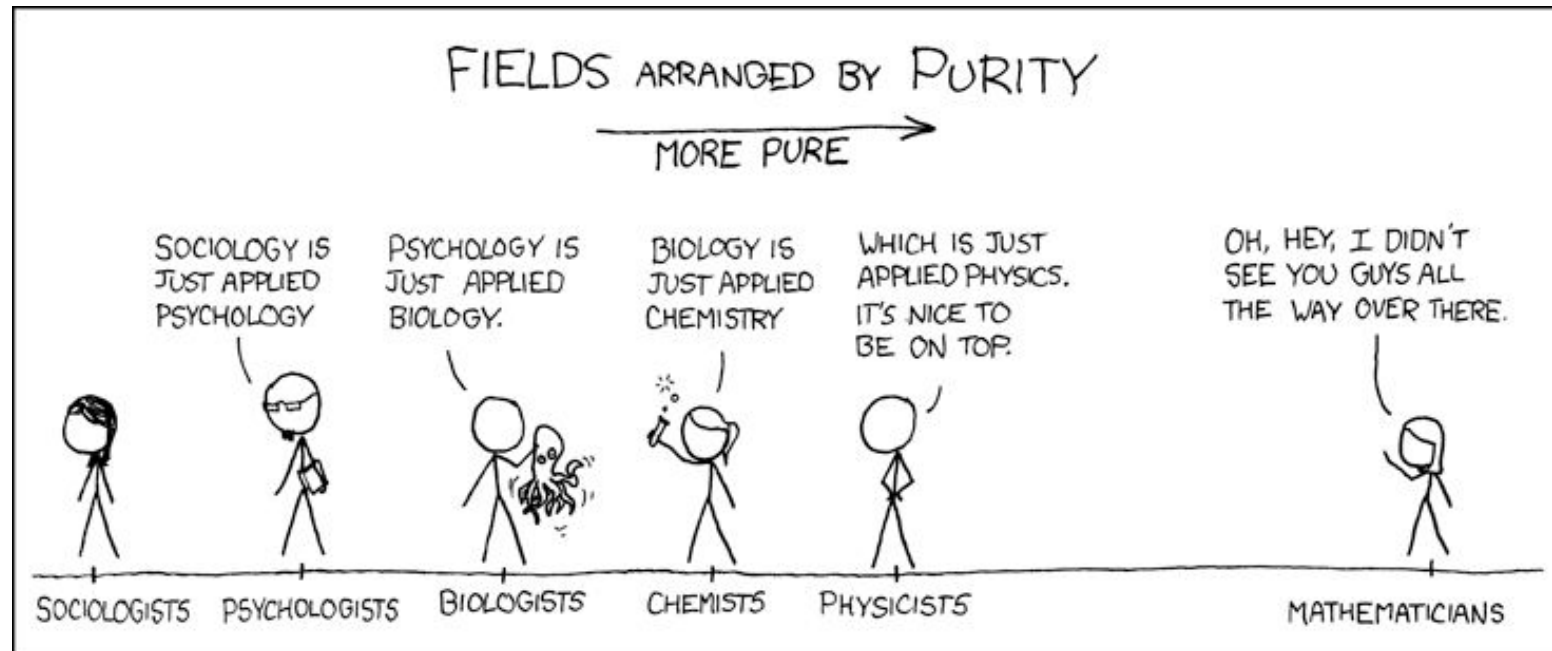
The linear view of drug discovery



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

Purity

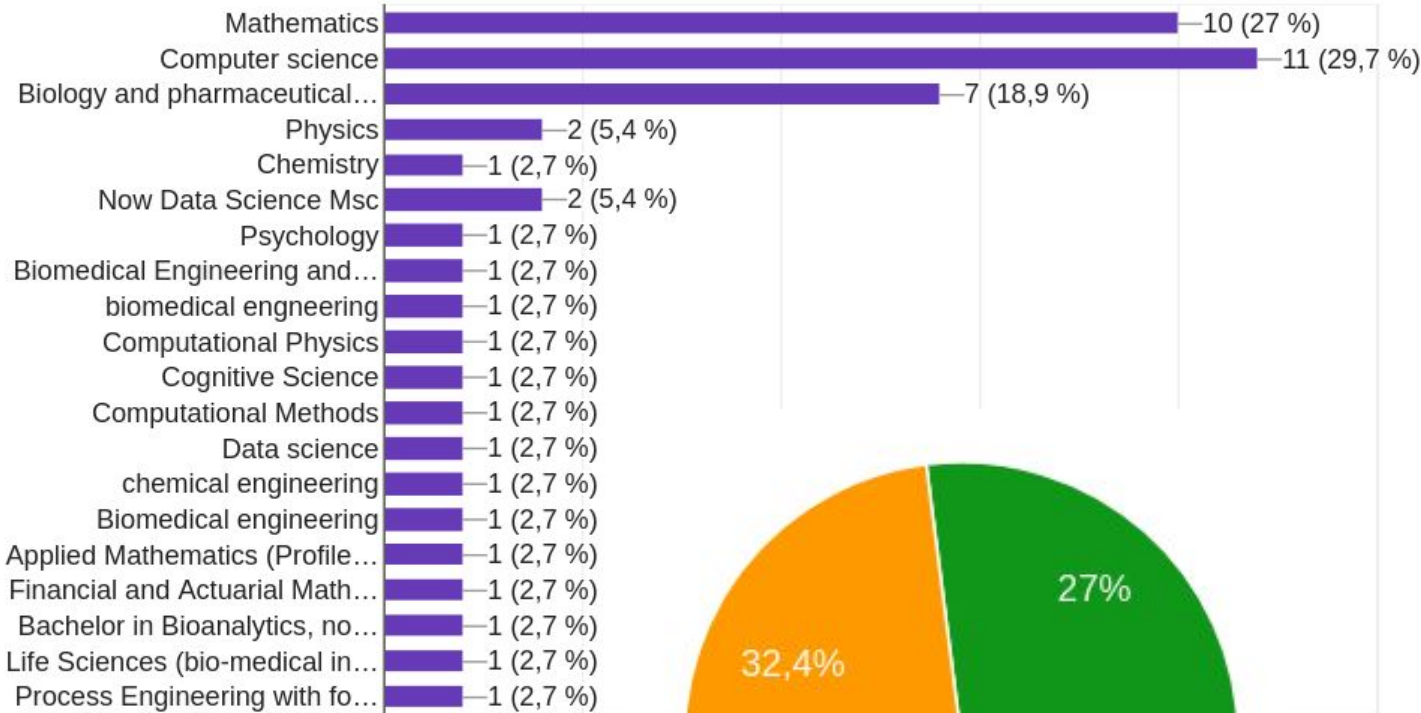
<https://xkcd.com/435/>



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

Our strength: we have a diverse classroom!

Background

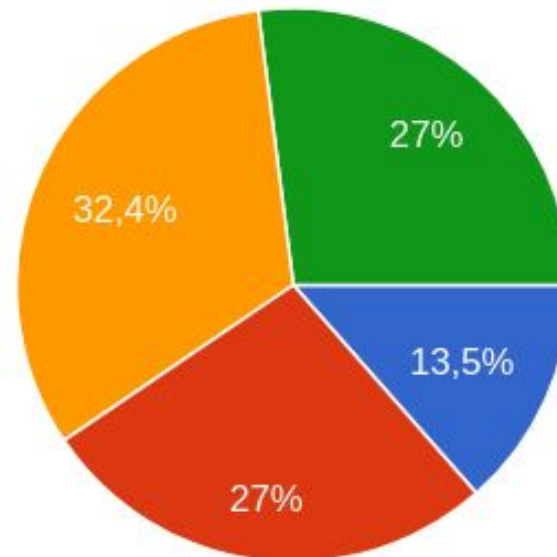


Selected Motivations

- 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

Stage of learning

- Undergraduate (year 1-2)
- Undergraduate (year 3+)
- Master student
- PhD student



Course information for AMIDD 2024

- Lecturer: Jitao David Zhang
(jitao-david.zhang@unibas.ch)
- Website: [AMIDD.ch](http://www.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!

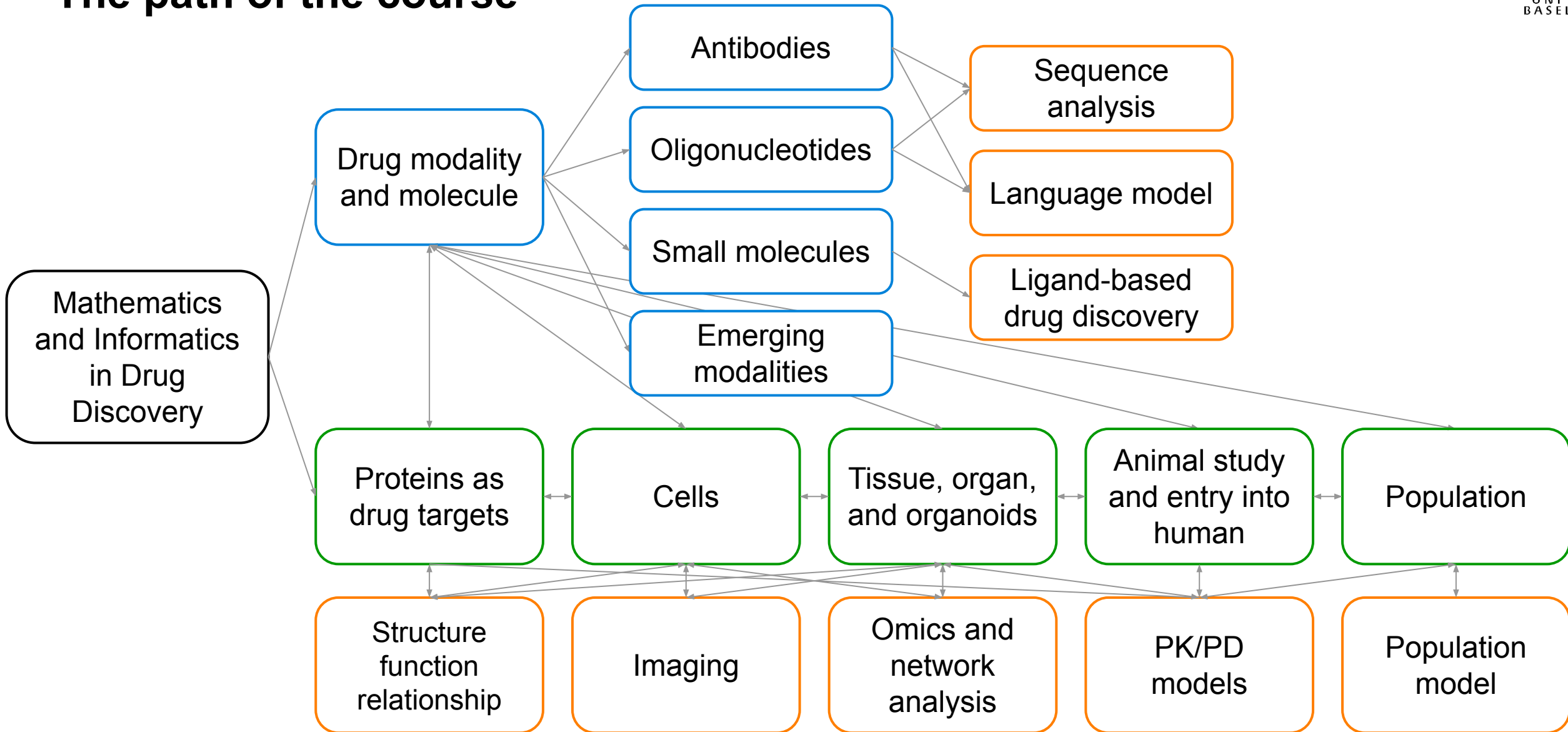
Disclaimer

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



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