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Nowhere To Go But Up: The Return of Medicinal Chemistry

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ABSTRACT: Medicinal chemistry, as a field, has moved into new and unwelcome territory. How did we get here, and what might be the way out?

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After all of the recent upheavals in industrial drug research, it is worth revisiting a question that has become more pressing: What, exactly, is the place of medicinal chemistry?

At first, that seems like a strange (or even rather stupid) thing to ask. Most medicinal chemists will be glad to tell you where their place is in drug discovery: why, front and center, where it is always been. However, it is only the employed medicinal chemists who will speak up so quickly, and there are fewer of those than there used to be. Far fewer. Longtime Big-Pharma researchers who've found themselves hunting for new jobs and the chemists who've had more than one small startup shot out from under them now have more motivation (and, unfortunately, more time) to ask where their specialty is going. That is, naturally, part of the even more pressing question of where they're going themselves.

Even when times were better, there was still room to argue. Has there ever been a large drug discovery organization without some good-natured (or sometimes not so good-natured) bickering between the different departments? Medicinal chemists and the various types of biologists have always had opinions about which of them were more central to the whole business. "Without us," the chemists would say, "the rest of you wouldn't have anything to work on. After all, the drug that goes out the door is nothing more than one of our compounds". "But," replied the biologists, "without us, you'd never know that it was a drug at all". These discussions were rather like listening to a liver arguing with a heart about which one of them was more important, but that still did not resolve the question.

Medicinal chemists themselves often had some adjustments to make to their worldview, even just back in their own laboratories. Most new hires had come from academic laboratories where chemistry was an end in itself. You discovered new synthetic methods because discovering new methods was a useful thing—after all, it helped you make more new kinds of molecules, and no one could argue against that as a worthy goal, right? Or you did total synthesis, a field whose traditional rationalizations have taken some hits over time. That is a subject that sets off plenty of arguments on its own. However, no one ever doubted that natural product synthesis turned out very capable and well-trained chemists, and no other area has ever made organic chemistry more like a complex art form.

Coming from a big-time synthetic background, though, industrial drug discovery could be a bit of shock. You did not actually spend much time doing the latest and fanciest reactions. In fact, you tended to avoid them unless you absolutely needed them, which was quite a reversal from how some academic laboratories viewed the world. It turned out that you could often do very respectable med-chem with nothing but some very routine reactions. Medicinal chemistry, it gradually occurred to many new employees, was really just a means to an end. It was the only means in most cases, sure, but that is just because no one had figured out any other way to make drug molecules.

That was not for lack of trying. A neutral observer could be forgiven for seeing the history of industrial med-chem over the past 25 years or so as one attempt after another to shake off all of those chemists. There was the initial rush of enthusiasm for molecular modeling—yes, we're going to stop stumbling around in the dark and instead go zipping right to the answer with our computers and software. Our late 1980s computers and software...oh, dear. Looking back, it all seems kind of bright-eyed and sweet, considering how difficult that task has really turned out to be. Then, there was rigorous modeling's exact opposite, lots and lots of high-throughput screening, and to fill the ravenous screening robot arms, well, there was combinatorial chemistry. No, came the cry, we don't know exactly how these compounds bind, and what's more, we do not care! Not with millions upon millions of molecules to screen day and night! We will get the answers anyway; how hard can it be to find good drug candidates when you have robots on your side?

Pretty hard, as it turned out. While some good things came out of that era, we also produced a lot of junk and wasted a lot of time (and far more of both than we could have done by hand the old-fashioned way!) The more extravagant promises of combichem ended up in the same bin as the more extravagant promises of modeling, stored in the basement alongside some dusty but snazzy-looking hardware for which no one now can locate the manuals. However, in recent years, the industry has finally found a truly effective way to ditch its expensive chemists: lay them off. No one could find another way to get their jobs done, so the only thing left was to find people who would do them for less money. How far you can go with that strategy is a question that is still provoking heated debate, but no one can deny that saving money is the goal or that it has not remade the med-chem world.

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All this means that it is now the absolute worst time ever to be an ordinary medicinal chemist in a high-wage part of the world. The days when you could make a reliable living doing methyl−ethyl−butyl−futile work in the United States or Western Europe are gone, and what mechanism will ever be found to bring them back? There's still a lot of that work that needs to be done, but it is getting done somewhere else, and as long as "somewhere else" operates more cheaply and reasonably on time, that situation will not change.

This means that the best advice is not to be ordinary. That is not easy, and it is no guarantee, either, but it is the only semisafe goal for which to aim. Medicinal chemists have to offer their employers something that cannot be had more cheaply in Shanghai or Bangalore. New techniques, proficiency with new equipment, ideas that have not become commodified yet: Those seem to be the only form of insurance, and even then, they are not always enough.

However, that leads to thoughts of a larger strategy that might help keep the entire field in better shape. One of the other big changes over the past 25 years has been the rise of biologic drugs, and those have not involved much medicinal chemistry at all—but there's no reason for that to always be the case. There are plenty of interfaces between small-molecule chemistry and biologics: drug−protein conjugates, aptamers, chemically stabilized proteins and oligonucleotides, carbohydrates, modified enzymes, and more. These things are going to need the synthetic organic expertise that we can bring (and that no one else has); no one's going to bioengineer a bacterium to make them.

When you think about it, adaptability has always been chemistry's advantage. Medicinal chemists do not specialize as much as biologists do—we can make drugs for whatever part of the body you like, if you give us a few extra days to order up the reagents and hit the literature. We should be using this to our advantage, expanding the limits of our science, helping to drive these areas of study, and making them our own. No one else is better placed to do it. The answer to the problems of medchem just might be to have a bit less chem, to make more med.

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Notes

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