

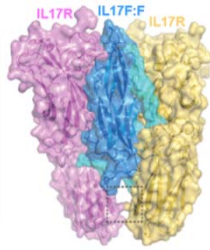
Drugging the undruggable: systematic identification of drug candidates which specifically inhibit targeted protein-protein interactions

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Motivation

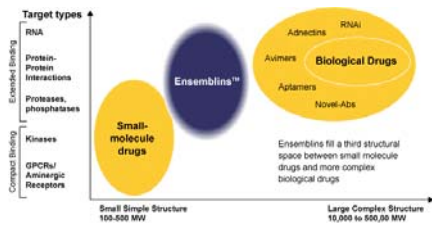
Protein-Protein Interactions are attractive as drug targets due to their role in multiple diseases

However, many of these interactions have proven intractable to small molecule drug discovery efforts



IL-17 Complex

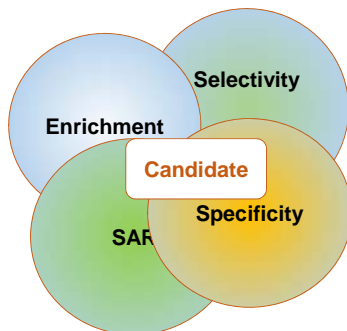
DPC-generated Ensemblins offer a solution



DNA programmed chemistry(DPC) allows us to generate DNA-tagged combinatorial libraries of macrocycles

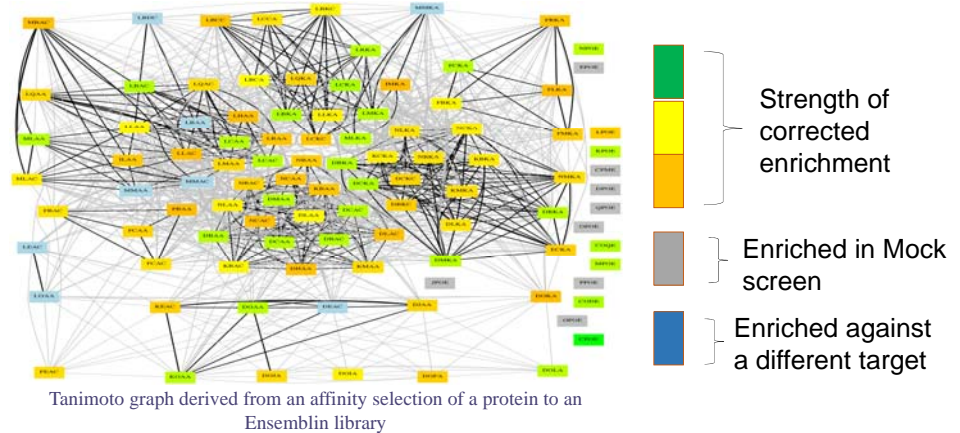
These Ensemblins are placed in affinity screens to test their ability to disrupt targeted protein interactions

Criteria to synthesize and test a given Ensemblin

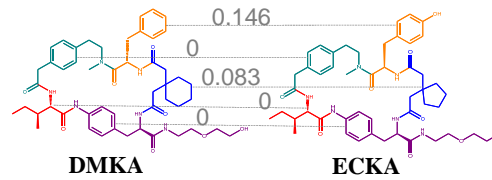


Chemical synthesis criteria

Structure Activity Relationship (SAR) of Ensemblins is determined by generating Tanimoto distance based network graphs



Strongly Related Ensemblin Pair



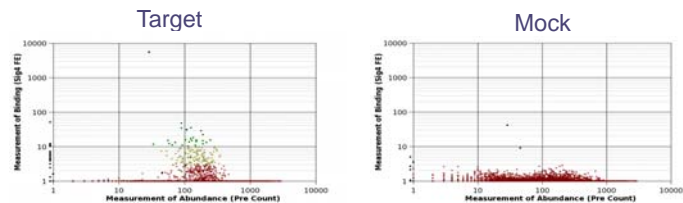
Pairwise Tanimoto distances are shown for components of two Ensemblins. These macrocycles are linked by a bold line in the above graph

Distance Function

$$T_d = 1 - T(A, B) = \frac{|A \cup B| - |A \cap B|}{|A \cup B|}$$

Distances between each functional group are computed using this formula to compare their respective bit strings

Enrichment and Selectivity in Affinity-based Screen



Candidates for chemical synthesis must demonstrate both significant enrichment in the selection screen against the targeted protein as well as a lack of enrichment in the Mock screen