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What is medicinal chemistry? – Demystifying a rapidly evolving discipline!

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Medicinal chemistry is a scientific discipline that has progressed rapidly over the last few decades. Facilitated by the technological advancement, the early understanding of medicinal chemistry as "synthesizing bioactive molecules" has become the connecting bridge of a variety of related scientific disciplines. This opinion article will guide you through a brief evolution of this discipline and discuss what medicinal chemistry has evolved to be in this era.

"What is medicinal chemistry?" This question still puzzles even the most experienced researchers working in this scientific discipline and generates a lot of discussions amongst those entering as well as those mature in the profession. The American Chemical Society (ACS)[1] and the European Federation of Medicinal Chemistry (EFMC)[2] have both provided different definitions/descriptions of what they believe to be medicinal chemistry. This opinion article summarizes answers to this broad and controversial question obtained from over 60 people from "all walks of life", including people from academia and industry, ranging from graduate students to established researchers and professors.†

Based on the definitions currently available and the answers that we gathered, a simplified definition would be "the design and synthesis of biologically active molecules to address unmet medical needs". However, this oversimplification ignores the larger historical context of medicinal chemistry and its ongoing evolution. To truly understand this discipline, we need to examine its past, present, and future to determine how it has come to encompass many different scientific domains, and how it is still shaping the world today.

Past

Even though the specific term "medicinal chemistry" was coined after World War II, the early concept of using chemicals to treat ailments can be traced back to antiquity. Ancient people noticed that certain herbs (which we now know to contain natural products with medicinal properties) had therapeutic effects without any explanations of how they magically heal the body. The Sumerians' use of opium dates back to around 2100 BCE.[3] The ancient Chinese herb *ma huang* (ephedra) has been used to treat fevers since 3000 BCE.[4]

During the Renaissance period, Paracelsus urged the early alchemists to discover the chemical essence to develop chemical medicines, especially the inorganic components such as mercury and antimony, forming a primitive idea of "active ingredients". The French courts used to forbid the utilization of chemistry in medicine until Louis XIV was cured of chronic digestive problems with an antimony purge.[5]

World War II is a turning point when the definition of medicinal chemistry developed. After World War II, our advancement in the understanding of pharmacology at the molecular level made it possible to express the biological activity of a compound as quantifiable molecular properties. For example, an IC_{50} represents a substance's ability to inhibit its target. At the genesis of rational drug design, scientists gradually began to manipulate various parts of the molecules and observe the resulting changes in their biological activities. This allowed scientists to determine the crucial structural features of a molecule that contribute to its biological activity. This assay later developed into popular and informative studies called structure–activity relationship studies, which are still a mainstream technique used in the drug discovery and development processes today and often equated by many to medicinal chemistry itself.

Present

Medicinal chemists today are not only making new bioactive molecules, but also improving existing pharmaceuticals. They optimize the structure and, hence, properties of molecules to improve their interactions with target(s) as well as their metabolism, toxicities, and drug delivery dynamics to create medicines

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† The last names of some of those from which parts of the text were inspired are written into parentheses (see Table 1 for details). We thank everyone who provided his/her opinion and apologize for not citing all contributors within the text. Below please find a list of all of those who contributed their answers to the question "What it medicinal chemistry?" that helped write this short opinion article (note: some of our responses came from anonymous sources).

that are selective and have limited side effects (George). Our ever-growing understanding of the various biological pathways makes it possible for us to elucidate a compound's biological target. The advancement of analytical techniques helps us understand how medicines are absorbed, distributed, and eliminated from the human body. The emergence of high-throughput screens combines automated robotic advancement and microliter-scale reactions to achieve the screening of hundreds of thousands of compounds with extremely small amount of sample. This significantly improves the scientific and economic efficiency of the drug screening process and broadens our library of potential drug candidates. In fact, bedaquiline (trade name Sirturo), a recently approved medicine against multidrug-resistant tuberculosis, was first identified in a high-throughput screen.[6]

Our repertoire of potential drug candidates is no longer limited to small molecules but has expanded to biologics that used to be considered exceedingly complicated as drugs. These include, but are not limited to, protein therapy, biological probes and linkers, and antibody-drug conjugates (Ley and Meanwell). Additionally, some pathology has been proven to require multi-protein interactions or complexes. In such cases, developing new classes of molecules that promote or disrupt the formation of multi-protein complexes has been a new forefront in medicinal chemistry (Spielmann). Alternative methodologies, such as exploiting natural product biosynthesis, allow us to access medically relevant molecules that are produced by various organisms while the use of chemical probes help us explore biochemically important processes (Van Lanen). Medicinal chemists are no longer just mixing chemicals to make new drugs. They are utilizing the power of Nature to chemoenzymatically generate new compounds (Garneau-Tsodikova).

Even though most people today still consider medicinal chemistry as the design and synthesis of biologically active molecules, no one would deny that medicinal chemistry has evolved to be the center of a vast variety of related scientific fields. Medicinal chemists connect the communities of analytical chemists, computational chemists, biochemists, chemical biologists, molecular biologists, cell biologists, structural biologists, microbiologists, pharmacologists, toxicologists, and translational medicine experts. They direct the orchestra of medicinal chemistry to collaboratively produce a harmonious composition that generates solutions to health related problems (López Rodríguez) (Fig. 1).

Historically, we have chemists, but now we have a plethora of subfields in chemistry: (bio)organic, (bio)inorganic, biological, physical, theoretical, analytical, material, and nuclear chemistry. All of these can make molecules that are active, but a medicinal chemist makes an active compound into a drug (Garneau-Tsodikova). Medicinal chemists have the additional training/expertise that enables them to take those next steps in developing a drug product from a molecule with *in vitro* activity (Garcia).

Indeed, the innovation of new technologies has sparked imagination and creativity amongst scientists, and made possible what was previously only fantasy. However, even in the Omics era, one should never forget how it is the structure of a molecule, the structure engineered during design and synthesis, that is ultimately responsible for a molecule's activity, side effects, and attrition (or lack of attrition) in clinical states (Bottegoni). Medicinal chemistry joins experts from various fields into a single army, fighting for the common good. Although challenges still exist and await improvement, we use our creativity and collaborative efforts to overcome such shortfalls. For instance, the complex human biology and its countless interconnected biological pathways can make targeting a specific molecule rather difficult, resulting in undesirable off-target effects. However, even these off-target effects can be beneficial for the development of new medicines. Even though Viagra was originally developed for blood pressure control, scientists observed a common side effect, which was later exploited for patients with erectile dysfunction.[7] Additionally, the development of computational chemistry has provided valuable guidance to rational drug design and yielded successful medicines, such as Gleevec, a treatment for a specific type of leukemia.[8] Nevertheless, such cases are relatively sparse and more/better computational models need to be developed (Ngo).

Future

The challenges in medicinal chemistry motivate new generations to collaborate and innovate. At the rate of current technological advances in this era, the boundary between possible and impossible has been blurred. As our knowledge of biology expands, we strive to eliminate unwanted off-target effects. In addition, personalized medicine, which provides treatment tailored to each patient based on the distinctive biology of each human body, will continue to be at the forefront of drug development (Green). This strategy is budding in the field of cancer and infectious diseases and has attracted a lot of collaborative interests. Developing personalized treatment for patients in other areas will allow us to provide the most effective and efficient treatment for that specific patient. Automated synthesis and purification is also on the horizon to free the hands of medicinal chemists and improve the efficiency, and therefore, cost of synthesis (Fosso). However, one should not forget that there is still an urgent need for the identification of new drug targets, which will play a major role in determining the future of medicinal chemistry (Timmerman).

Medicinal chemistry is a precise science and a heavily data driven discipline (Congreve, Thomas). In order to make great medicinal chemistry, one needs to rely on the accuracy of previous discoveries that have provided massive amount of precious information and databases for the current medicinal chemists as a solid foundation to move forward. Medicinal chemistry is also an art where the artist uses a subtle mixture of knowledge, experimental learning, creativity, intuition, boldness, and serendipity to paint the right canvas (Jung and Radi). Medicinal chemistry is an adventure, a treasure hunt that seeks to offer us higher life quality. The

Table 1 List of all contributors (in alphabetical order)

Industry	
Yves P. Auberson	Novartis, Switzerland
Miles Congreve	Heptares, UK
Pascal George	Consultant, former Sanofi-Aventis, France
Laurence Jung	Prestwick Chemical, USA
Nicholas Meanwell	Bristol-Myers Squibb, USA
Gordon Saxty	Fidelta, Croatia
Uli Stilz	Novo Nordisk, Denmark
Andrew Thomas	Roche, Switzerland
Ming-Qiang Zhang	Amgen, Shanghai, China
Academia	
Experienced researchers/professors	
Midori Arai	Chiba University, Japan
Timor Baasov	Israel Institute of Technology, Israel
Giovanni Bottegoni	Istituto Italiano di Tecnologia, Italy
Young-Tae Chang	POSTECH, Korea
Frank Dekker	University of Groningen, Netherlands
Stephen Frye	University of North Carolina at Chapel Hill, USA
George Garcia	University of Michigan, USA
Barry Gold	University of Pittsburgh, USA
Steven V. Ley	University of Cambridge, UK
María Luz López Rodríguez	Complutense University of Madrid, Spain
Vânia Moreira	University of Helsinki, Finland
Rui Moreira	University of Lisbon, Portugal
Shinya Oishi	Kyoto University, Japan
Christian A. Olsen	University of Copenhagen, Denmark
Marco Radi	University of Parma, Italy
Yu Rao	Tsinghua University, China
Maria Santos	University of Lisbon, Portugal
Peter Spielmann	University of Kentucky, USA
Takanori Suzuki	Kyoto Prefectural University of Medicine, Japan
Joseph Sweeney	University of Huddersfield, UK
Katsunori Tanaka	RIKEN, Japan
Henk Timmerman	Vrije Universiteit Amsterdam, Netherlands
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Maria Rosaria Ferraro	University of Bologna, Italy
Marina Fosso	University of Kentucky, USA
Keith Green	University of Kentucky, USA
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And 20 anonymous responses

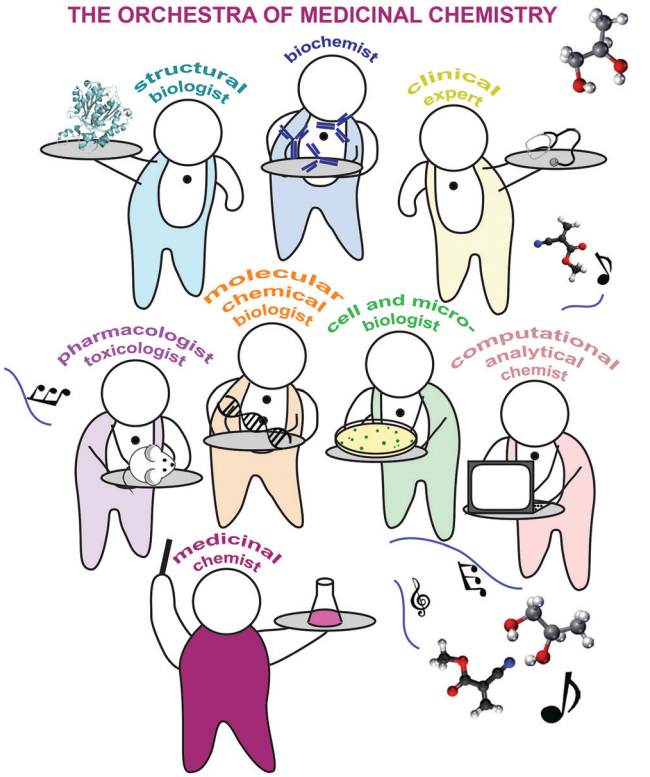

Fig. 1 A cartoon showing how medicinal chemists orchestrate the discovery of new molecules to improve health by coordinating efforts amongst numerous disciplines.

treasure often lies outside the box. Medicinal chemistry is hope for people fighting against diseases (Arai) with medicinal chemists being the front-line solders with an up-lifting attitude.

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