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Improving the Efficiency of the Drug Development by Expanding the Scope of the Role of Medicinal Chemists in Drug Discovery

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ABSTRACT: Improvements in the efficiency of the drug discovery process are needed in order to deliver life-saving medications to patients in a more cost-effective manner. While there are many reasons that the efficiency of this process has not gotten better, this Viewpoint proposes that the lack of integration of the three major disciplines (discovery, development, and clinical trials) plays a significant role in the ongoing high rate of failure in clinical trials for innovative drugs. Several specific proposals are made that may help to provide more integration, so that the gears of the human-driven drug discovery machine may mesh better in the future.

Medicinal chemistry began well over a century ago with a theoretical framework (the pharmacophore or "magic bullet" concept)[1] and a general experimental workflow (synthesis, *in vitro* biological screening, *in vivo* efficacy, and safety evaluation in animal models, followed by clinical application), which was based on the prescient insights of a physician−scientist named Paul Ehrlich.[2] Dr. Ehrlich was awarded the Nobel Prize in Medicine in 1908 for his achievements in immunology. However, most notable to medicinal chemists, his accomplishments also included the discovery and the clinical implementation of Salvarsan, a synthetic organoarsenic derivative that was the first effective treatment for syphilis and the first synthetic drug.[2,3] Ehrlich's farsighted wisdom is especially notable with the recognition that, despite numerous advances since his time, the overall experimental approach that he developed (multiple iterations of compound collection synthesis and *in vitro* screening, followed by *in vivo* efficacy determination) has not fundamentally changed and would be readily recognizable to Ehrlich, were he alive today; see Figure 1.

For the past 12 years I have been involved in a project targeting the collaborative discovery, development, and clinical planning around an innovative cancer drug (sudemycin D6, currently in IND enabling toxicology studies) with a large team of scientists, physician−scientists, and drug development experts.[4,5] During this time I have been focused on bridging the gaps in our not-for-profit drug discovery and development 'pipeline' due to my intense interest in keeping this project moving toward the ultimate goal of benefit for patients. This experience has led me to adopt my current viewpoint, which is that too many experts in the fields of drug discovery, drug development and medicine have become insular in their own perspectives. I am sure that many others have a similar opinion, so in the following I will make some specific recommendations that might facilitate a process of reintegration among the siloed fields within drug discovery, development, and clinical trials. I also recognize that this is not a trivial goal, but I believe that it is worth the effort and think that medicinal chemists can play an important role in this process.

Practitioners of drug discovery know all too well that the challenges in the field have only increased over the past century, despite the dramatic advances in molecular biology, organic chemistry, target validation, pharmacology, and drug development.[6] This fact is demonstrated by industry metrics, which show that small molecule FDA drug approvals have remained mostly flat on average over the last two decades (see Figure 2). More importantly the efficiency of the process (number of INDs succeeding in FDA approvals) remains at a disappointing 5−10%, depending on the indication.[7] In fact, the rate of clinical success per IND has actually *decreased* since the 1970s.[8] This is despite many periods of highly touted "new technologies" that were expected to improve the efficiency of the drug discovery process, which have collectively increased the opportunities in drug discovery without increasing the quantitative effectiveness of the process.[7] Naturally many experts have correctly argued that the flat rate of annual new NDAs is in part due to the fact that the "low hanging fruit" have already been picked. However, this does not explain our lack of progress in improving the success rate of INDs to NDAs, and this lack of efficiency is a major problem in our field.

Though it is possible to identify many potential weaknesses in the drug discovery process as currently practiced,[8] perhaps it is informative to examine the most basic architecture of the collective drug discovery, development, and clinical practice processes, and to look there for overlooked weaknesses. Along these lines it strikes me that the most notable weaklink in these processes is the ongoing and increasing fragmentation at

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Figure 1. Three major drug discovery and development stages. Normally as a drug candidate advances through each stage the project personnel will change dramatically because of the need for different expertise. However, the handoff process often occurs with a great loss of continuity, and often with a loss of the individuals who are the best project advocates.

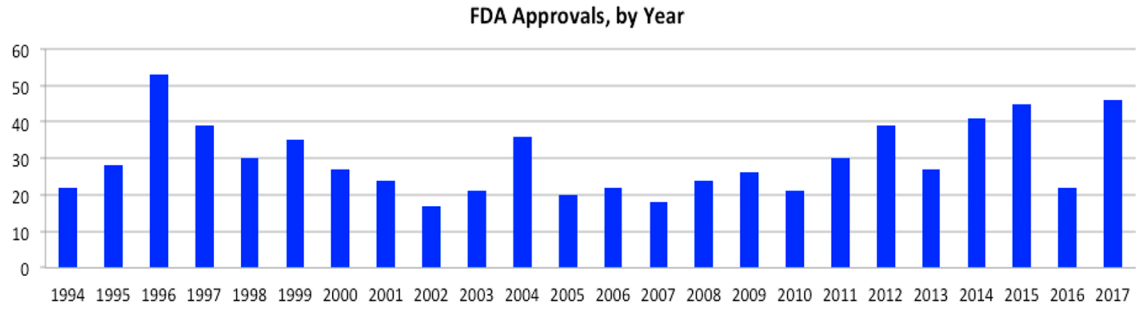

Figure 2. FDA approvals, by year. Reprinted from ref 9. Copyright 2018 American Chemical Society.

the interfaces between discovery, development, and clinical trials. Dividing these different fields has many obvious advantages from a process management perspective, since each requires a very different skill set. Also, these fields have evolved different cultures, unique technical lexicons and their own discipline-oriented thought-patterns. *Unfortunately, this disintegration of the fields within drug development has become monolithic in its self-reinforcing amplification*. Medicinal chemists and discovery biologists will often interact at project meeting and scientific conferences but do not interact with development scientists and mostly consider each other's fields as "cut and dry". Clinicians may interact with discovery scientists in academia but not on a project basis in industry, and almost never with scientists in development. The English language even lacks a single technical term for the unified process that spans discovery to clinical practice, which indicates that this process is not perceived of as an integrated process by many of us. The culture of discovery is correctly based on the idea that free-wheeling brainstorming is critical to the work, which is in stark contrast to the clear need for strict regimentation and protocol adherence in the drug development workflow. My own experience shows me that though these divisions seem natural and comfortable, they can come at a high cost to the overall success of a project, unless significant competent effort is provided to maintain continuity. Many discovery and development groups consider a project "successful" if it leads to an IND filing and the *initiation* of a clinical trial. However, too many drugs fail in Phase I–III for this metric to be an accurate representation of anything more than a very provisional success. My viewpoint is that more "grassroots" effort needs to be applied and that much more cross-training needs to be implemented, along with better metrics for success through the IND and clinical trial design phases.

Naturally the question arises, "How do we better integrate the entire process of drug discovery, development, and clinical practice?". I think that many medicinal chemists can step up and smooth out the gaps between disciplines by becoming longer-term project advocates at all stages within this process. Realistically, this would best be done from the bottom up by increasing the inclusion of suitably skilled discovery scientists in development project teams and more involvement of development teams in the clinical trial design. Currently it is not unusual to see pharmaceutical executives discourage discovery scientists from significant participation in development projects, and most development scientists are not extensively trained in clinical design. Ironically it is has been argued that discovery scientists may be too strong of an advocate for their molecules, despite the fact that an evidence-based advocacy may be the missing ingredient in many project teams. In my experience, devil's advocates are never in short supply, but good scientists will often find solutions to the problems that matter to them, if their voices are not drowned out by reflex pessimists.

Another way to improve the integration of the drug development pipeline would be through improvements in formal education scope and by broader training of young scientists, especially in medicinal chemistry. A recent perspective has been published that does an excellent job of describing the characteristics of a great medicinal chemist.[9] Historically many companies have favored hiring chemists from "hard-core" synthetic groups, especially with a focus on natural product synthesis, since this type of training develops solid problem-solving skills and outstanding expertise in organic multistep synthesis. These chemists are then expected to learn biochemistry, biology, pharmacology, ADMET, and other aspects of the art of medicinal chemistry on the job, over an 8–10 year period before they can be considered "seasoned" and therefore scientifically independent. Medicinal chemistry doctoral programs in schools of pharmacy have not usually been seen as the best training grounds for medicinal chemists, though these views may be softening recently. One of the dynamics that has been going on for decades in departments of chemistry is the often-seen desire among academics to maintain "pure" chemistry; this is in direct conflict with the need for multidisciplinary integration. It is worth mentioning that some top notch upcoming academic groups have excellent records in regard to balancing "pure" natural product synthesis with excellent training and industrial collaborations.[10] This is an excellent model for the more integrated training of the next generation of medicinal chemists, but this will also require continued growth in the discovery of new biologically active natural products!

My observations indicate that medicinal chemists have the opportunity to improve how we discover drugs, by individually broadening the horizons of medicinal chemistry through our

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Table 1. Some Possible Steps for Medicinal Chemistry Involvement in the Integration of Drug Discovery, Preclinical Development, and Clinical Development

Education

- **Continue to train chemists in natural product total synthesis but include analog synthesis and biological assays as an integral part of dissertation projects**
- **Require biochemistry for synthetic chemists pursuing doctorates**
- **Medicinal chemistry post-doctoral programs can strive to be more relevant to industrial training with industry input and partnerships**

Industrial On-The-Job Training, Project Organization and Scientific Culture

- **Cross disciplinary symposia and seminars for discovery scientists and developmental scientists focused on topics at the interface of medicinal chemistry with pharmacodynamics, assay development, toxicology, and formulation sciences**
- **Include discovery 'program advocates' in the preclinical and clinical development process to assure scientific continuity and updated project related scholarship at all stages of development**
- **Cross disciplinary journals should include both discovery and development publications**
- **More cross disciplinary meetings and talks should be developed through partnerships between professional chemistry organizations and medical organizations**

own work, by seeking more integration, and by moving beyond the metric of how many drug candidates are delivered to development groups. Those of us who are engaged in this work know very well that advocates are essential to moving a drug discovery project forward, yet the standard methods for advancements of projects through discovery into development normally involves personnel changes that may lead to the loss of important advocates, including discovery medicinal chemists. My recommendations are summarized in Table 1, foremost among these thoughts is the idea that medicinal chemists should seek to be more involved in IND development, and even clinical design, with the implementation of clinical success as the most important metric of project success. Of course, this can only be truly successful if medicinal chemists can more productively interact with clinicians and drug development experts! These are very challenging goals but, if implemented, they could surely increase the efficiency of the drug discovery process and therefore ultimately deliver more effective medicines, at a reduced cost to patients. I do hope that these ideas will provoke a discussion between experts in education in chemistry and medicine, and pharmaceutical and biotech executives. Medicinal chemists in academia and industry should take the initiative to start these discussions since they play a central role in the process and are major stakeholders in the process.

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Notes

The author declares no competing financial interest.

REFERENCES

(1) Guner, O. F.; Bowen, J. P. Setting the record straight: the origin of the pharmacophore concept. *J. Chem. Inf. Model.* **2014**, *54* (5), 1269−83.

(2) Riethmiller, S. From Atoxyl to Salvarsan: searching for the magic bullet. *Chemotherapy* **2005**, *51* (5), 234−42.

(3) Lloyd, N. C.; Morgan, H. W.; Nicholson, B. K.; Ronimus, R. S. The composition of Ehrlich's salvarsan: resolution of a century-old debate. *Angew. Chem., Int. Ed.* **2005**, *44* (6), 941−4.

(4) Webb, T. R.; Joyner, A. S.; Potter, P. M. The development and application of small molecule modulators of SF3b as therapeutic agents for cancer. *Drug Discovery Today* **2013**, *18* (1−2), 43−9.

(5) Lagisetti, C.; Palacios, G.; Goronga, T.; Freeman, B.; Caufield, W.; Webb, T. R. Optimization of antitumor modulators of pre-mRNA splicing. *J. Med. Chem.* **2013**, *56* (24), 10033−44.

(6) Campbell, I. B.; Macdonald, S. J. F.; Procopiou, P. A. Medicinal chemistry in drug discovery in big pharma: past, present and future. *Drug Discovery Today* **2018**, *23* (2), 219−234.

(7) Kamb, A.; Wee, S.; Lengauer, C. Why is cancer drug discovery so difficult? *Nat. Rev. Drug Discovery* **2007**, *6* (2), 115−20.

(8) Hay, M.; Thomas, D. W.; Craighead, J. L.; Economides, C.; Rosenthal, J. Clinical development success rates for investigational drugs. *Nat. Biotechnol.* **2014**, *32* (1), 40−51.

(9) Murcko, M. A. What Makes a Great Medicinal Chemist? A Personal Perspective. *J. Med. Chem.* **2018**, *61* (17), 7419−7424.

(10) Baran, P. S. Natural Product Total Synthesis: As Exciting as Ever and Here To Stay. *J. Am. Chem. Soc.* **2018**, *140* (14), 4751−4755.

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