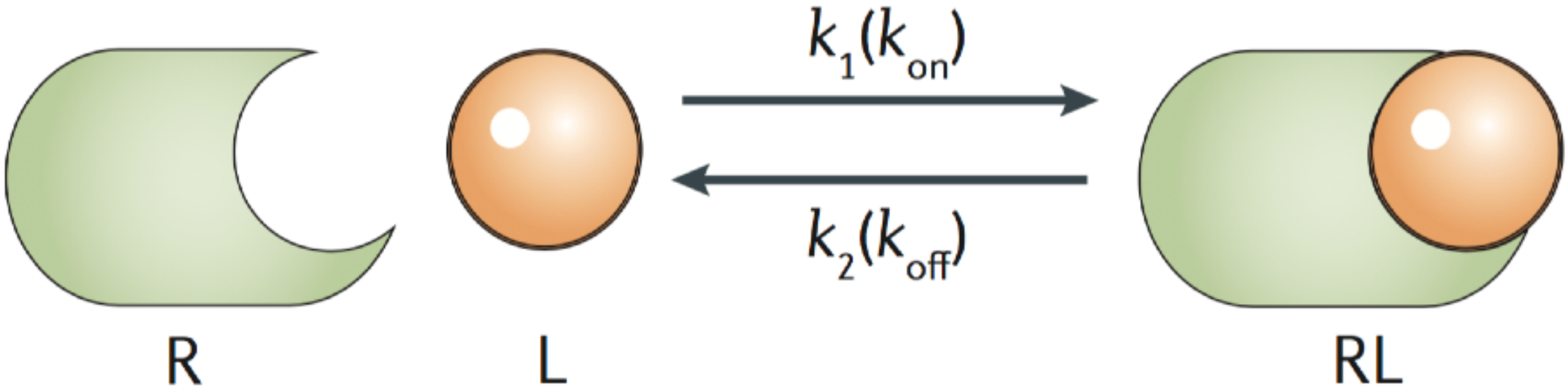
Drug Binding and Unbinding



Drugs work when they are bound to the target!

Reversible inhibitors: equilibrium constant

$$K_d = \frac{k_{\text{off}}}{k_{\text{on}}}$$

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

k_{off} determines K_d

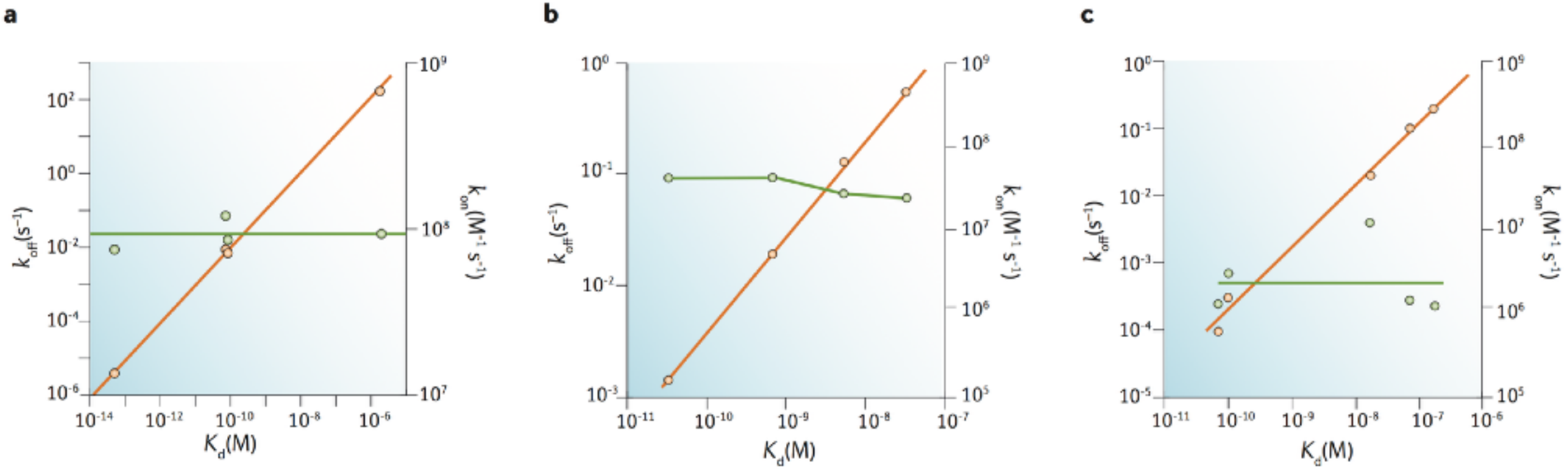


Figure 2 | **Drug affinity (target potency) is often driven by drug–target residence time.** Correlation between the dissociation rate constant (k_{off}; orange circles) or association rate constant (k_{on}; green circles) with the equilibrium dissociation constant (K_d) for biotin binding to wild-type 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).