

Drug discovery: the delicate dance between biology and chemistry.

The 1970's were the era of phenotypic screening in-vivo in animal models and most compounds went into the clinic without knowing mechanism. The 1990's were the era of mechanistic screening where every compounds mechanism was known but rules and filters were needed to obtain orally active compounds. In the 1970's drug like properties were not a problem, but getting into new discovery approaches was indeed a big problem. From the 1990's onward the problem of getting into new approaches was solved but at the expense of adding a new problem, namely that breadth in biology does not necessarily equate to improved target validation and drug discovery success.

What are some of the future challenges and opportunities in the early stages of drug discovery? I believe to answer this question one must look at the intricate dance between biology and chemistry.

Phenotypic screening will it come back? Maybe, but a phenotypic screen works best against high chemistry topology libraries, egg. natural products and DOS. While phenotypic screening offers advantages in target opportunity space not knowing mechanism is a big disadvantage and chemists may balk at attempting optimization of a phenotypic starting point. Fragment screening would not have been predicted as a hot area ten years ago. Today it is part of the drug discovery arsenal of every large pharmaceutical organization and will I predict soon impact medium and small drug discovery and chemical biology organizations. The major plus of fragment screening is the better coverage of biologically interesting chemistry space with fewer compounds. The downsides are: 1) the necessity of growing a MWT 200 starting point to a MWT 400 clinical candidate and 2) the difficulty of using normal HTS screening technology to detect weak millimolar level ligand target interactions. Ten years after publication of the "rule of 5" we now appreciate the difference between druggability and developability. The properties of orally active legends change in a predictable manner through clinical stages and the profile of marketed drugs has remained stubbornly constant over the last 40 years.

The facts raise all kinds of politically incorrect and provocative questions. Has the breadth in biology research actually harmed drug discovery? Is federal funding too biology centric at the expense of the chemical sciences? Is biological activity evenly distributed throughout chemical space and if not maybe screening diverse libraries to find drugs is not such a good idea. Do you need the same type of chemistry for chemical biology as for drug discovery? And finally, what do you do if your biology target is very appealing but the chemistry side has been historically very challenging?