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Medicinal Chemistry: Defining Itself

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What is Medicinal Chemistry?

*M*ost of us can probably visualize a clear answer to this question, but may find it challenging to put a comprehensive yet concise definition of 'medicinal chemistry' into words. The International Union of Pure and Applied Chemistry (IUPAC) definition of the discipline does the job quite well, but how soon will it need refinement? Ten, or maybe even just five years from now? If a group of experienced medicinal chemists were to confidently submit dictionary-ready definitions of this field in their own words, would their submissions agree with each other well enough to be effectively interchangeable? Probably not. The Venn diagram of all the various subdisciplines of chemistry, biology, statistics, pharmacology, and computer science that overlap to classify what is generally accepted as medicinal chemistry is constantly changing its shape through rapid progress and technological advancements.

Like many other scientific disciplines, medicinal chemistry has seen a number of important developments over the past few years that have dramatically changed the way researchers in this field pursue their work. The current face of medicinal chemistry is quite different from what it was even a decade ago. To cite just a few examples of this progress, advances in mass-spectrometry-directed automated purification technologies and the widespread introduction of supercritical fluid chromatography (SFC) for the purification of intermediates and final products has greatly increased throughput and turnaround time for getting new molecules into the drug-discovery pipeline; the adoption of automated catalysis screening has seeded the process for making chiral molecules at both the discovery and development stages; the implementation of in silico screening methodologies has significantly decreased the number of compounds that must be synthesized in order to arrive at a druglike lead compound; the use of computational methods in the early assessment of targets for their drugability continues to improve the selection of high-quality targets.

The fact that such developments come from both the academic and industrial sectors is likely the simultaneous cause

and effect of the fast-paced and highly competitive research environment in which nearly all medicinal chemists find themselves. Medicinal chemistry is not alone in this regard, as researchers in most other scientific and technological disciplines experience a certain degree of time-related stress, be it from market forces or the pressure to publish; indeed, the presence of such pressure is usually a mark of a given discipline's vitality. What is unique to medicinal chemistry, however, is the nature of the academic–industrial relationship, as the two sides have complemented (and on occasion competed with) each other for a long time, and they have been bridged in recent years by an increasing number of collaborative research efforts. In the ideal sense, such collaborations take advantage of the traditional strengths of each side: academic research groups have the flexibility to take on relatively high-risk projects with novel concepts, whereas drug companies have the financial capacity to elaborate very quickly on proven concepts and to develop and fine-tune the chemistry methodology in the course of their typically more risk-avert R&D projects.

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Challenges Facing Today's Medicinal Chemists

An industrial perspective

With or without collaborative projects, the complementarity between academia and pharmaceutical companies is by no means perfect. All too often academics engage in futile refinements of something that may very likely lead nowhere in their hands, but which may benefit from being 'handed over' to private sector R&D. On the other side, the growing concern for intellectual property (IP) protection has led many industrial R&D groups to become increasingly cautious about publishing results before phase III clinical studies are complete, lest they give their competitors anything deemed proprietary. This leads to fewer and fewer truly interesting articles being published on novel drug targets, mechanisms, and approaches, as companies are more protective of their IP advantage, be it real or perceived. In short, due to the highly competitive world of industrial pharmaceutical research, truly novel medicinal chemistry from the private sector takes a long time to reach the journals, if it ever does at all.

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The public and political focus on safety and side-effect profiles of new drugs means that pharmaceutical companies must be very proactive in addressing off-target activities and non-mechanism-related toxicity early on in their medicinal chemistry programs. Thus, safety lead optimization is becoming an increasingly important topic. Studying this is resource-intensive, from both a biology and chemistry perspective, and such resources are costly. This demand comes at a time when the public wants drugs that are less expensive while being safer and more efficacious. The problem is, and will continue to be, finding cost-effective ways of doing the top-tier research needed for novel drugs while keeping costs at a minimum.

An academic perspective

Although medicinal chemists generally work a number of steps upstream of a given drug's appearance in the clinic, all are united by the common ultimate goal of treating disease. Therefore, it is important for both young researchers considering potential projects as launch points for their career, as well as seasoned investigators looking to add to their existing research program, to step back occasionally and assess the global picture of diseases that require particular attention.

Some current examples include diseases that are long standing, such as the inflammatory diseases at large, their pathogenesis, and early stages; psoriasis and associated dermatological conditions are part of the inflammation research field, and more progress is needed in this area. Perusal of any up-to-date textbook in clinical dermatology will show the reader an impressive variety of conditions and an equally impressive paucity of available medicines to treat them.

Additional problems requiring intensified research efforts include: the relationship between diabetes, obesity, and hypertension, and how these three conditions might be treated collectively through a single drug rather than three or four different drugs; vision problems and other age-related health issues that have attracted less attention than what they would deserve in view of the increased average population age in most developed countries; and the treatment of depression, which is another major field for which novel pharmacological models are badly needed. The entire list is very long, unfortunately, as the diseases that we can truly cure are far fewer than those that we can control more or less satisfactorily.

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Finally, *Trypanosomatidae*-mediated disease is another important field of research that has not received due attention, along with a host of tropical infections aptly and unfortunately known as neglected diseases. The drug companies' apparent lack of interest in addressing these persistent problems that affect the majority of the world's population has been criticized, and such sentiments are naturally understandable. The fact remains, however, that the discovery and development of safe and effective drugs requires an enormous investment of time and creative and intellectual resources that need financial support.

There is no easy way around this dilemma, but one approach would be for more academic medicinal chemists to

direct their research efforts toward combating neglected disease. Because doing so may be unfeasible from an industrial point of view given the high risk of these projects, the difficulty of testing the drugs in the field, and limitations in the market, the situation could be assisted by the academic sector. It is easier for academic researchers to establish cooperative efforts with other academic centers and nonprofit institutions dedicated to the discovery and development of drugs for developing countries. With a growing number of people working in this field, not only would there be an overall benefit from the resulting advancements in academic knowledge, but there would be a greater chance of alleviating—and perhaps sooner than otherwise—some of the many needs that are present in regions hardest hit by infectious disease.

Another encouraging approach is through the various public–private partnerships that have been established in recent years. These partnerships make drug company expertise and technology available to their academic/nonprofit partners involved in exploring drugs for the treatment of neglected disease.

An Elusive Definition

It would be interesting to see how many Nobel laureates there are who were awarded the Prize for discoveries that could be considered within the realm of medicinal chemistry. They are likely few and far between. This once again raises the question: what is 'medicinal chemistry'? If one were to try to formulate a list of the kinds of accomplishments a medicinal chemist would have to have in order to ascend the figurative Mount Olympus of this field, an answer seems no easier to come by.

Generally speaking, our modern society enjoys an ever-increasing number of technological and scientific advances made per unit time. It stands to reason, then, that this trend is amplified for fields, such as medicinal chemistry, that are highly interdisciplinary. The excitement of working in such a field is attractive to intelligent and creative people who embrace a healthy challenge. The resulting high concentration of bright and energetic scientists working around the world in industry and academia is the most important reason why medicinal chemistry, for lack of a stable definition, is such a vital discipline today. Indeed our field's ability to elude firm classification is probably a good thing. It may not be easy to define medicinal chemistry, but how much does this really matter? Our field will continue to change with time, but we will always recognize it when we see it, especially if we stay passionate about what we do.

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