



**How can disease relevance be predicted?**

- 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 preservative 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>.



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- Chemical probes affect disease progression
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**Brainstorm: What is necessary/  
desirable about the structural  
properties of a SBDD target?**