INSIGHTS FROM THE INVENTOR OF CRIZOTINIB
A shift in drug development priorities brings the patient in focus and demands more from medicinal chemists.
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Dr. Jean Cui is an expert oncology drug designer with over 18 years experience in the pharmaceutical industry. Dr. Cui led the design and development of crizotinib (Xalkori®, Pfizer), one of the most celebrated precision medications for non-small cell lung cancer, and has been instrumental in the development of numerous other oncology medications. Her contributions to the field of cancer therapy have been recognized with multiple prestigious awards. In 2013, Dr. Cui founded TP Therapeutics, a structure-based drug design company dedicated to the discovery and development of precision medicines for cancer and other diseases. Dr. Cui shares her views on precision medicine and the role of the medicinal chemist in the future development of targeted drugs.
YOU HAVE FOUNDED A NEW DRUG DEVELOPMENT COMPANY CALLED TP THERAPEUTICS, WHERE “TP” STANDS FOR “TURNING POINT”. WHY THIS NAME?

Oncology and the development of cancer treatments has undergone a transformation since the first targeted medications, like gleevac, were approved for clinical use. Evidence of this transformation comes from the increasing number of streamlined drug approvals that are bringing high-efficacy medications to cancer patients with a specific genetic profile. At the turn of the 21st century, drug development companies were still looking for “blockbuster” cancer drugs. The development focus lay in targeting as many diagnosed patients as possible and companies were repeatedly disappointed during clinical trials when the drugs exhibited low efficacy. Development focus has now shifted to identifying the right target for a drug and consequently also identifying the right patient for the clinical trial. This model was at one point considered a specialized case. Now it is a widely used model that is generating an arsenal of precision medicines, like crizotinib and ceritinib, that exhibit extremely high efficacies in small subgroups of the patient population. We have witnessed a turning point in the way we design and develop drugs and the goal is that these drugs are also a turning point in the patient journey.

IN YOUR VIEW, WHAT FACTORS HAVE DRIVEN DRUG DEVELOPMENT TOWARD THIS TURNING POINT?

Catalyzing this turning point in the development of cancer drugs is undoubtedly that the first targeted medications blazed the path for the latter ones. These first medications led to the insight that observed low efficacies were at least in part due to heterogeneous patient populations in clinical trials. These first medications introduced the critical component of a diagnostic tool that serves to stratify the patient population and identify those individuals who benefit the most from a given drug. Then, increased knowledge about disease and drug action mechanisms, as well as new technologies that facilitate patient stratification, have made more efficient the application of what was learned from these first medications to the development of more precision medicines.

WHAT CHANGES HAVE CHARACTERIZED THIS TURNING POINT IN CANCER DRUG DEVELOPMENT AND WHAT WILL BE SOME OF THE CHALLENGES LOOKING INTO THE FUTURE?

There has been a distinct shift in the priorities of drug development workflows to accommodate the new mentality underlying precision medicines. Criteria for decisions about the direction of a development program emphasize drug efficacy rather than market share. The patient now occupies a central role in development from the very beginning, rather than first making an appearance once the drug is released for clinical trials. Development teams have evolved from siloed units looking for a “magic bullet” for disease to agile collaborations that work toward a narrower goal, generate insights at the interface of multiple disciplines and respond quickly to an ever increasing influx of data and knowledge about disease mechanisms, target characterization, and compound properties.

Awareness about and assimilation of precision medicine has increased. This will lead to greater pressure — from regulatory agencies, from healthcare providers, from tax payers — to deliver the highly effective medications that physicians need. Another trend I see is that precision medicine is an ongoing and cumulative process. The work will not end when we have developed a medication targeting each known cancer patient group. Each developed drug brings us to the next cycle where predicting drug resistance informs the development of next-generation medications.

One of the biggest challenges in the development of precision medicines is finding the right patients for a clinical trial. The patient subgroups that benefit
from these drugs are generally small so a large starting population has to be screened to get sufficient trial participants to generate statistically relevant results. This is an issue that affects all drug developers and discussions are underway to find solutions. One option is a collaborative, central trial registration process where patients are screened centrally and assigned to clinical trials based on their genetic characterization.

Another challenge is the need to systematically reduce development costs, especially at early stages. Smaller drug companies will play a crucial role here because they are more flexible and successful in creating lean development workflows. The identification of a target should be based on medical need and the development should be informed through personal contact with patients and physicians so that relevant pharmacokinetic and pharmacodynamic requirements are identified and resolved as early in development as possible. Streamlining the process, emphasizing quality of the drug in development, collaborating to accomplish all necessary development components as efficiently as possible, are all ways of keeping costs down. However, with early drug development taking place in smaller biotech companies, the translation of their work to the clinical stage remains a bottleneck. Here, business development teams need to be savvy and make strong business cases for the continued development of a drug candidate. Furthermore, they must expand their scope to include non-profit and governmental organizations, in addition to the larger members of the pharmaceutical industry.

WHAT IS THE ROLE OF THE MEDICINAL CHEMIST IN THE DEVELOPMENT OF PRECISION MEDICINE AND HOW CAN YOUNGER GENERATIONS PREPARE TO MAKE CONTRIBUTIONS IN THIS AREA OF RESEARCH AND DEVELOPMENT?

The medicinal chemist carries a great responsibility. Ultimately, it is his or her job to take all the knowledge and work from stakeholders involved in the development of a drug and transfer it to the patient in the form of an effective and safe medication. Thus, he or she strives to make a drug as perfect as possible; to maximize its therapeutic index.

The adjective “medicinal” already alludes to the complexity of the work and, consequently, the demands on a medicinal chemist. He or she must understand biology, must be a data scientist, must be familiar with the full spectrum of assays and analyses that inform his or her design work. A medicinal chemist must remain up to date on developments, always look for new potential targets, new applications for a candidate drug and new ways of designing molecules to meet often contradictory requirements. Looking into the future, as more discovery and optimization work is conducted at smaller biotech companies, the medicinal chemist will also be expected to control development costs, to seek new resources, and to interact collaboratively with a growing number of stakeholders that can inform his or her work. Though perhaps a daunting prospect, this increased responsibility will be accompanied by a greater and more direct impact of his or her work on the well-being of patients.

For a future career in medicinal chemistry,
nothing can replace knowledge acquired through experience. Academic training is only the beginning of the medicinal chemist’s preparation. He or she must continue to learn from the work of designing and optimizing a compound, from the often overwhelming information that he or she must integrate, and from the people with whom he or she interacts. Important to remember is that this chosen profession is at times very frustrating, but also has moments where you advance in solving a problem and that satisfaction is unmatchable. Be always flexible and creative, and strive to do something different.

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