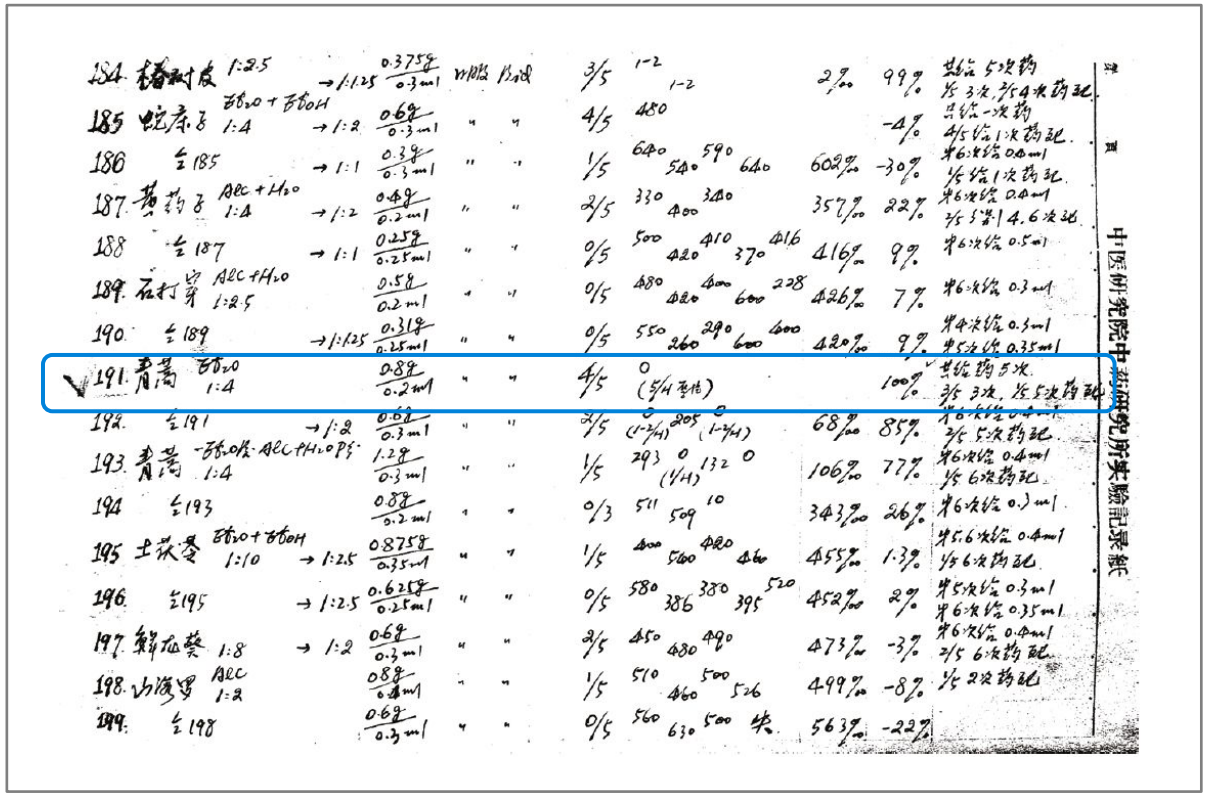
Applied Mathematics and Informatics In Drug Discovery (2020)



Copy of the original laboratory notebook record, showing 100% inhibition of malaria parasites by the Qinghao neutral extract when tested on a rodent malaria model (in blux box, edited by J.D.Z.).

Artemisinin — A Gift from Traditional Chinese Medicine to the World, Youyou Tu, Nobel Lecture 2015.

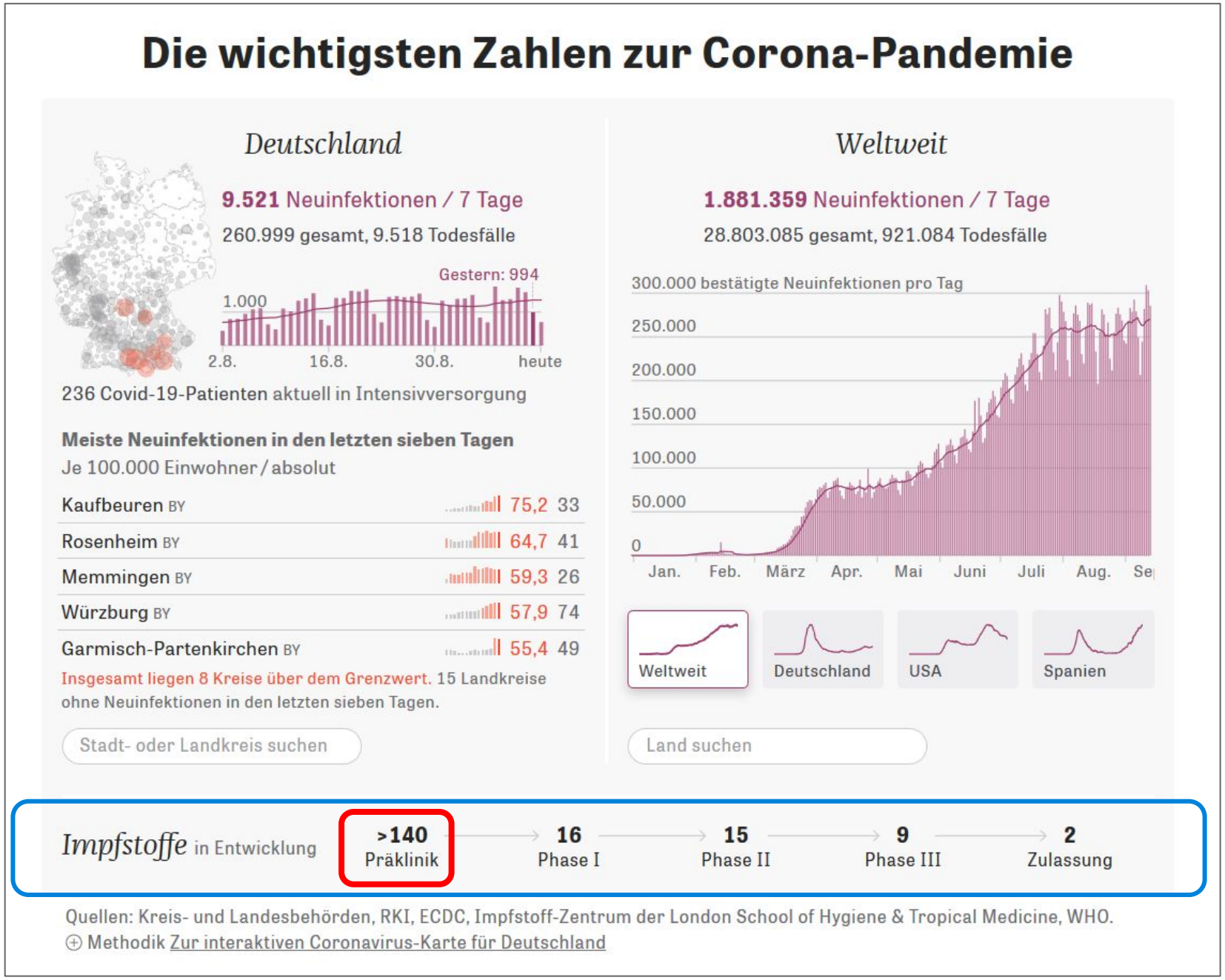
Dr. Jitao David Zhang, Computational Biologist

[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

Contact the author

Today's goals

- **Introduction to the course**
- **A brief introduction to drug discovery, or, why mathematics and informatics matter?**
- **Two views of the drug discovery and development process**
  - The linear view
  - The multiscale modelling view



The most important numbers about the Corona pandemic. Source: zeit.de, assessed on 13.09.2020. The latest WHO report can be assessed on the WHO's website.

Course information

- Lecturer: Jitao David Zhang
  - jitao-david.zhang@unibas.ch
- Website: AMIDD.ch
- Thirteen lectures this semester
  - Introduction to drug discovery (1 session)
  - Molecular level modelling (2 sessions)
  - Omics- and cellular level modelling (2 sessions)
  - Organ- and system-level modelling (2 sessions)
  - Population modelling and reverse translation (2 sessions)
  - Invited guest speakers (2 sessions)
  - *Dies Academicus - Ask Me Anything (optional)*
  - Near-end-term presentations (2 sessions)

- Fridays 12:15-14:00
- Slides, exercises, pre-reading and post-reading articles, as well as videos, are shared on the course's website http://www.amidd.ch.
- No exercise hour yet. One-to-one virtual sessions are possible upon request and reservation.
- The final note is given by participation (20%), presentation (30%), and ~~an oral examination~~ project work (50%).
- The project work will be about concepts that we learned together and their applications in practice. The work will be judged by how you work within a team, how you find and integrate information, and how well you explain your findings to a general, non-expert readership. Details will follow.
- **Questions**?

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

Computational Biology & Biostatistics PhD
Network analysis and applications in cancer

Bioinformatics MSc
high-throughput screening data analysis

Life Sciences BSc
with German Studies as minor

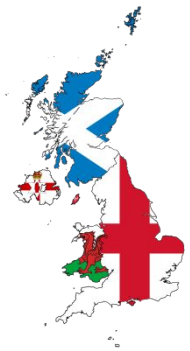
STEM high school

Academia

Computational Biologist @ Roche since 2011
Preclinical research on drug efficacy and safety

Mathematical statistics

Theoretical Bioinfo



Mol Biol MSc

Marine Biol MSc

German Studies BSc

Sport journalist

Medicine, Chemistry, CS BSc

My career path

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.

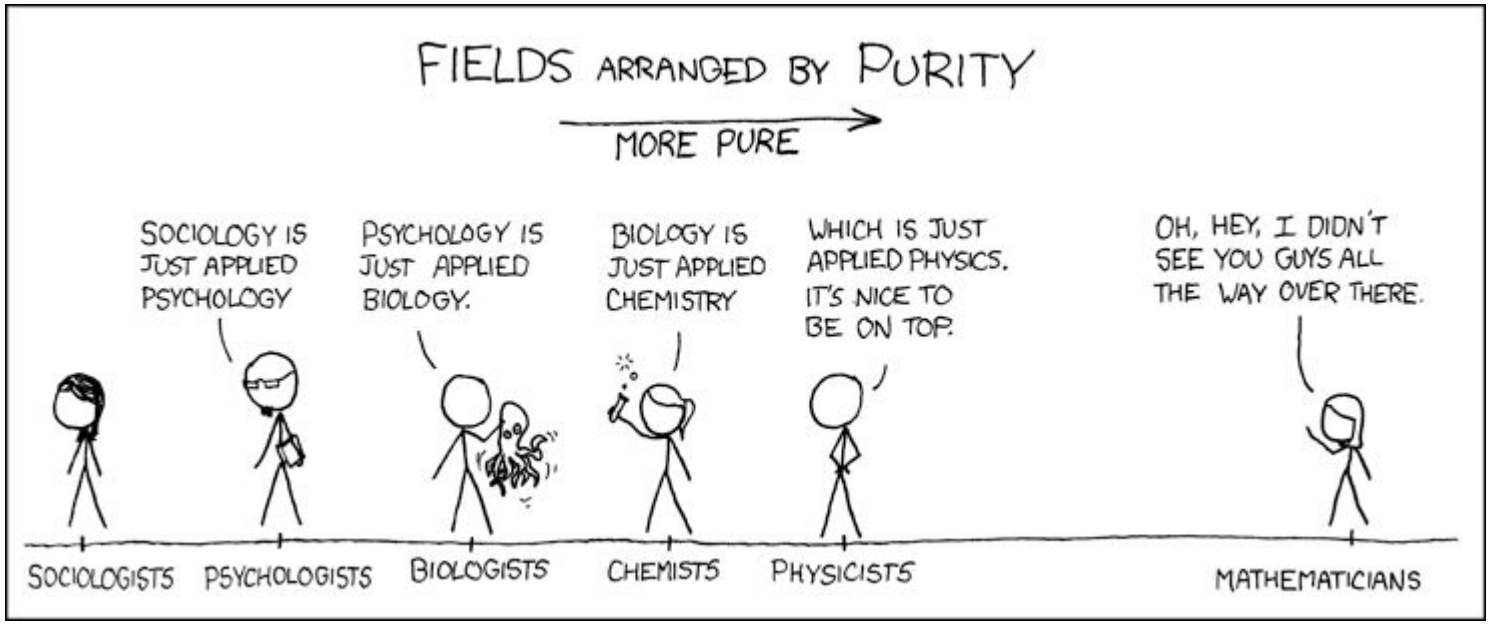
- I am neither a mathematician nor a computer scientist by training. I am a computational biologist working in drug discovery.
- I see my task is to share with you the mathematical concepts and computational approaches used in drug discovery that I find beautiful and useful.
- I look forward to learning from you mathematics and other expertise that I did not know.

Why applied mathematics and informatics in drug discovery, why now?

- Now is the best time in human history to fight diseases
- Applied mathematics and informatics approaches are indispensable to modern drug discovery
- Applied mathematics and informatics will join interdisciplinary efforts to transform drug discovery in the coming decades

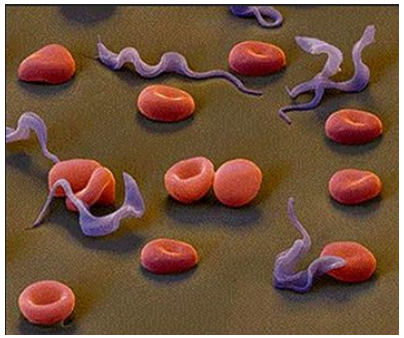
Purity

https://xkcd.com/435/

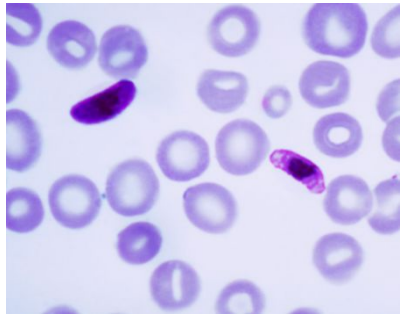


This course aims to bring people together and to promote interdisciplinary research

The history of *Homo sapiens* is a history of living with, understanding, and fighting diseases



Trypanosomes



Plasmodium

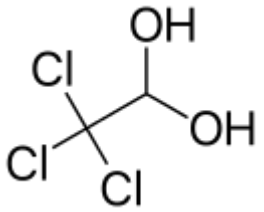
Tropical diseases

~500,000 years ago

A young patient of smallpox,
the first eradicated infectious disease

Hygiene, vaccination, and antibiotics

~250 years ago



Chloral hydrate,
the first synthesized drug

Pharmaceutical drugs

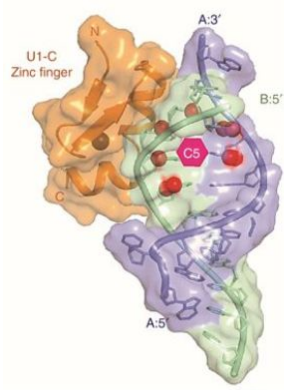
~150 years ago

Nobel prize laureates 2018,
immune checkpoints,
and drugs targeting the pathways

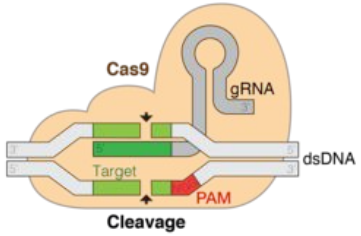
Personalized precise healthcare

~20 years ago

Now is the best time in human history to fight diseases



SMN2 splicing modifer
Naryshkin *et al.*, Science 2014; Sivaramakrishnan & McCarthy *et al.*, Nat Comm, 2017



CRISPR-CAS9 gene editing system

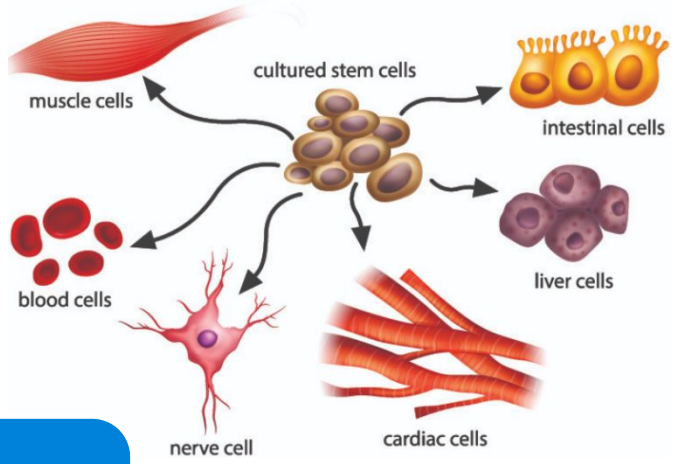
More biological, chemical, and medicinal knowledge

New disease-modelling systems

Digitalization of molecular mechanisms in living organisms

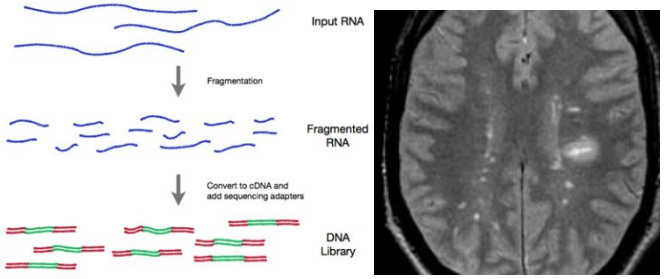
Better algorithms, models, and more computing resources

New therapeutic modalities



Stem cells

Comprehensive Sensing

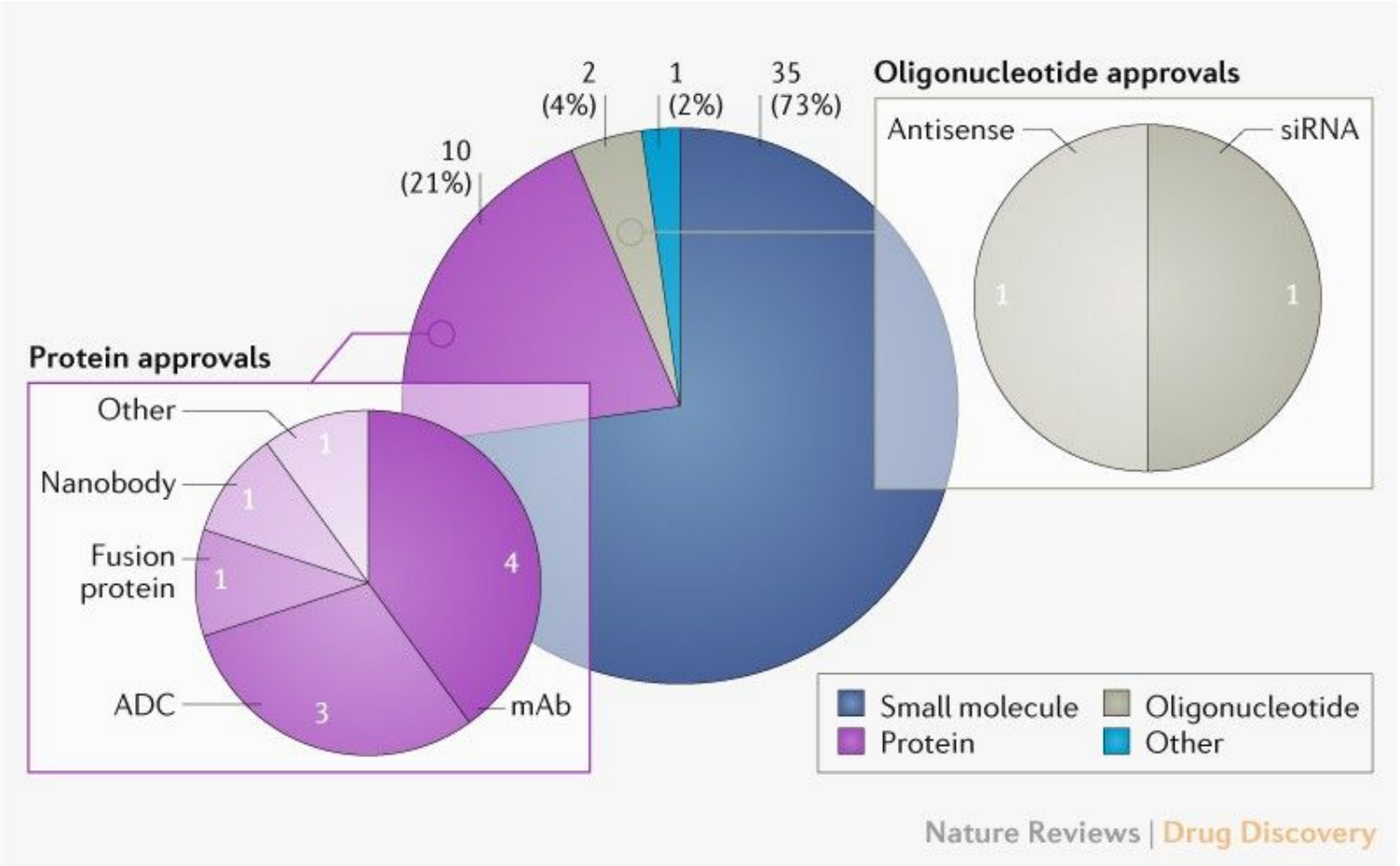


Gene expression profiling and imaging

Novel drugs approved by the FDA's Center for Drug Evaluation and Research (CDER) in 2019

Top three modalities by approval in 2019

- Small molecules (molecular weight under 900 daltons)
- Antibodies
- Oligonucleotides



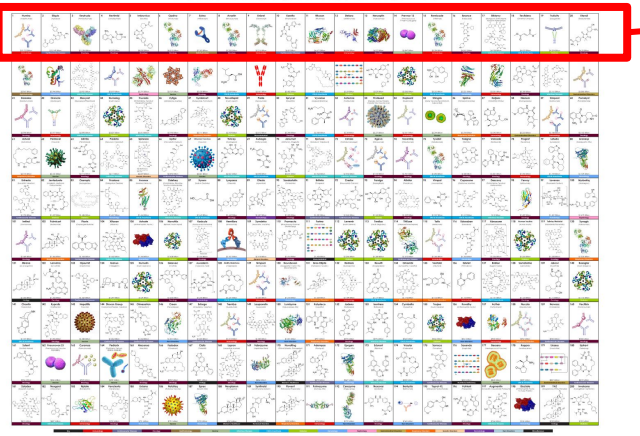
2019 FDA drug approvals, Asher Mullard, Nature Reviews Drug Discovery, https://www.nature.com/articles/d41573-020-00001-7 mAb: monoclonal antibodies; ADC: antibody-drug conjugate.

Top 20 pharmaceutical products by retail sails in 2019

1 Humira (Adalimumab)	2 Eliquis (Apixaban)	3 Keytruda (Pembrolizumab)	4 Revlimid (Lenalidomide)	5 Imbruvica (Ibrutinib)	6 Opdivo (Nivolumab)	7 Eylea (Aflibercept)	8 Avastin (Bevacizumab)	9 Enbrel (Etanercept)	10 Xarelto (Rivaroxaban)
$19.723 Billion	$12.149 Billion	$11.084 Billion	$9.378 Billion	$8.085 Billion	$8.015 Billion	$7.363 Billion	$7.285 Billion	$7.216 Billion	$6.81 Billion
Immunology	Cardiovascular Diseases	Oncology	Oncology	Oncology	Oncology	Ophthalmology	Oncology	Immunology	Cardiovascular Diseases

11 Rituxan (Rituximab)	12 Stelara (Ustekinumab)	13 Herceptin (Trastuzumab)	14 Prevnar 13 (Pneumococcal 7-Valent Conjugate)	15 Remicade (Infliximab)	16 Ibrance (Palbociclib)	17 Biktarvy (Bictegravir, Emtricitabine, Tenofovir Alafenamide)	18 Tecfidera (Dimethyl Fumarate)	19 Trulicity (Dulaglutide)	20 Xtandi (Enzalutamide)
$6.671 Billion	$6.594 Billion	$6.22 Billion	$5.847 Billion	$5.304 Billion	$4.961 Billion	$4.738 Billion	$4.433 Billion	$4.394 Billion	$4.35 Billion
Oncology	Immunology	Oncology	Vaccine	Immunology	Oncology	Infectious Diseases	CNS & Anesthesia	Diabetes	Oncology

Top 200 Pharmaceuticals by Retail Sales in 2019



Poster compiled by the Jon Njardarson group from the University of Arizona. Source: https://njardarson.lab.arizona.edu, accessed on 17.09.2020. Citation: J. Chem. Ed. 2010, 87, 1348

Questions:

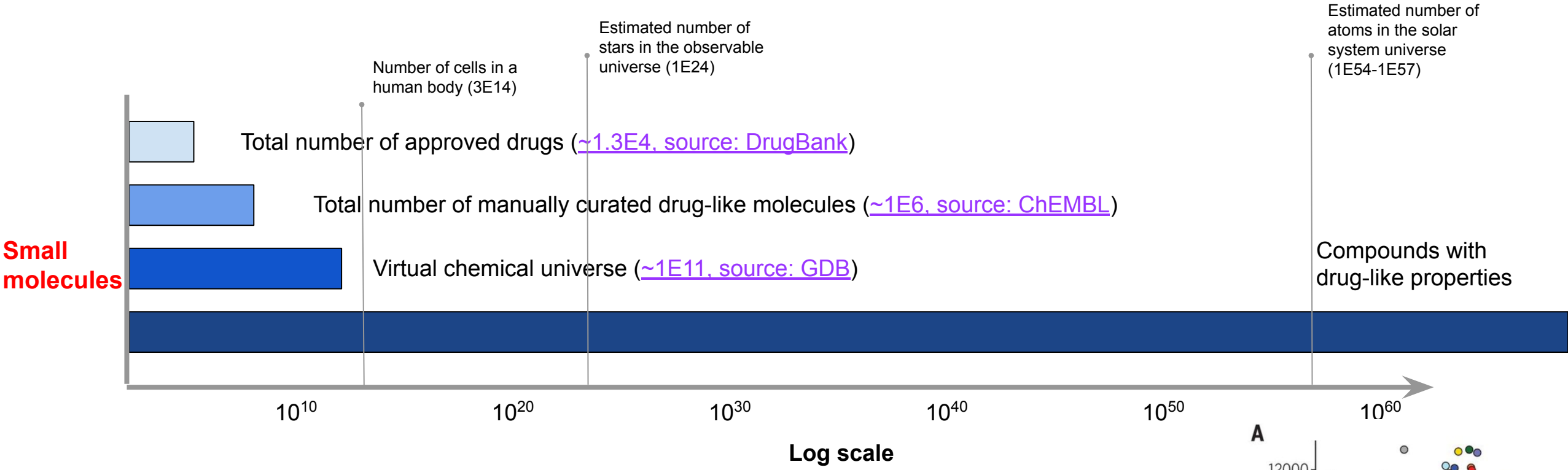
1. How many are small molecules, proteins, and oligonucleotides each? What other modalities are there?
2. What patterns do you observe? Do you have explanations for these patterns?

How Do You Make A Drug?

It sounds simple, but…

Source and copyright: roche.com, assessed on 1.2.2019

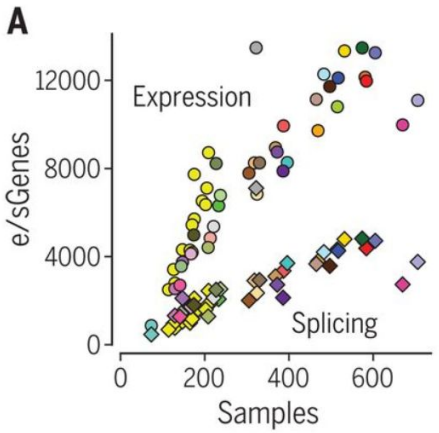
Why drug *discovery*?



Human protein interactome (BioGrid)

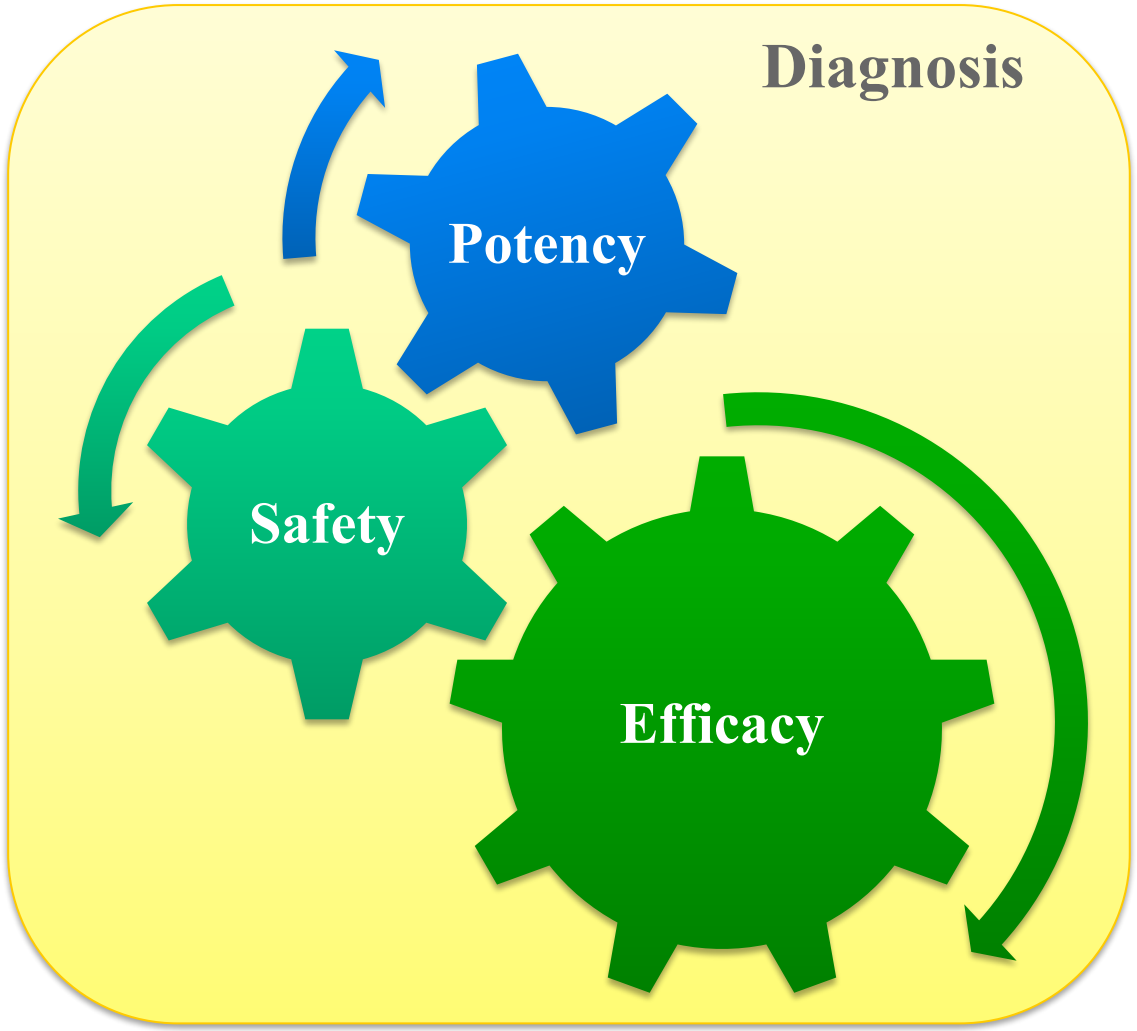
Organism	Experiment Type	Raw Interactions	Non-Redundant Interactions	Unique Genes
Homo sapiens	PHYSICAL	631,623	480,099	25,528
	GENETIC	9,122	8,996	3,732
	COMBINED	640,745	488,387	25,941

Single-nucleotide polymorphisms affecting nearby gene expression or splicing (eQTL, GTEx consortium, Science 2020)



Even if we understood everything, the search space of drug hunting is huge

Prerequisites to make a good drug that works



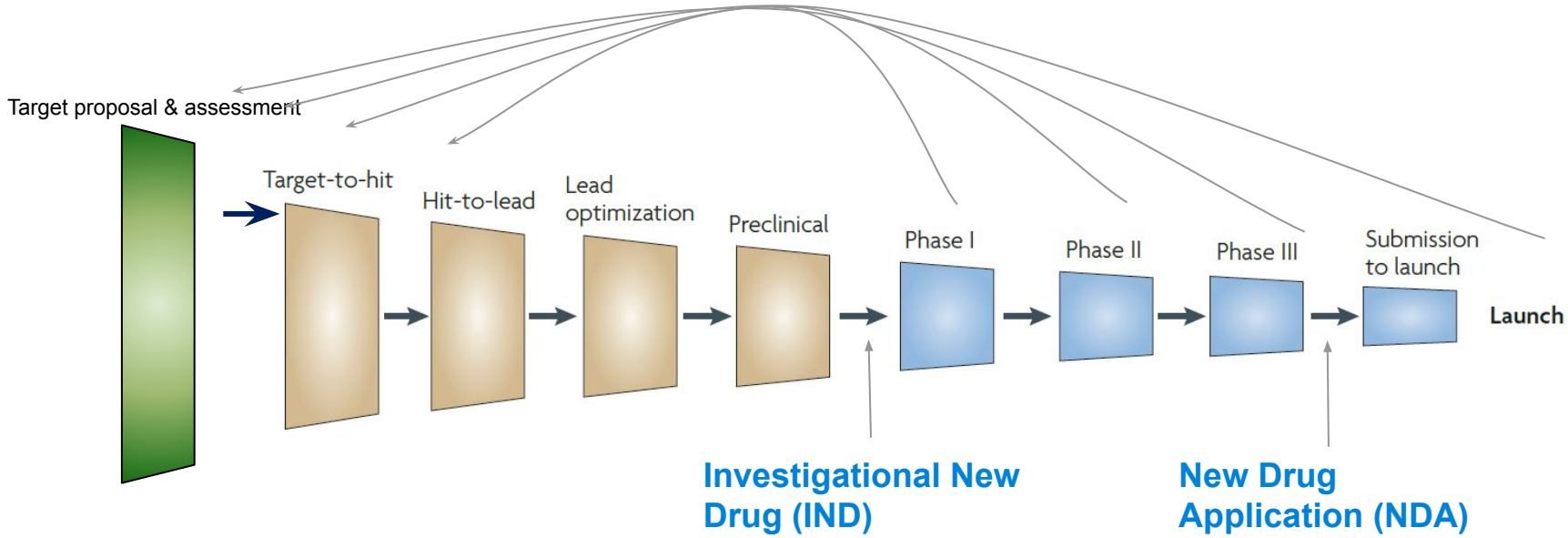
- **Potency**
- **Safety**
- **Efficacy**
- **Diagnosis**: doctors' judgement + *biomarkers*
  - *Biomarkers* are informative features derived from measurements of patient or patient material, *e.g.* blood chemistry, genetic make-up, imaging, *etc.*
- Other criteria: commercial rationale, development ability, intellectual property, *etc.*

Success in drug discovery is determined by potent, safe, efficacious drugs and accurate diagnosis

The essence & THE challenge of Drug Discovery

Constrained optimization and decision making based on incomplete, noisy and heterogeneous data, and limited prior knowledge.

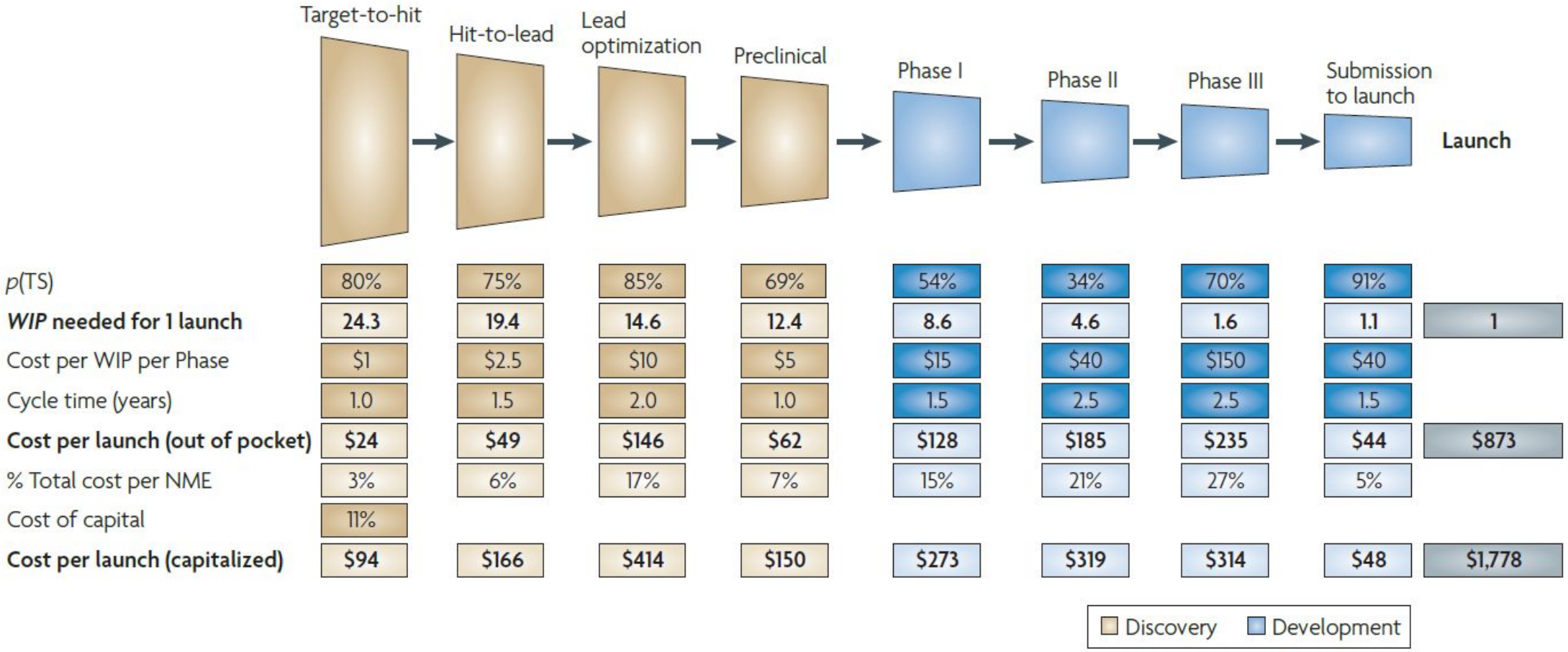
The linear view of drug discovery



Acronym	TI/TA/TV	Screening	LI	LO
Description	Target identification/ target assessment/ target validation		Lead identification	Lead optimization

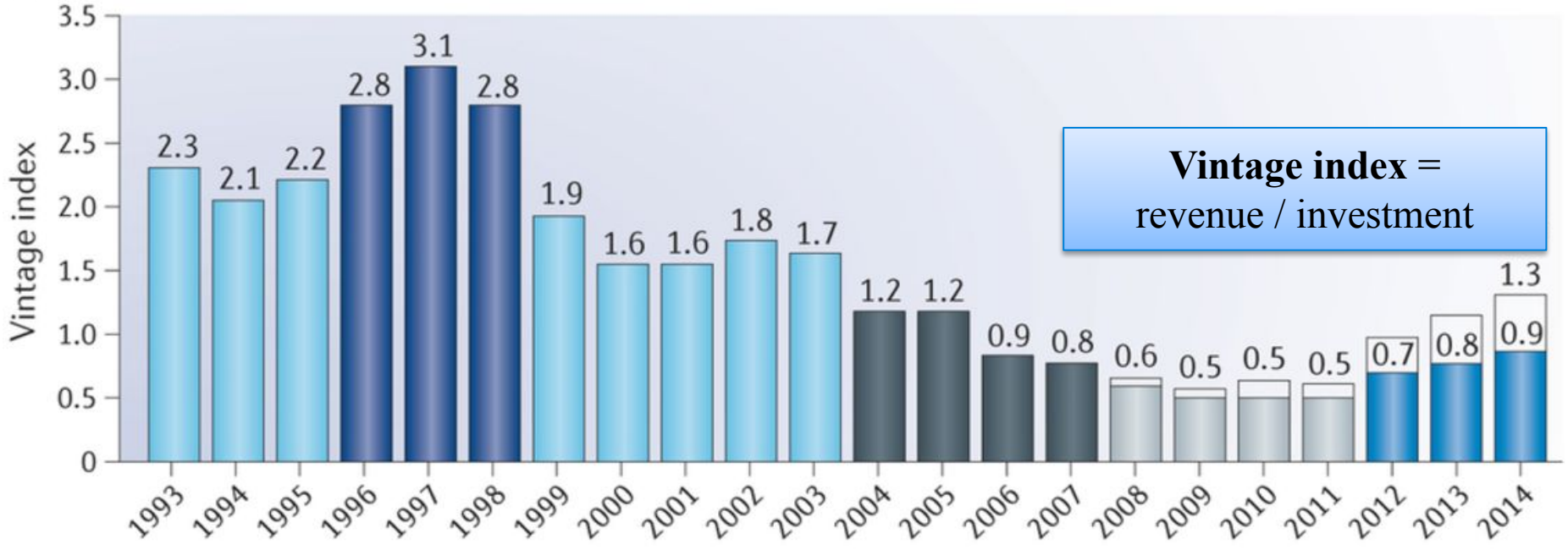
Adapted from Paul *et al.* "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery, 2010

Risks and costs associated with each stage of the linear view of drug discovery



pTS: probability of technical success. **WIP**: work in progress; **Capitalized cost**: Out-of-pocket cost corrected for cost of capital, standard for long-term investments; **Out-of-pocket cost**: total cost required to expect one drug launch, taking into account attrition, but not the cost of capital; **Cost of capital**: annual rate of return expected by investors based on the level of risk of the investment. Paul *et al.*, Nature Reviews Drug Discovery, 2010.

Increasing cost and decreasing return of investment in drug discovery



Modified from Smietana *et al.* "Improving R&D Productivity." Nature Reviews Drug Discovery, 2015

Finding new drugs has become more challenging and expensive

危机

~~*n.* crisis~~

Danger + Opportunity

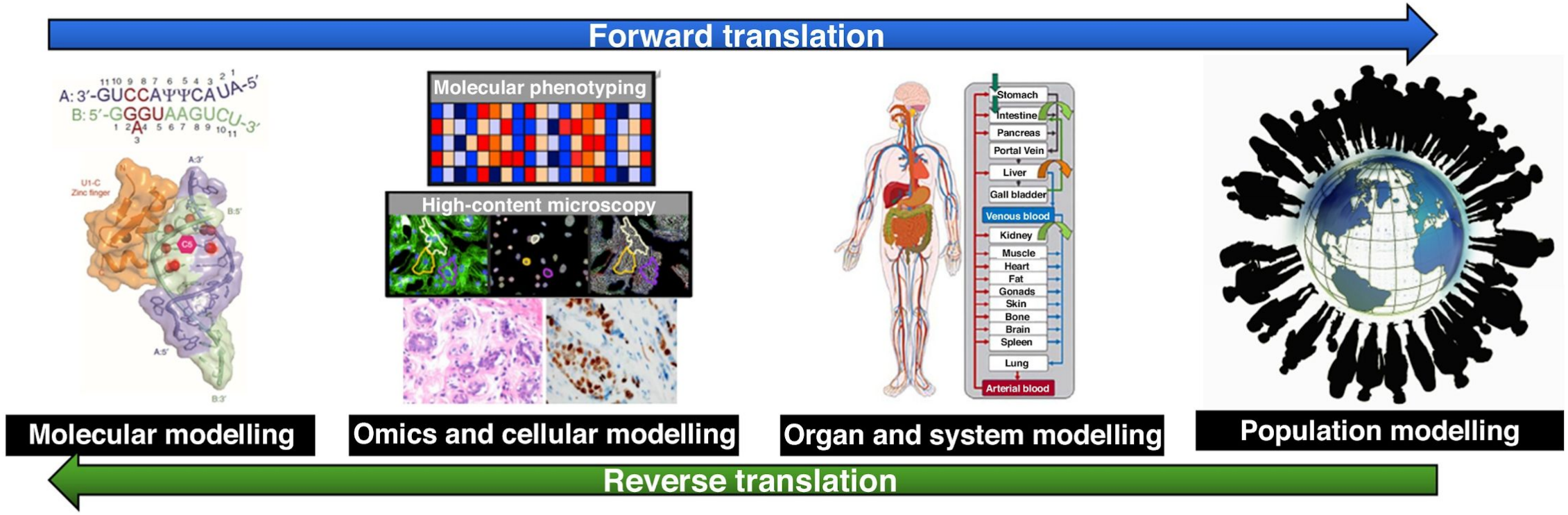
Applied mathematics empowers drug discovery in many ways

Applied mathematics *in drug discovery*
is not a definable scientific field
but a human attitude.

Richard Courant
(1888-1972)

Statistics, Data Mining and Machine Learning	Applied Combinatorics and Graph Theory	Stochastic Simulation	Geometric Modeling
Ordinary / Partial/ Stochastic Differential Equations	Network Analysis	Dynamical Systems	Molecular, Quantum, and Continuum Mechanics

The alternative, 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.

Introduction to Applied Mathematics and Informatics in Drug Discovery (*AMIDD*)

A course series at DMI, University of Basel

- **Introduction to drug discovery**
- **Molecular modelling**
  - Biological sequence analysis
  - Protein sequence and structure
  - Molecular modelling and dynamics
- **Omics and cellular modelling**
  - From drug-target interactions to networks
  - Gene expression profiling
  - Cell-based phenotypic drug discovery
- **Mathematical modelling**
  - Principles and applications of modelling in pharmacology
  - Pharmacokinetics (PK) and pharmacodynamics (PD) modelling
  - Clinical pharmacology and pharmacometrics
- **Population modelling**
  - Non-linear mixed-effect models (NLMEs)
  - Essentials of clinical trials
- **Guest lectures**
- **Your presentations**

It is hoped that AMIDD builds a bridge between students and quantitative aspects of drug discovery

Acknowledgements

F. Hoffmann-La Roche Ltd	
Clemens Broger†	**Faye Drawnel**
Martin Ebeling	Markus Britschgi
Manfred Kansy	Roland Schmucki
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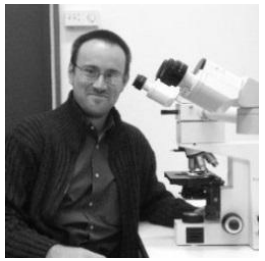
Kurt Amrein	Isabelle Wells
Annie Moisan	**Lu Gao**
Luca Piali	Lue Dai
John Young	Ravi Jagasia
Lisa Sach-Peltason	**Marco Prunotto**
Mark Burcin	**John Moffat**
Christoph Patsch	Gang Mu
Michael Reutlinger	Jianxun Jack Xie
Matthias Nettekoven	Filip Roudnicky
Andreas Dieckmann	Holger Fischer
Klas Hatje	Iakov Davydov
Laura Badi	**Ulrich Certa**
Tony Kam-Thong	Detlef Wolf
Corinne Solier	Ken Wang
Thomas Singer	Nikolaos Berntenis



External to Roche
Stefan Wiemann
Wolfgang Huber
Ozgür Sahin
Agnes Hovrat
Katharina Zweig
Sally Cowley
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Michael Prummer
Mark D. Robinson
Michael Hennig
Philipp Mekler
Jung Kyu Canci
Verdon Taylor
Maria Anisimova
Lorenzo Gatti
Erhard van der Vries
Ab Osterhaus
Nevan Krogan
Oliv Eidam

Conclusions and perspectives

- **It is now probably the best time in human history to join the fight against diseases.**
- **We learned about modalities and the drug discovery and development process.**
- **Interdisciplinary research**, especially applying mathematical approaches and tools to biological, chemical and medicinal questions, **is imperative** to fill the knowledge gaps and to make potent, safe, and efficacious drugs and to perform accurate diagnosis.
- **Mathematics and informatics will continue transforming drug discovery**
  - From correlation to causation
  - From qualitative description to quantitative prediction
  - From trial-and-error to systematic understanding
  - From population inference to individual prediction and continuous intervention
  - From observations to engineering and synthesis of the biological system
- **In the AMIDD course, we will learn some basic concepts and tools we use to model interactions between biological systems and drugs at multiple levels (*multiscale-modeling of drug mechanism and safety)*.**

Will you please introduce yourself?

- **Name?**
- **Background?**
- **Which part of mathematics (or other background) are you mostly interested in? Why?**
- **What do you want to take away from this course?**

Questions on the video on Herceptin by Susan Desmond-Hellmann

Link to the video

Questions for the video

1. What is the **indication** of *Herceptin*? What is its generic (USAN, or United States Adopted Name) name?
2. What is the **gene target** of Herceptin?
3. In which year was the **target** of Herceptin described? When was Herceptin **approved**?
4. What was the **improvement** of Herceptin compared with earlier antibodies?
5. Why does a **biomarker** matter besides developing drugs?
6. In the clinical trial of *Herceptin* for **metastatic breast cancer**, how much improvement in the **median survival** did Herceptin achieve? And how much improvement is in the **adjuvant setting** (Herceptin applied directly after operation)?

Questions for further thinking

- Susan Desmond-Hellmann summarizes successful drug development in four aspects: (1) having a deep understanding of the basic science and the characteristics of the drug, (2) targeting the right patients, (3) setting a high bar in the clinic, and (4) working effectively with key regulatory decision makers. Where do you think mathematics and computer science play a crucial role?
- She emphasized the importance of collaboration. What skill sets do we need for that?
- How do you like her presentation? Anything that you can learn from her about presentation and storytelling?

Offline Activities

Required and recommended reading

[Required]

Principles and workflow of early drug discovery:

Hughes, JP, S Rees, SB Kalindjian, and KL Philpott. 2011. “Principles of Early Drug Discovery.” British Journal of Pharmacology 162 (6): 1239–49. https://doi.org/10.1111/j.1476-5381.2010.01127.x.

[Recommended]

History of drug discovery and the rise of pharmaceutical company:

Jones, Alan Wayne. 2011. “Early Drug Discovery and the Rise of Pharmaceutical Chemistry.” *Drug Testing and Analysis* 3 (6): 337–44. https://doi.org/10.1002/dta.301.

Mathematics and biology:

Cohen, Joel E. 2004. “Mathematics Is Biology’s Next Microscope, Only Better; Biology Is Mathematics’ Next Physics, Only Better.” PLOS Biology 2 (12): e439. https://doi.org/10.1371/journal.pbio.0020439.

Extensive reading about history of medicine:

- Taking the Medicine: A Short History of Medicine’s Beautiful Idea, and our Difficulty Swallowing It by Druin Burch (ISBN: 1845951506, ISBN13: 9781845951504)

Questions on the package insert info

Please read the package insert info for *ZYRTEC* (adapted for the course) and answer the following questions:

1. What is the **indication** of *ZYRTEC*? What is its generic name?
2. What is the **gene target** of ZYRTEC?
3. How much time does ZYRTEC reaches **maximum concentration** following oral administration?
4. How long do normal volunteers have to **wait** until the skin wheal and flare caused by the intradermal injection of histamine is inhibited after taking 10mg ZYRTEC?
5. What types of **adverse reactions** are observed in volunteers taking ZYRTEC?
6. Is there a **biomarker** for ZYRTEC?

Questions for further thinking

- What are the commonalities between Herceptin and Zyrtec, and what are the differences?