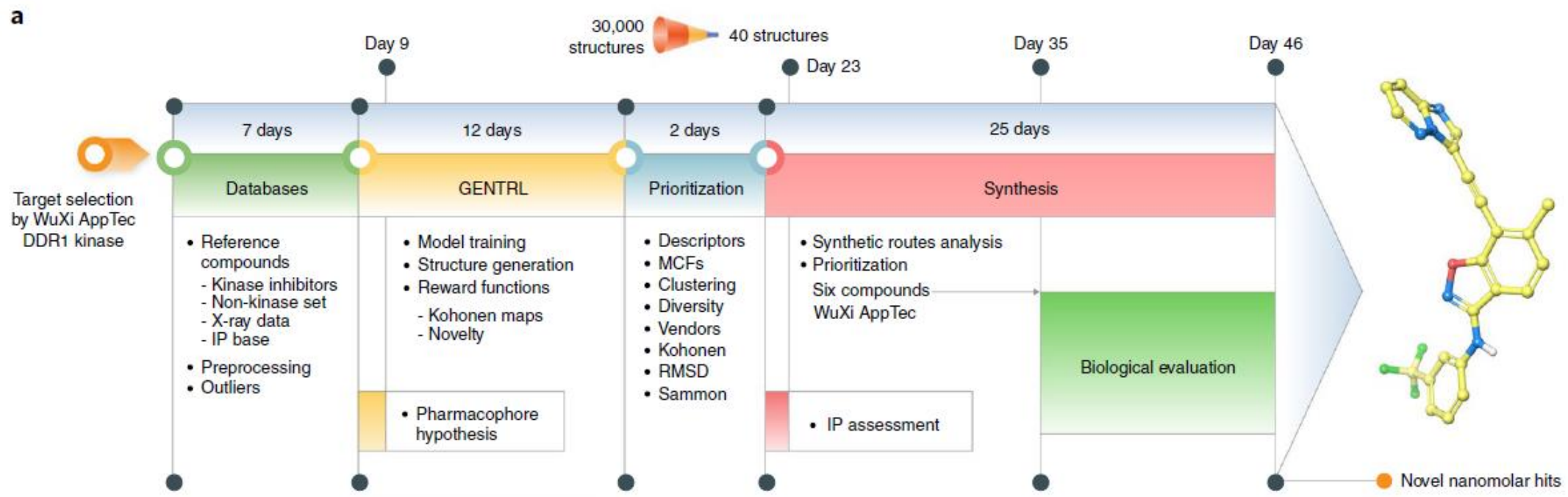
# AMIDD Lecture 4: Principles of screening




*Deep learning enables rapid identification of potent DDR1 kinase inhibitors*, Zhavoronkov *et al.*, Nature Biotechnology, 2019. Source code: https://github.com/insilicomedicine/gentrl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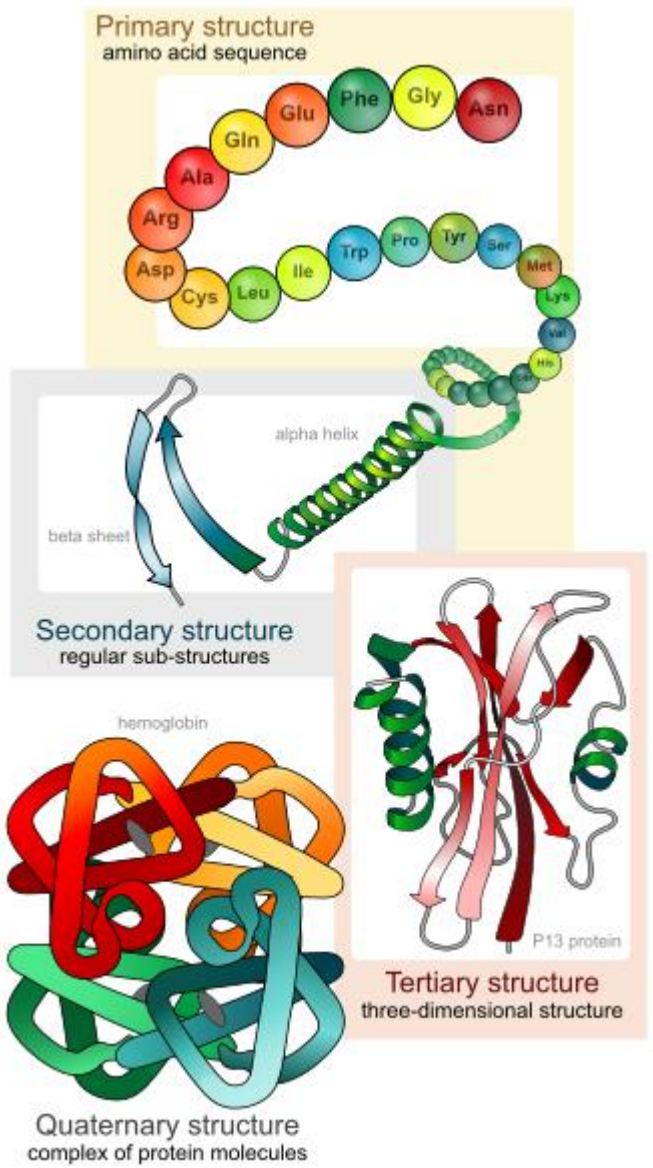
Contact the author

# Protein structure



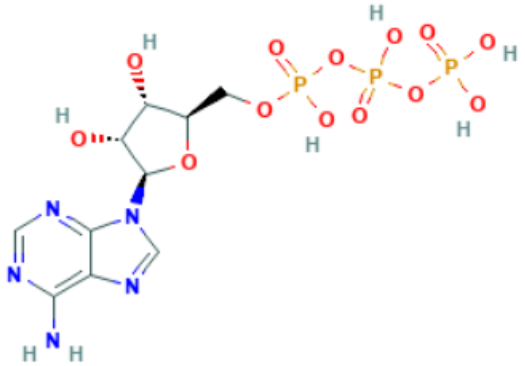

https://de.wikipedia.org/wiki/Datei:Main_protein_structure_levels_en.svg

# Questions on the PNAS paper by Tsai *et al.*

1. **How many** compounds were screened? What information is available about their **properties**?
2. **How** were the compounds **screened**?
3. What was the **initial chemical structure** that was found to bind to the ATP-binding site?
4. By overlapping structures, the team aimed to optimizing what **two properties of the compounds**?
5. What types of compounds were tested in the **subsequent screenig**?
6. What properties does the PLX4720 compound have that make it **particular attractive** as a drug?

# Lipinski's rule of five

- No more than **5 hydrogen-bond donors,** *e.g.* the total number of nitrogen–hydrogen and oxygen–hydrogen bonds
- No more than **10 hydrogen-bond acceptors**, *e.g.* all nitrogen or oxygen atoms
- A **molecular mass** less than **500 Daltons**, approximately 500 g/mol.
  - As a reference: ATP has a molecular mass of ~507.
- An **octanol-water partition coefficient (log P)** that does not exceed **5.**



ATP

# Principles of screening

| Ligand (chemical starting point) | Target and its protein structure: Available | Target and its protein structure: Not Available |
|---|---|---|
| **Available** | **Structure-based drug design**, e.g. docking, **and improvement** | **Ligand-based drug design**, e.g. Similarity and QSAR, **and target/MoA identification** |
| **Not Available** | **Screening *or de novo* drug design** | • Target identification<br>• Phenotypic screening |

# Summary and Q&A

# BACKUP

# Course information

- Lecturer: Jitao David Zhang
  - jitao-david.zhang@unibas.ch (Email)
- 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 (1.5 sessions)
  - Populational level modelling (1.5 sessions)
  - Case studies (1 session)
  - Invited guest speakers (2 sessions)
  - *Dies Academicus*
  - Near-end-term presentations (2 sessions)

- Fridays 12:15-14:00, two sessions of ~45 min each.
- No exercise hour yet; pre-reading and post-reading articles, as well as videos, are shared and recommended.
- We focus on interdisciplinary research with mathematics as the language and informatics as the tool.
- Both slides and board are used. Slides and notes are shared.
- The final note is given by participation (20%), presentation (30%), and an oral examination (50%).
- The oral examination will be about concepts that we learned together, and about explaining mathematical concepts (or concepts in your domain of experts) to a layman.
- **Questions**?

**I am glad to share my expertise in drug discovery, and to learn from 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 package insert info

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 vonlunteers 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?