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Tough Times for Medicinal Chemists: Are We to Blame?

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ABSTRACT: In the United States, medicinal chemists continue to face job insecurity and high rates of unemployment. The situation is unlikely to improve in the near future. Is there a light at the end of the tunnel? Is there anything we can do to revitalize our community? The answer may be right in front of us.

Due to the declining number of new drug approvals despite the increase in R&D investment, many pharmaceutical companies were forced to implement downsizing of research operations and aggressive out-sourcing of jobs to low-cost providers. There is no doubt that medicinal chemists have suffered a great deal from the recent consolidation efforts. My heart goes out to the many skilled and experienced medicinal chemists affected by the wave of restructuring measures. Needless to say, it is equally difficult, if not more so, for college and graduate students as well as postdoctoral fellows to cope with the sense of uncertainty as they face arguably the worst entry-level job market in years.

There have been many discussions about what went wrong and who is to blame. Perhaps, easy diseases have been addressed and we are dealing with the remaining complex diseases of which we have little understanding. The ever-increasing regulatory burden has played some role in the increasing costs and time spent on bringing a drug candidate to the market. Obsession with blockbuster drugs has prompted many companies to pursue a similar pool of therapeutic targets (and, as a result, they failed together). In hindsight, maybe our industry has overinvested in medicinal chemistry with the expectation that the findings from the Human Genome Project would bring tremendous drug discovery opportunities, and we are now simply regressing to where we were in the pregenome era.

Unfortunately, as medicinal chemists, we have little control over these problems and challenges. The more disturbing concern is that, even if the pharmaceutical industry regains lost ground in the future, this may not necessarily lead to a rebound in the number of medicinal chemistry jobs in this country. What can we change to reverse the current downward trend in our field? It is a question that haunts many of us now more than ever. After some thought, I came up with one element that we can change——ourselves.

When I began my professional career as a medicinal chemist 16 years ago, drug discovery research operations were turning into a game of numbers. Screening technology has made a substantial improvement over the years and has enabled screening of a larger number of compounds in a short period of time. Medicinal chemists had to make some adjustments to satisfy the appetite of the fast-paced screening paradigm. Synthetic routes that produce a large number of analogs by incorporating a variety of fragments in fewer steps were considered the preferred strategy. Consciously, or subconsciously, molecular design has been driven more by "what we can synthesize" rather than "what we believe is the best molecule".

Unfortunately, this movement has had some unintended consequences. Compounds being made by medicinal chemists nowadays are increasingly becoming modular with a number of flat fragments connected by routine coupling reactions. This is consistent with a recent analysis by Dr. Patrick Walters' group, who found that the fraction of sp^3 carbons for molecules published in the *Journal of Medicinal Chemistry* steadily decreased between 1995 and 2009.[1] These types of compounds turned out to be quite effective for some therapeutic targets, most notably protein kinases. On the other hand, this makes me wonder if we have been exploring a very small area of drug-like chemical space using these compounds.

One of the concerns is the likelihood of identifying drug-like ligands for a given therapeutic target, the so-called "druggability" of the target, has been defined by these compounds, representing a small section of drug-like chemical space. Are aminergic G protein coupled receptors (GPCRs) actually more druggable than other types of targets? Or are we simply overconcentrating on the area of chemical space which contains compounds likely to hit aminergic GPCRs? Is it impossible to disrupt protein−protein interactions with a small molecule? Or do we keep missing the yet unexplored chemical space for protein−protein interaction modulators because we continue making compounds similar to those already synthesized?

Nearly 10 years ago, Dr. Eric Lander eloquently stated his view on druggable targets.[2] "What is 'druggable'? I remember when protein kinases were not considered druggable! So, I don't take much stock in 'druggable' as being a definition of nature. Druggable is merely a description of the current state of our abilities." If I am allowed to make a minor (and biased) change to his statement, I would replace "our abilities" with "chemists' abilities". It is in the hands of medicinal chemists to explore new chemical space and transform targets considered undruggable into druggable.

If penicillin-binding proteins are presented as new therapeutic targets (without the knowledge of penicillin) today, we would have a slim chance of discovering β-lactams through our current medicinal chemistry practices. Penicillin-binding proteins would be unanimously considered as undruggable targets. I sometimes wonder how many other

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potentially significant therapeutic targets have been labeled as undruggable just because the chemical space representing their ligands has never been explored. The declining number of new drug approvals may be at least partially attributed to our biased focus on the limited range of therapeutic targets that we consider druggable. And maybe we are paying the price for our neglect of targets labeled as undruggable.

Another unintended consequence of the feasibility-driven medicinal chemistry practice has had a more direct impact on medicinal chemists, particularly in the United States. In the process of staying current with the numbers game, medicinal chemistry has gradually evolved into "anyone-can-do-it" chemistry. Complex reactions that require considerable knowledge and technical skills are being avoided as much as possible. The choice of target compounds are more often determined by what can be assembled from commercially available starting materials. When entry-level chemists fresh from academic laboratories propose complex target molecules that can only be made by a series of unconventional reactions, how often do we dismiss them by saying, "That's very interesting, but let's be realistic. Why don't you make this series of compounds instead? Three easy steps and you can make several analogs."?

I will admit I am guilty of being a part of this devolution. I later realized that, over the course of time, we have been unknowingly transforming medicinal chemistry into an ideal commodity to be outsourced. The first phase of the outsourcing took place domestically. But it has gradually migrated into other countries, such as China and India, where strong technology infrastructure has been established during recent years and, more importantly, where the skilled work force has become more readily available at lower labor costs. We have little competitive advantage if we continue making products that can be made in the lower-wage parts of the world. This is evident from the thousands of medicinal chemistry positions that have been eliminated in this country.

In his viewpoint article concerning the current status of medicinal chemistry, Dr. Derek Lowe stated that "Medicinal chemists have to offer their employers something that cannot be had more cheaply in Shanghai or Bangalore."[3] I could not agree with him more. Dr. Lowe suggested adaptability as one of the core advantages of chemists. It occurred to me, however, that another way out of the current crisis might be in the opposite direction. How about specializing in what most of us are trained to do, and what we do best, synthetic organic chemistry? Can we take it to the level of our full potential, bring everything we have to the table, take extra steps, and start making molecules that cannot be made elsewhere?

Obviously, this would not make much sense if chemists are working on the existing druggable targets for which efficient ligands can be easily synthesized. However, molecules emerging from the new level of commitment can be applied to the targets long considered undruggable. An insightful analysis by Dr. Brian Shoichet's group revealed that nearly 80% of the ring scaffolds among the natural products were unrepresented among the commercially available molecules,[4] probably due to their limited synthetic accessibility. This may be a good example of unexplored chemical space that can be conquered by chemists with considerable practical experience and technical skill. As wisely pointed out by Dr. Derek Tan's group,[5] this may be the sort of approach that expands the range of druggable targets. If more druggable targets are identified by exploring more challenging chemical space, that should lead to more job opportunities for the most capable and skilled medicinal chemists, many of which can be found right here in the United States.

It sounds cliché, but innovation has created the bulk of American jobs today, and it will most certainly be the force that creates the jobs of tomorrow. We have arguably the most talented and well-trained pool of synthetic chemists in the world, who could contribute innovative ideas to solve the most difficult challenges. However, we have, instead, discouraged innovative and unconventional ideas in the practice of medicinal chemistry. We have not raised the bar for our most capable and skilled chemists. We failed to provide them with the opportunity to achieve their full potential and push the boundaries of medicinal chemistry.

Steve Jobs once said, "When you grow up, you tend to get told that the world is the way it is, and your life is just to live your life inside the world. Try not to bash into the walls too much. Try to have a nice family life. Have fun, save a little money." Computers and drugs are not quite the same, but his statement captures the current mind-set of many medicinal chemists. Maybe we, the medicinal chemists, ought to bash into the walls more often, break some walls once in a while, and explore the unexplored. Is it difficult? Absolutely. Is success guaranteed? Not at all. But this may be one of the few options for medicinal chemists to "have a nice family life, have fun, save a little money" in this country.

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Notes

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REFERENCES

(1) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. What do medicinal chemists actually make? A 50-year retrospective. *J. Med. Chem.* **2011**, *54*, 6405−16.

(2) Eric, S. Lander. *Nat. Rev. Drug Discovery* **2004**, *3*, 730−730.

(3) Lowe, D. B. Nowhere To Go But Up: The Return of Medicinal Chemistry. *ACS Med. Chem. Lett.* **2012**, *3*, 3−4.

(4) Hert, J.; Irwin, J. J.; Laggner, C.; Keiser, M. J.; Shoichet, B. K. Quantifying biogenic bias in screening libraries. *Nat. Chem. Biol.* **2009**, *5*, 479−83.

(5) Bauer, R. A.; Wurst, J. M.; Tan, D. S. Expanding the range of 'druggable' targets with natural product-based libraries: an academic perspective. *Curr. Opin. Chem. Biol.* **2010**, *14*, 308−14.