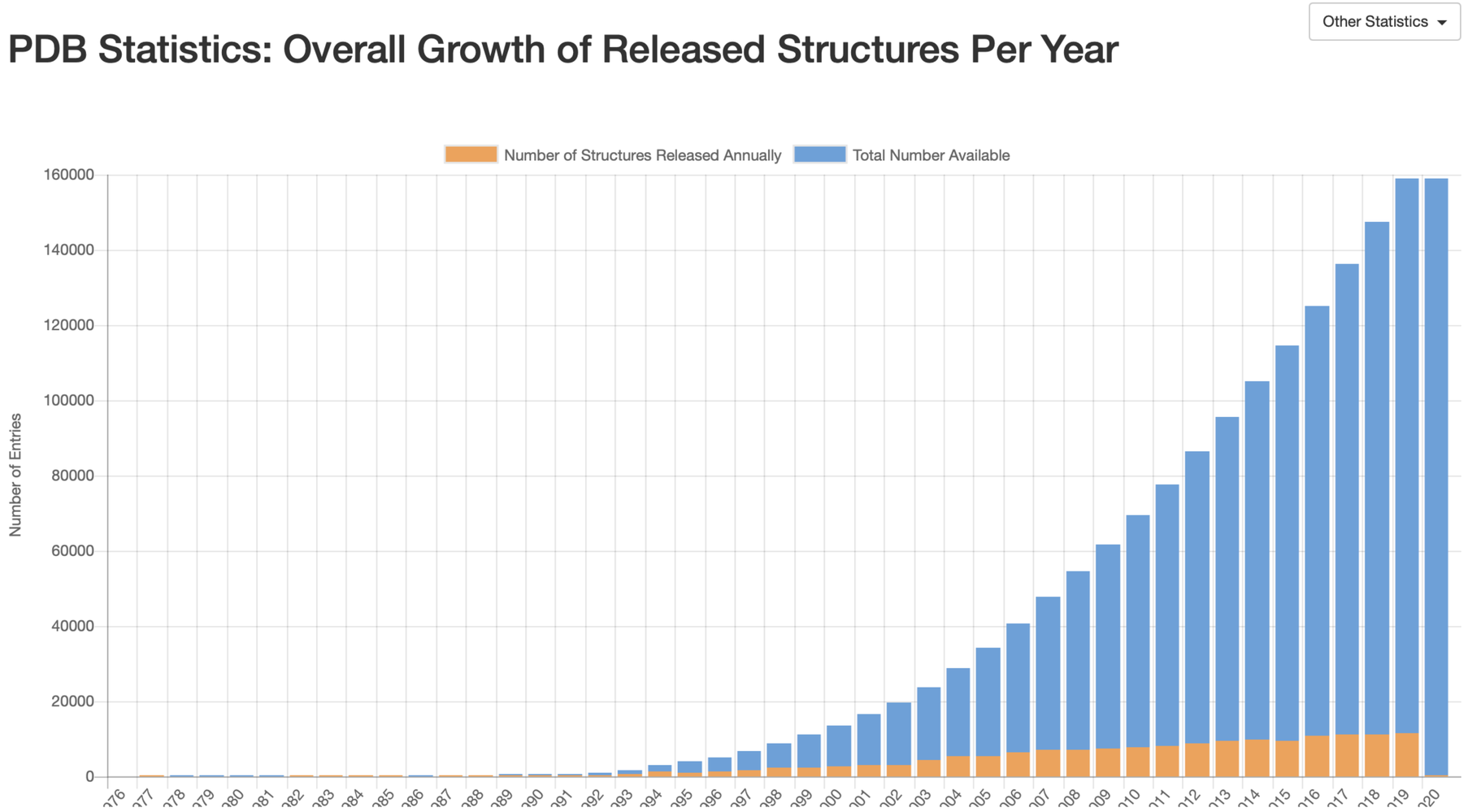
1/16/2020 Week 1 Module 2
Selecting a Target for SBDD

- This module will consist of a lecture interspersed with discussions, an interactive database search exercise, and a review
- At the end of this module, you should be able to address the question of what is necessary and what is desirable for a biological macromolecule to be a suitable target for structure-based drug design.
  - What is necessary/desirable about the physiological role?
  - What is necessary/desirable about the structural properties?
  - What are some business considerations that pharmaceutical companies use to decide whether to develop a drug for a particular target?
- You should also know about some databases that you can use to help find a suitable target for SBDD

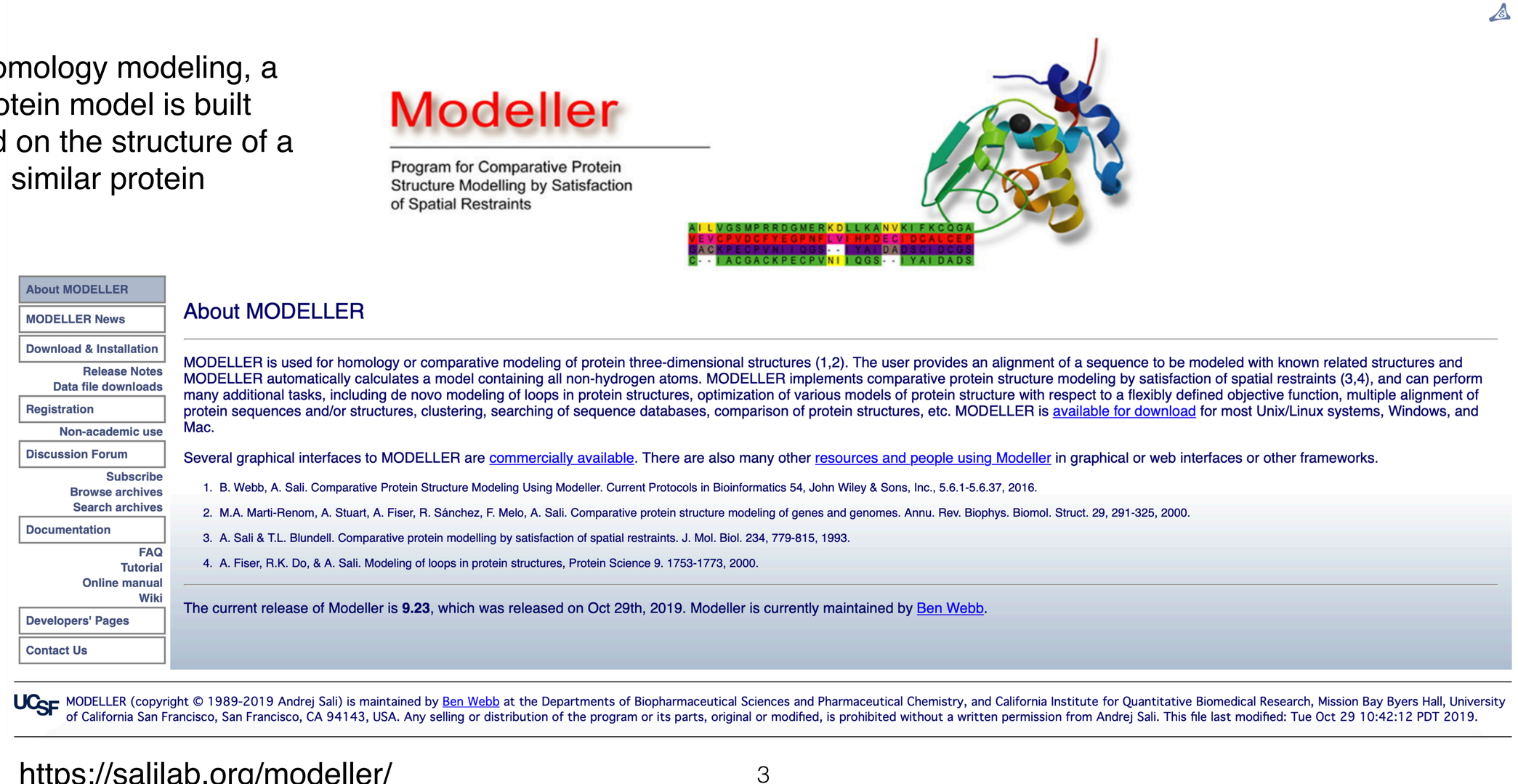
The exponential growth of biomacromolecule structures is an opportunity for SBDD



https://www.rcsb.org/stats/growth/overall

Homology modeling further expands the range of accessible targets

In homology modeling, a protein model is built based on the structure of a similar protein



https://salilab.org/modeller/

What is necessary/desirable about the physiological role of a SBDD target?

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Disease Relevance. Altering activity (usually by inhibition) should affect disease progression.

Brainstorm: How can disease relevance be predicted?

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- Mechanistic rationale, e.g.
  - the enzyme HIV protease has key role in viral life cycle. blocking it will slow viral reproduction.
  - the H+/K+-ATPase system is involved in stomach acid production. blocking it will reduce stomach acid and can be used to treat acid reflux.
- Mutations in a protein known to affect disease progression
  - in the clinic
  - in the laboratory
- Chemical probes affect disease progression
- Essential targets are better, e.g. NADH:ubiquinone oxidoreductase (NQR) is essential for *Vibrio cholerae* (common gut infection in developing tropical countries) and *Chlamydia trachomatis* (common STD) [1] but not *Pseudomonas aeruginosa* (common hospital infection)

Liang, P.; Rosas-Lemus, M.; Patel, D.; Fang, X.; Tuz, K.; Juárez, O. Dynamic Energy Dependency of Chlamydia Trachomatis on Host Cell Metabolism during Intracellular Growth: Role of Sodium-Based Energetics in Chlamydial ATP Generation. J. Biol. Chem. 2018, 293 (2), 510–522. https://doi.org/10.1074/jbc.M117.797209.

Brainstorm: What is necessary/ desirable about the structural properties of a SBDD target?

What is necessary about the structural properties of a SBDD target?

- High-resolution structure available
  - Resolution of < 2.5 Å [1]
  - Homology models less trustworthy
    - can still be useful, perhaps to guide structure determination
  - Experimental structures/homology models can be refined by molecular dynamics simulation
- “Druggable”
  - precedence - previously targeted
  - structure-based
    - cavities or pockets
    - comparing physicochemical and geometric properties of pocket with known druggable targets
  - as a caveat, concept is about history and does not account for innovation

[1] Anderson, A. C. The Process of Structure-Based Drug Design. Chemistry & Biology 2003, 10 (9), 787–797. https://doi.org/10.1016/j.chembiol.2003.09.002.

What is desirable about the structural properties of a SBDD target?

- Small
  - less ambiguity regarding binding site
  - more amenable to molecular simulation
- Rigid
  - molecular docking is more accurate
  - molecular simulation requires less sampling
- Binding site is
  - unique, favoring specificity
  - evolutionarily conserved, less susceptible to resistance

There are multiple online databases to help you identify suitable targets

- The Special Programme for Research and Training in Tropical Diseases (TDR) Targets (https://tdrtargets.org/) - A database that allows you to apply various filters to identify drug targets. Focuses on neglected tropical diseases
- Pocketome (http://ablab.ucsd.edu/POCKETOME/) - An encyclopedia of conformational ensembles of druggable binding sites that can be identified experimentally from co-crystal structures in the Protein Data Bank. It can help you investigate whether a structural motif has is druggable and whether it is unique.
- Therapeutic target database (http://idrblab.net/ttd/) - “A database to provide information about the known and explored therapeutic protein and nucleic acid targets, the targeted disease, pathway information and the corresponding drugs directed at each of these targets.” This can help you determine precedence for a target.
- BindingDB (http://www.bindingdb.org/bind/index.jsp) - “BindingDB is a public, web-accessible database of measured binding affinities, focusing chiefly on the interactions of protein considered to be drug-targets with small, drug-like molecules.” BindingDB can help you determine whether a any small molecule (not necessarily a drug) has been found that binds to a target.

Interactive Database Exercise

In the pharmaceutical industry, target selection is not only based on science, but also business

- How do pharmaceutical companies make money?
  - Costs
    - research and development is very expensive
    - manufacturing is relatively cheap
  - Income from drug sales
- In the current system, research and development(opposed to making old drugs) is incentivized by <u>patents</u>
  - must be novel, non-obvious, and useful. usually true for drugs.
  - provide monopoly on legal sales for a temporary period (in the U.S., 20 years from earliest filing)
  - need to be filed country-by-country
- In general, this system means that for a drug development campaign, the market must be
  - large enough
  - rich enough
  - not too competitive

Review questions

- What is necessary and what is desirable for a biological macromolecule to be a suitable target for structure-based drug design?
  - What is necessary/desirable about the physiological role?
  - What is necessary/desirable about the structural properties?
  - What are some business considerations that pharmaceutical companies use to decide whether to develop a drug for a particular target?
- What are some databases that you can use to help find a suitable target?

Homework

- Select a personal target to do further research on.
- The target or a close homolog must have a public crystal structure in the Protein Data Bank (https://www.rcsb.org).
- After making sure that nobody has selected the same target, enter your name and target in the Google spreadsheet (https://docs.google.com/spreadsheets/d/1iaSiJNi3YfHuG2_asuYWpRpvoEVHWazjbY5Ebx0BKGY/edit?usp=sharing).

Suggested targets to investigate

- Some targets that have been suggested to me but I have done no work on
  - Human Cystathionine gamma lyase (CSE), sleep apnea drug target of interest to biologist David McCormick
  - Mycobacterial membrane proteins Large (Mmpl3), *Mycobacterium tuberculosis* drug target of interest to Oluseye Onajole at Roosevelt University and Benjamin Swartz at Central Michigan University
- A target that I have done some work on
  - Tyrosyl-DNA phosphodiesterase 1 (TDP1), cancer drug target of interest to organic chemist Hyun-Soon “Joy” Chong