Journal of Medicinal Chemistry

Perspective

Cite This: J. Med. Chem. 2018, 61, 7419−7424

pubs.acs.org/jmc

What Makes a Great Medicinal Chemist? A Personal Perspective

Miniperspective

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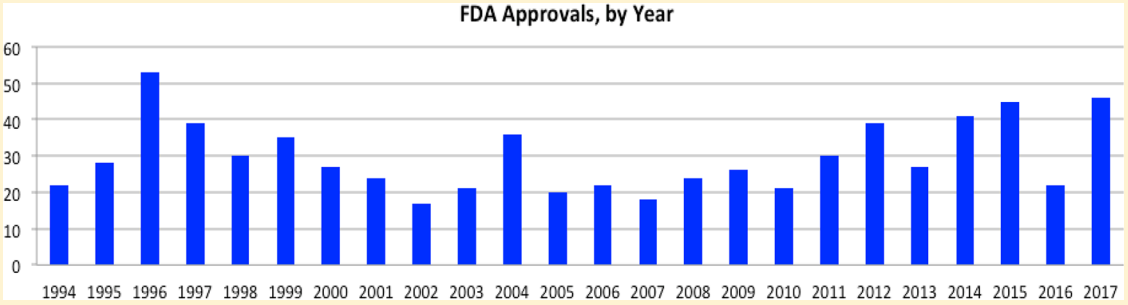

ABSTRACT: Although it is extremely challenging to invent new medicines, I have observed that certain behaviors seem to be commonly found among successful medicinal chemists. Those who exhibit most of these character traits are far more likely to bring new drugs into the clinic and onto the market. And, importantly, organizations that encourage these behaviors are far more likely to be successful. These traits can be broken into two categories: "general" and "discipline-specific". General traits are those that are common to all great scientists, while the discipline-specific ones are more specialized behaviors relevant to the medicinal chemistry enterprise. I describe these traits, and include some specific examples for each of the medicinal chemistry characteristics that I hope will be illustrative. While success in drug discovery is never guaranteed, I believe that embracing and encouraging these behaviors increase the probability of a successful outcome.

It goes without saying that it is very hard to invent new medicines. Breakthrough medicines, and even spectacular drug candidates, are rare indeed because drug discovery is a multiparameter optimization problem: many conditions must simultaneously be met in order for a new compound to have a chance to dramatically improve the lives of patients.

Despite these challenges, in my travels I have met a handful of medicinal chemists who seem to have a real knack for it and genuinely deserve the title of "drug discoverers". What makes those people special?

Here are some behaviors I've observed over the years. Each of these, in my opinion, is just as relevant today as it was decades ago. The pace of change may always continue to accelerate, and success is never guaranteed in drug discovery, but in my experience, the medicinal chemists who exhibit most of these character traits are far more likely to bring new drugs into the clinic and onto the market. And, importantly, organizations that encourage these behaviors are far more likely to be successful.

These traits can be broken into two categories: "general" and "discipline-specific". The complete set of traits is listed in Chart 1. General traits are those that are common to all great scientists, while the discipline-specific ones are more specialized behaviors relevant to the medicinal chemistry enterprise. I include some specific examples for each of the medicinal chemistry characteristics that I hope will be illustrative.

I should say at the outset that experienced medicinal chemists will probably not find this article startlingly original. Perhaps everything worth saying has already been said.[1−11] Certainly there have been many insightful books written about the general characteristics of great scientists[1−5] and quite a few instructive articles about ways to overcome the myriad challenges of drug discovery.[6−11] But I believe there could be value, especially for those earlier in their careers, in a brief communication that summarizes the characteristics of outstanding scientists with an emphasis on the specialized practice of medicinal chemistry.

GENERAL CHARACTERISTICS

They are intellectually curious and constantly learning throughout their entire lives. They have broad interests, read widely, and "connect the dots". They are thinking constantly about their projects.

They stay tightly focused on important problems. They are fearless and relentless in tackling them, no matter how challenging. They want to be moving forward, so they welcome rigorous debate and see the benefits of having to defend their ideas.

They are pragmatic. They look for the most practical ways to solve problems and keep moving forward. They generate the critical data to enable decision-making. They know they have to

Received: September 28, 2017
Published: May 10, 2018

DOI: 10.1021/acs.jmedchem.7b01445
J. Med. Chem. 2018, 61, 7419−7424

Chart 1

General characteristics of great scientists	Discipline-specific characteristics of medicinal chemists
• Intellectually curious and constantly learning	• Always thinking about the target product profile
• Tightly focused on important problems	• Creative drug designers
• Pragmatic	• Manage the properties of their compounds
• Obsessed with data	• Think in three dimensions
• Sweat the details	• Always want another scaffold
• Sense of urgency	• Don't panic over IP
• Recognize great science happens everywhere	• Don't give up on validated targets
• Savvy about and open to new technologies	• Care deeply about biology
• Challenge assumptions	• Always have a good idea of what to make next
• Passionate about their work	• Aren't afraid of tough syntheses
• Aware of their own ignorance; they "know what they don't know"	• Avoid unnecessary complexity
• Resilient	• Re-use whatever they can
• Good communicators	• Know the history of drug discovery
• Often have a very high emotional intelligence	
• Often selfless "unsung heroes"	
• Seek out mentors, and become mentors	

make decisions without perfect information; they can take calculated risks.

They are obsessed with data. They crave it, agonize over it, and constantly question it.

They sweat the details. They look at the raw data, ponder the outliers, and respect the "craftsmanship" of a well-designed experiment.

They have a sense of urgency and always seem to be pushing for the next breakthrough. Often this is driven by a deep-seated sense of compassion or a response to the suffering of a loved one. They are driven more by the hope of being successful than the fear of failure.

They recognize that great science happens everywhere. They want to know about it and to tap into it. They are very aware of relevant progress being made in the wider world. Often, they are highly networked and collaborative.

They are savvy about and open to new technologies. However, at the same time, they are skeptical of grandiose claims. They require clear validation and do not get pressured into deploying unproven tools.

They challenge assumptions and dogma. This trait sometimes makes others uncomfortable, but this does not stop them. They are often contrarians. They are open to new ideas from anyone or anywhere. As a result, they are adaptable, able to "pivot" in the face of new information.

They are passionate about their work. In some cases there is even a kind of joie de vivre about them. Their enthusiasm can help a team to maintain a positive attitude through the many ups and downs, the twists and turns, of a research program. They motivate a team to stay engaged and focused through the years of effort that are essential to crack hard problems.

They are aware of their own ignorance; they "know what they don't know". In some cases they may even appear quite humble despite their manifest successes. They know that drug discovery is a team sport requiring a wide range of talents and perspectives to be assembled in just the right way. Successful scientists have deep respect for colleagues from other disciplines and always try to learn from them.

They are resilient in the face of the constant failure that everyone in drug discovery knows all too well. And they learn from mistakes: their own and those of others. Note that resilience applies not just to scientists but to managers, who must also recognize the twists and turns that science can take and create a supportive environment for great work to take place. Two textbook examples of how to build and maintain productive research environments are Max Perutz' leadership of the Laboratory of Molecular Biology at the University of Cambridge[5] and Peter Medawar's direction of the National Institute for Medical Research in London.[3]

They are effective communicators with their teams, their colleagues, and the wider community.

In my experience, often the truly great scientists possess a **very high emotional intelligence**, being mindful of the complexities of human relations and the needs of their colleagues. (I realize this is not always the case!)

Along similar lines, **often these scientists are "unsung heroes"**, selfless at offering ideas to their colleagues, helping to build effective interactions within a team, giving credit wherever appropriate, and working behind the scenes to anticipate and prevent problems.

They seek out mentors, and when the time is right, **they become mentors.** Exceptional scientists wish to constantly improve and see no shame in seeking out guidance of all kinds from more experienced colleagues. In return, they do not hesitate to offer their time and wisdom to younger scientists whenever asked.

DOI: 10.1021/acs.jmedchem.7b01445
J. Med. Chem. 2018, 61, 7419−7424

DISCIPLINE-SPECIFIC CHARACTERISTICS OF MEDICINAL CHEMISTS

They are always thinking about the target product profile. From the very earliest days of a program, great medicinal chemists always have a clear "target product profile" (TPP)—the characteristics their molecules must achieve in order to be of clinical interest. A clear TPP gives them a good sense of when a molecule is "good enough" in all dimensions to take forward. They also recognize that the TPP can and does evolve in light of new information about the target biology, the likely patient profile, or the competition.

During Vertex's HCV protease inhibitor program we decided to consciously pursue compounds that would distribute preferentially to the primary site of HCV infection, the liver. This changed our thinking about the nature of the design challenge and had the advantage of potentially reducing systemic toxicity by lowering systemic exposure.[12]

They are creative drug designers. They are frequently able to come up with novel ideas, often seemingly out of left field. While many of these ideas, naturally, do not pan out, most of them are worth trying because they are highly instructive and sometimes successful.

Instructive examples abound. A trifluoroethylamine group was employed as an amide isostere in the Merck-Frosst cathepsin K program. This nonhydrolyzable, nonbasic moiety led to compounds that were orally bioavailable, avoided concentrating in the lysosome, and were efficacious in the rhesus monkey bone resorption model.[13] Zanda and others have also found this bioisostere to be effective.[14] DMP-450 (mozenavir) is a diazepine-based C2-symmetric HIV-1 protease inhibitor that displaces a tetracoordinated water molecule that normally serves as a link between a bound inhibitor and the flexible glycine-rich β strands ("flaps") found in the C2 symmetrical HIV-1 protease dimer. This highly creative chemotype was fundamentally different from all other HIV-1 protease designs at the time.[15,16] Finally, the incorporation of boron into drug design has provided a novel and creative warhead for the crafting of reversible covalent inhibitors, leading to several approved drugs so far, such as bortezomib, ixazomib, and tavaborole.

They manage the properties of their compounds. Great medicinal chemists do not fixate on potency; they are always looking for ways to manage the properties of their compounds. At the same time, they do not slavishly follow "rules"; yes, they understand that excessive lipophilicity can lead to challenges, but they let the data guide them. Large, complex, lipophilic compounds can be drugs too if the team stays focused on optimizing the right properties.

Perhaps the "marquee" example in recent history is NS5A, where numerous drugs have already been approved, with additional compounds working their way through the clinic. It took some time for chemistry teams to identify chemical starting points, and at first glance, these molecules look terrifying to many medicinal chemists, with molecular weights in the 750−900 range, and log P values as high as 8. Without doubt, many pharmaceutical companies were hesitant to pursue these NS5A leads. However, quite a few did eventually rise to the challenge, and in each case the successful team was able to optimize these challenging molecules to produce useful medicines.[17,18]

They think in three dimensions. Of course they are quick to take advantage of protein structural information. But even when that is not available, notable drug discoverers are constantly imagining what their molecules look like in 3D, both in water and in lipid, outside of cells and inside, when bound to their receptors or free. Great medicinal chemists welcome any information that helps them visualize their molecules and understand their conformational preferences.[6]

Breakthrough techniques for predictive modeling on membrane permeability have come from the Jacobson lab at UCSF during the past 6 years.[19] This method has been used in combination with a mix of experimental techniques in a collaboration between Jacobson, Professor Scott Lokey at UC Santa Cruz, and Pfizer to study the effect of three-dimensional structure on membrane permeability.[20,21]

They always want another scaffold. Things can go wrong at any moment: PK, tox, synthesis, manufacturing, intellectual property (IP). These are often unpredictable. Having a second, novel, well-behaved chemotype is often the best way to ensure success.

In conversations with medicinal chemistry leaders, my impression is that some organizations will refuse to declare a program to be in the lead optimization stage unless a second promising scaffold has been identified. A personal example comes from one of the first programs at the Cambridge start-up company, Relay Therapeutics (target not disclosed). From the start of the program, the team consciously set out to discover multiple diverse chemotypes for three reasons: to maximize the chances of achieving molecules with good oral bioavailability; to be able to broadly protect their work; and to validate the drug discovery platform that Relay was constructing. Within the first year, the team discovered more than a dozen distinct compound classes with nanomolar biochemical potency. This breadth of chemical matter has enabled the team to move rapidly toward clinical development.

They do not panic over IP. They are very aware of competition and pay close attention when they are working in "crowded" chemical space but also understand that chemical space is vast, and usually it is possible to find and protect another medically relevant molecule.

There are of course many examples of targets for which there are multiple approved drugs with diverse chemotypes. A *few* of the many such targets are HMGCoA reductase, angiotensin converting enzyme, serotonin, the angiotensin-II receptor, the H2 receptor, PDE5, HIV-1 protease, HCV-protease, and HCV-NS5A. While different compounds against the same target will generally share some features in common, each research team has carved out some unique "corner" of chemical space and has optimized to a different end point, with each molecule possessing its own unique strengths and deficiencies. In my experience, great medicinal chemists do not let intellectual property concerns dissuade them from pursuing a well validated target.

They do not give up on validated targets. Great medicinal chemists know that validated targets are rare and wonderful things, worthy of significant effort. Artificial deadlines do not matter with such targets; an effective team will pursue drug candidates despite all obstacles and setbacks, either continually refining the existing compounds or relentlessly looking for new approaches.

There are many instructive examples of this. In the infectious disease space, the confidence in the essential role of the target in the life cycle of the infectious agent can approach 100%. So even in situations where the chemical challenges are enormous, teams are emboldened to persevere. A few examples include

DOI: 10.1021/acs.jmedchem.7b01445
J. Med. Chem. 2018, 61, 7419−7424

HIV-1 protease, HIV-1 integrase, HCV-protease, and HCV-NS5A.

Outside of infectious disease, the work by Schering-Plough that led after many tribulations to the approval of the thrombin receptor antagonist vorapaxar stands out.[22] Starting from the natural product himbacine, an early nonpeptidal antagonist discovered in the mid-1990s, the team did heroic synthetic work on an extremely challenging framework. A first development candidate was found to cause CYP induction, and a *second* was found to accumulate in monkeys. Rather than abandoning the program, the team soldiered on and ultimately discovered a *third* development candidate, SCH-530348 (vorapaxar). And the tribulations were not over. The drug was halted in 2011 in phase III clinical trials because of bleeding issues but later studied in patients who had previously experienced heart attack, stroke, or peripheral artery disease, and in this population, the drug was found to reduce cardiovascular end points and was ultimately approved in 2014.

On a personal note, the idea of sticking with validated targets despite the chemical challenges was hammered into me early in my career by Paul Anderson at Merck. It had been known since the 1950s that oral carbonic anhydrase inhibitors (CAI) could lower intraocular pressure and treat glaucoma. But dogma stated that topical CAI were impossible. The team at Merck refused to believe this, and after a decade of research produced dorzolamide,[23] which was commercialized in two medicines, Trusopt and Timoptic.

They care deeply about biology. Great medicinal chemists know that a deep understanding of disease biology is essential. How will the up- or down-regulation of their targets by drug candidates affect the disease process? Cellular and pharmacological assays must recapitulate, to the best of the team's ability, the relevant target biology in humans, and the medicinal chemist must attain a deep understanding of those assays. They know that the wrong assay is disastrous. Establishing the right assay often takes longer, but the successful scientists understand that such assays are worth the wait. Often such assays may come from academic collaborations, which the experienced chemist welcomes wholeheartedly. Productive medicinal chemists also recognize the value of well-crafted tool compounds that can be used to help shed light on complex biology. They understand that supporting the right biological experiments by providing such tool compounds is one of the most valuable contributions they can make to drug discovery.

Every successful drug exemplifies this. I was privileged to witness Tim Neuberger, a cell biologist at Vertex's San Diego site,[24] wrestle for years with the challenge of developing validated pharmacology models employing cultured human bronchial epithelial cells derived from cystic fibrosis patients.[25] Tim is a true "unsung hero", a quiet but incredibly dedicated and passionate scientist with an uncanny ability to make cells perform in ways that no one else could. It was similarly exciting to watch Minh Vuong's engineering team develop a miniaturized Ussing chamber assay that used Tim's cells to give the discovery team routine access to cell data that much more faithfully recapitulated the disease biology.[26]

A less happy experience came from a consulting visit where it was clear that the discovery team recognized the limitations of their cell assay which they believed was producing misleading structure−activity data. They had a much more physiologically relevant assay in mind, and they were confident they could establish this assay, but they estimated it would take 6−9 months. Unfortunately, because they were under intense time pressure to complete the project, they had been explicitly told to not switch assays. As Sir James Black said,[6] "The great enemy is impatience."

They always have a good idea of what to make next. By constantly sifting information from all around them, productive medicinal chemists usually have a clear path forward. They avoid getting lost in the data; they integrate complex, often conflicting information and make decisions. And in the process, they are open to all manner of models, hypotheses, and design concepts, willing to critically test any good idea from any source.

Vertex started an influenza program entirely based on a phenotypic assay using MDCK cells. This cell assay provided a powerful tool for the early chemistry efforts, enabling the team to quickly advance the series to submicromolar potency while maintaining suitable physical properties and diversifying the chemical matter. These tools enabled mechanism-of-action studies that confirmed inhibition of influenza-specific RNA against several different influenza A strains. Subsequent target identification studies using reverse genetics revealed the target to be the PB2 domain of the RNP polymerase complex. At this point the team shifted seamlessly to a structure-based approach, using crystallographic data to optimize the lead series to produce VX-787,[27] which has since gone into phase III clinical trials directed by Janssen Pharmaceuticals. At both the phenotypic and the structure-based stages, the team knew exactly what compounds they needed to make and how the available data could best be used to support their decision-making.

They are not afraid of tough syntheses. Great medicinal chemists always avoid unnecessary complexity, but sometimes the best molecule is challenging to make. The fact is, synthesis is *not* a commodity; sure, the easy compounds can be made by anyone, but there is still craft, true artistry, in making just the right molecule. How often it seems that the most interesting compounds are the hardest to make! Having powerful synthetic capabilities can make all the difference. And there are countless new ring systems to explore, and there is still huge value in natural products if only we could efficiently make and derivatize them. Plus there is a constant stream of innovation: new catalysts, DNA-encoded libraries, high-throughput optimization of reaction conditions, flow chemistry, PROTACs. Academic collaborations often provide new approaches to synthesis that the great medicinal chemists eagerly embrace.

A fantastic example of this comes from the commercial manufacture of Halaven (eribulin mesylate) by Frank Feng and colleagues at Eisai. The compound contains 19 stereocenters and is the structurally most complex drug substance on the market prepared by total synthesis. Over a period of many years and building on previous work by Kishi on the related halichondrins, the Eisai team developed a scalable 62-step synthesis to provide drug product for clinical trials.[28−30]

A second example comes from the BACE program at Lilly.[31] On the basis of sound conformational analysis and in hopes of optimizing the metabolic and physicochemical properties of their series, they set out to synthesize two highly complex polycyclic analogs. This was successful after heroic synthetic effort, with the two compounds requiring 17 and 21 steps respectively, with overall yields of roughly 0.1%. Unfortunately, neither analog offered any improvement in binding or pharmacokinetic properties. While this effort ultimately did not advance the program, it was well considered, bold, and efficiently executed. The Lilly work highlights the importance

DOI: 10.1021/acs.jmedchem.7b01445
J. Med. Chem. 2018, 61, 7419−7424

of both deep synthetic know-how and courage, exactly the skills and character traits needed in order to crack very hard problems.

They reuse whatever they can. As the saying goes, "great artists steal". Drug hunters unashamedly repurpose anything and everything (whole molecules, scaffolds, functional groups, synthetic methods, assays, animal models), remaining focused not on novelty per se but rather on doing whatever is necessary to make the drug.

A noteworthy example of this happened on the IL1β converting enzyme (ICE; caspase-1) program at Vertex. In early 1994 we had solved the crystal structure of ICE[32] with a tetrapeptide aldehyde covalent inhibitor and were trying to select from among various peptidomimetic design strategies. Guy Bemis noticed that the active site of ICE closely resembled that of chymotrypsin fold proteins. It must be stressed that this was totally unexpected because the global fold of caspase-1 was entirely different from chymotrypsin. The ICE peptide inhibitor was making the same patterns of hydrogen bonds and adopting the same backbone conformation as were typically found in inhibitors of chymotrypsin-family serine proteases such as trypsin or elastase. On the basis of Guy's observation, the medicinal chemistry team leader, Michael Mullican, prioritized a range of bicyclic S2−S3 peptidomimetic scaffolds that had been successfully used against other serine proteases, including the pyridazinodiazepines.[33] This work led to VX-740 (pralnacasan), which was taken into phase IIb clinical trials for rheumatoid arthritis. In a classic example of simultaneous discovery, the same scaffold had been explored at approximately the same time by the team at Sterling-Winthrop.[34]

They know the history of drug discovery. They have absorbed the "lore" of the field. They effortlessly recognize existing drugs and often know the history of how those drugs were discovered. They know what has been tried before and what to watch out for. They celebrate the craft of medicinal chemistry and are always interested in trading stories with other accomplished colleagues.

I have attended the Gordon Research Conference on Medicinal Chemistry many times, and quite a few of us try to go hiking every afternoon. During these hikes, it is common for broad-ranging conversations to ensue. I am constantly amazed at how knowledgeable great chemists are about the history of the field and how effectively they can fold this expertise into their current practices.

As mentioned at the outset, I am not sure that this perspective offers any truly new advice, but I hope it is useful to some medicinal chemists, particularly those just starting out in their careers. And perhaps it may even serve as a helpful refresher or checklist for the more experienced.

The last point to make is that of course success is never guaranteed in drug discovery, and no "checklist" can sufficiently capture the set of behaviors required to navigate the variegated and often baffling experience of drug-hunting. Nonetheless, I would contend that such a list provides an excellent *starting point* for medicinal chemists in search of breakthrough medicines.

I welcome comments, especially from those whose views are markedly dissimilar to those expressed here.

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Notes

The author declares no competing financial interest.

Biography

Mark A. Murcko has contributed to seven marketed drugs in the fields of glaucoma, HIV, HCV, and cystic fibrosis. He is a founder and board member and was interim CSO at Relay Therapeutics. In addition, Mark is a senior lecturer at MIT and serves on numerous diverse scientific and corporate boards. Formerly, Mark was CTO and SAB Chair at Vertex Pharmaceuticals. Prior to that, Mark worked at Merck Sharp & Dohme in West Point, where he contributed to the first marketed drug to result from a structure-based drug design program. Mark chaired the 2013 Medicinal Chemistry GRC and is currently a member of the GRC Board of Trustees. He is a co-inventor on 40+ issued and pending patents and has coauthored 85+ scientific articles. Mark holds a Ph.D. in Organic Chemistry from Yale.

ACKNOWLEDGMENTS

I acknowledge Paul Anderson, Jack Baldwin, Peter Bernstein, Bill Greenlee, George Hartman, and John Lowe, each of whom provided stimulating comments on this perspective. Of course I am thankful for that, but I am far more grateful for their mentorship over the years and for their exemplary success at discovering important new medicines, which has benefited countless patients and provided great role models for all of us.

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DOI: 10.1021/acs.jmedchem.7b01445
J. Med. Chem. 2018, 61, 7419−7424