Putting the Combinatorial back into Combinatorial Drug Discovery - Reimagining Early Stage Drug Discovery

Drug discovery within the biopharma industry has undergone a major paradigm shift over the past decade. Gone are the days of "low throughput" approaches in which small numbers of chemical compounds were tested in animals in the hopes of finding a biologically active molecule. Indeed for much of the past decade, drug discovery within all of the large pharmaceutical companies and many smaller biotechs has shifted towards high throughput screening (HTS) of massive chemical libraries in vitro against defined molecular targets. Expectations were that this rapid "needle in a haystack" approach to finding new chemical entities would yield a trove of promising new molecules to advance into the clinic and provide a solution to lagging industry productivity. Surprisingly though, ten years into this experiment industry productivity continues to drop as measured by the number of new chemical entities being advanced into the clinic and success rates in getting FDA approval for those that do make it into human testing.

One suggestion for the evident shortcomings of this HTS approach is that most of the compounds in these chemical libraries share the same core chemical structure with minor variations around this core. Testing massive numbers of these compounds is therefore unlikely to yield fundamentally new structures. With this in mind, quality, rather than quantity, is now emerging as a focus amongst a handful of drug discovery researchers developing a new approach known as diversity oriented synthesis (DOS). In particular, investigators like UCLA's Ohyun Kwon are pioneering new strategies like DOS to synthesize smaller but more chemically interesting libraries in which there is a much higher degree of structural diversity. Ohyun, who trained at a lab at Harvard University that developed many of the early chemical screening methodologies, is well positioned to develop this next generation drug discovery technology.

After just a few years, her work in collaboration with UCLA professor Fuyu Tamanoi a world-renowned expert in how cells
post-translationally modify proteins to perform their functions, is paying off. The pair has discovered a host of candidate drug molecules against an important set of drug target in the ras pathway that are implicated in cancer. Some of these drug targets have resisted years of traditional HTS-based drug discovery and yet are considered to be promising targets for cancer therapy. The discovery of these new molecules is therefore a particularly exciting proof of concept as well as the beginning of what promises to be an exciting drug discovery program based on these new DOS technologies.

The next steps for the UCLA team are to finish screening the libraries that Ohyun has designed and prioritize which of these "hit" molecules to further optimize. Based on this promising series of results, the group is also screening this library against new drug targets in cardiovascular diseases as well as other oncology drug targets in the hopes of finding additional drug candidates. Working closely with the technology transfer office at UCLA, a patent strategy for protecting these new drug candidates has been put in place so that as commercially promising compounds emerge these may be spun out into a new startup or a larger pharmaceutical company for pre-clinical and clinical testing.

Much has been made about lagging productivity within the pharmaceutical industry, but if these results are any indication it is likely only a matter of time before next generation drug discovery technologies being developed in labs like Ohyun's yield new drugs for major unmet clinical needs.

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