

Site Directed Ligand Discovery. Proximity; Summing Energies? Erlanson et al (2000) PNAS 97 9367 – 9372

Erlanson,DA; Braisted, AC; Raphael, DR; Randal, Mike; Stroud, RM; Gordon, EM; Wells, JA. **Site-directed ligand discovery.** PNAS. 2000 Aug 15, 97(17)9367-9372.

- *Facing problems for Drug Discovery*
- *Tethering – Why? How? Reducing potential*
- *Additivity of energy*

KHORANA

Cysteine

Traditional screening

Tethering

Disulfide libraries, cystamine

Screening sub-sets of libraries, Protein concentration, ligand concentrations

Mass spectra

CURIE

Figure 2

C146S reactivity

Conditions of rapid exchange

Figure 3

Figure 4

ANFINSEN

L143C

Binding untethered compounds, affinity difference

Figure 5

Figure 6

Linking to produce higher affinity compounds