DOI: 10.1002/anie.201402816

Academic–Industrial Partnerships in Drug Discovery and Development

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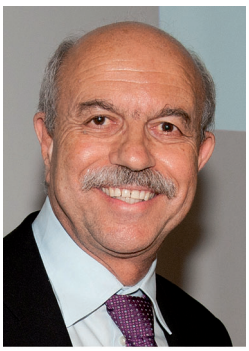

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Thanks to recent discoveries in chemistry, biology, and medicine, the drug discovery and development process is poised for further advances towards the treatment of uncurable diseases. In this context, the pharmaceutical enterprise is facing economic and strategic pressures and is searching for new models and paradigms to remain productive, competitive, and profitable. At the same time, academic investigators in basic research are facing their own problems as funding agencies and charitable foundations are shifting their emphasis to more applied and translational programs. These conditions are leading to merging interests and the emergence of academic–industrial partnerships (AIPs) between the two sectors that bring with them unprecedented opportunities and challenges. Defining and addressing these opportunities and challenges are crucial prerequisites for success of this academic–industrial paradigm of drug discovery and development.

Challenges and Opportunities in Establishing Academic–Industrial Partnerships

The interdisciplinary research programs currently adopted and practiced within the field of biomedical research in academic institutions are becoming more and more transdisciplinary and also include AIPs. This is a healthy development and should be cultivated and promoted by industry and welcomed by academia, since both will benefit from it. This sharing of resources and capabilities is highly complementary at a time when financial pressures do not allow for much fundamental research in industry (unlike past times), while limited resources to academic researchers hinders translation of their basic discoveries into products such as drugs and technologies. Academic researchers also suffer from decreased funding of basic research (compared to past times).

Success in these close AIPs depends heavily on mutual trust and respect of the different cultures and interests of both partners. Industrial institutions have streamlined their operations for optimal efficiency and productivity as measured by drug candidates, approval success, cost, and minimal risk. Academic institutions, on the other hand, pride themselves in the freedom they enjoy in teaching and research, and are willing to take risks, which are all highly conducive conditions for important discoveries. There are also the challenges of sharing intellectual property and timing of disclosure in lectures and publications. It is my belief that in order to preserve academic freedom and culture, dissemination of new results should be possible immediately after filing patent applications, a condition that should satisfy both parties. Bridging the interests and differences of the industrial and academic partners is challenging, but achievable. Willingness to understand the cultures of each other and appreciation of the potential benefits to science and medicine should serve as the motivation for the enthusiasm and commitment needed to embrace AIPs, and succeed in their intent.

Novel Structural Motifs for Medicinal Chemistry

The biological and pharmacological properties of molecules are, for the most part, a consequence of their constituent structural motifs and their connectivities. The latter are therefore of the utmost importance in drug design. Given the well-recognized issues with the traditional polyaromatic "flat" molecules, the recent efforts to escape from this molecular landscape are not surprising. Academic investigators are poised to make significant contributions in this area by venturing into novel structural motifs, particularly those possessing three-dimensionality, through applications of myriad new methods currently available within the armamentarium of organic synthesis. Desirable structural motifs include chiral centers and other three-dimensional moieties, halogen (especially fluorine) residues, macrocycles, and larger molecules. More importantly, the search for new synthetic strategies and technologies to construct novel structural moieties should be intensified with an eye for new molecular space resembling natural and designed molecules of proven biological value, clinical efficacy, and safety. New method discovery and development could, for example, include testing the scope of the new method with medicinally relevant structural motifs and molecules, an endeavor that could best be performed in AIPs. Such partnerships could lead to accelerated translation of new synthetic methods to unprecedented, and much desired, molecular architectures for drug-discovery purposes.

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Natural Products and Natural-Product-like Compounds as Lead Compounds and Drug Candidates

The striking successes of aspirin and penicillin and the revolutions they sparked are undeniable and should continue to inspire drug discovery and development. The same way biologists are continuously striving to demystify the molecules and mechanisms of human biology, chemists should be pursuing the unravelling and exploitation of the vast molecular diversity of living nature in search of novel molecular architectures, biological tools, and lead compounds for total synthesis, chemical biology, and drug discovery purposes. Marine creatures and their symbiotes remain largely unexplored and offer huge and lucrative potential. Remote parts of the land and flora around the world are inviting due to their rich, but as yet untouched biodiversity. Organic synthesis in general, and total synthesis in particular have advanced to such powerful levels of sophistication and efficiency that even the most complex natural products discovered and their analogues can be reached and made available in sufficient quantities for biological investigations and medical applications. Diversity-oriented synthesis as inspired by natural product structures is important to the drug discovery enterprise as it often provides biological tools and lead compounds for further optimization. If practiced with novelty of structure, synthetic strategy, and method development in mind, this branch of synthesis has the potential to make important contributions not only to chemistry and biology, but also to drug discovery and development. Collectively, these natural-product-related endeavors are of great value and special attraction for transdisciplinary academic programs and AIPs.

Biologics and Organic Synthesis

Recently on the rise, biologic drugs (biomacromolecular therapeutics created by biological processes, rather than being chemically synthesized) present different challenges and opportunities to scientists and clinicians than small-molecule drugs. The challenges are particularly acute with antibody–drug conjugates (adc's) for which specific antibodies, special chemical linkers, and highly potent cytotoxic payloads are needed (see Review by Ravi Chari et al. in Issue 15/2014). Linker development and payload synthesis fall primarily in the domain of organic synthesis. Robust linkers that can be selectively cleaved enzymatically within the targeted cells are in demand, and offer unique design and synthesis opportunities, as do payloads such as highly potent cytotoxic natural products. The latter are often rare and complex and their laboratory synthesis and modification become the bottleneck for further development. Calicheamicin γ_1^I, the first payload on an approved adc (Mylotarg), is exemplary of the potency, complexity, and synthetic challenge. The ever-increasing power of total synthesis is capable of rendering such molecules available for biomedical investigations. As an ally, synthetic biology could complement and support synthetic chemistry in this regard. Such adc projects could be carried out most productively in AIPs, for their sophistication and complexity requires not only cross-disciplinary approaches, but most importantly mergers of resources, knowhow, and talent.

Academic–industrial partnerships (AIPs) depend heavily on mutual respect of both cultures

Computational Sciences and Technologies as Tools for Drug Discovery and Development

Combining theoretical advances with the ever-increasing power of computers promises to propel computational chemistry and biology to even higher levels of performance as predictive disciplines for drug discovery and development. Developing efficient algorithms for compiling and mining appropriately designed databases could support creativity and imagination, thereby improving predictivity in drug design. Specific databases may include, for example, biological target–ligand matched pairs and matching molecular pairs that could facilitate ligand and lead identification of newly discovered biological targets, and lead optimization at the drug-discovery phase, respectively, thus turning the art of drug design into a more precise and predictive science. Academic researchers could also be participating both in the advancement and deployment of tools as molecular modeling, in silico docking, and computational suites to predict biological and pharmacological properties.

Cognitive technologies are ideal for application to all decision-making junctures of the drug discovery and development process from target identification to clinical trials, and even to decisions relating to administering the proper medications to patients.

Academic–industrial partnerships are here to stay, at least for a while, and should be embraced and pursued with enthusiasm and commitment by both partners. Preserving academic freedom and pursuing fundamental science, while applying it expeditiously should remain the top priorities in these partnerships.