k_{off} determines K_d

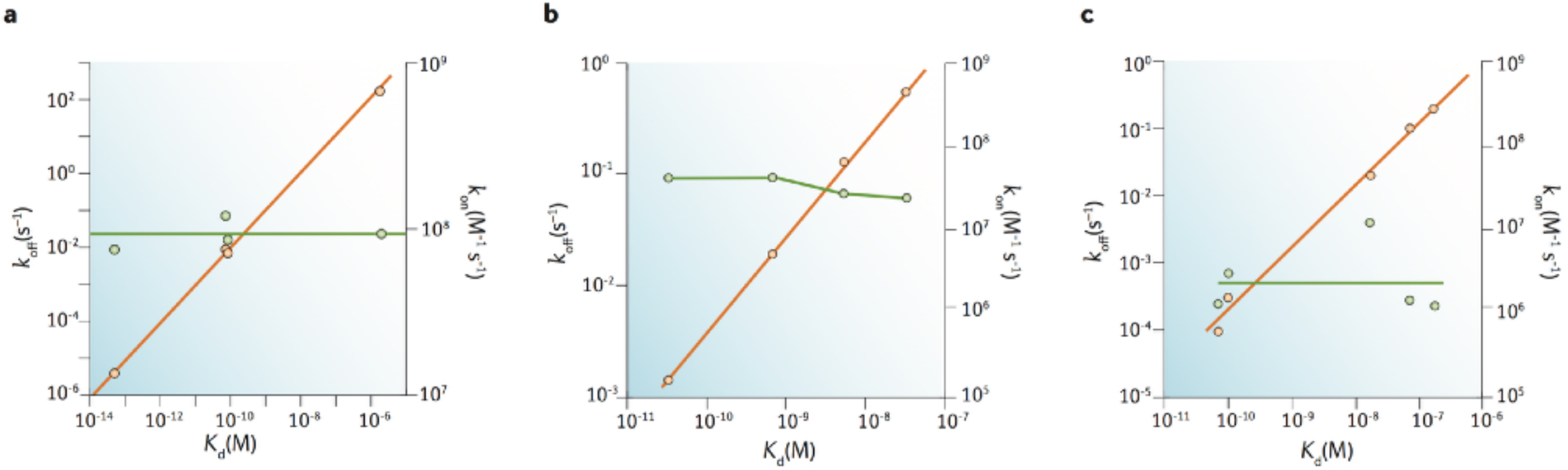


Figure 2 | **Drug affinity (target potency) is often driven by drug–target residence time.** Correlation between the dissociation rate constant (k_{off}; orange circles) or association rate constant (k_{on}; green circles) with the equilibrium dissociation constant (K_d) for biotin binding to wild-type and mutant forms of streptavidin[16] (part **a**), saquinavir binding to wild-type and resistant mutants of HIV protease[17] (part **b**), and a series of aminonucleoside inhibitors binding to the protein methyltransferase DOT1L[18] (part **c**).

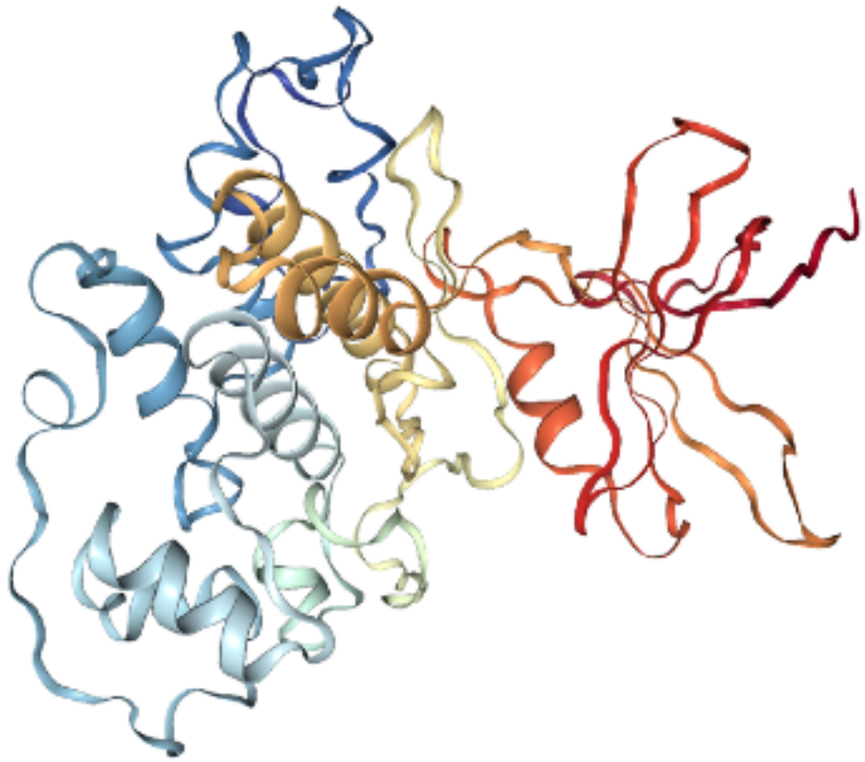
Strong correlation with k_{off}, no correlation with k_{on}

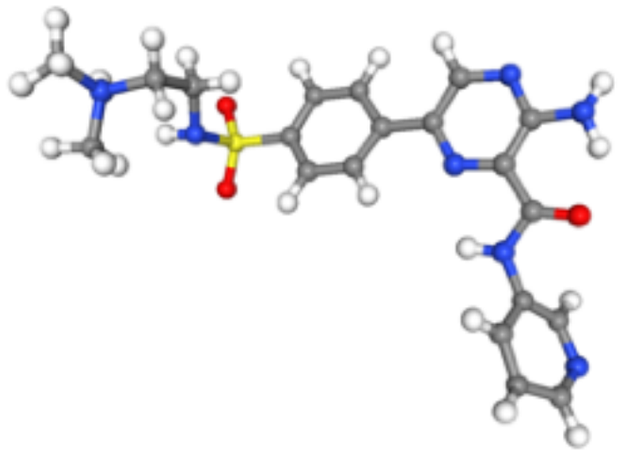
Unbinding rates have timescales of 1/minute or longer!

Copeland. Nature Rev. Drug Disc. **15**, 87 (2016).

Glycogen synthase kinase 3B

- Kinase involved in many signaling networks
- Possible druggable target for Alzheimer's
- Goal: Use TPS (eventually TIS) to study the unbinding of a selective inhibitor
- Initial trajectory provided by BiKi Technologies





Berg et al. J. Med. Chem. **55**, 9107 (2012).