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Perspective

The Chemistry-Biology-Medicine Continuum and the Drug Discovery and Development Process in Academia

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Admirable as it is, the drug discovery and development process is continuously undergoing changes and adjustments in search of further improvements in efficiency, productivity, and profitability. Recent trends in academic-industrial partnerships promise to provide new opportunities for advancements of this process through transdisciplinary collaborations along the entire spectrum of activities involved in this complex process. This perspective discusses ways to promote the emerging academic paradigm of the chemistry-biology-medicine continuum as a means to advance the drug discovery and development process.

Emerging in the early decades of the 19th century, modern chemistry, organic synthesis in particular, played a major role in the evolution of science by providing molecules, natural or designed, for further investigations and applications. Various enterprises, most notably the dye and pharmaceutical industries, relied heavily for their establishment and advancement on discoveries and inventions in organic synthesis. During the nineteenth and early twentieth centuries, this discipline remained for the most part an isolated science in academia, whose practitioners were interested primarily in advancing it for its own sake through discovery and development of new synthetic reactions and their applications to natural products chemistry. The latter were considered as targets for structural elucidation and total synthesis. This paradigm changed significantly in the second half of the twentieth century when a number of investigators turned their attention to producing sufficient quantities of scarce natural products for biological studies and medical applications. Following the discovery and development of penicillin as an antibiotic, the pharmaceutical industry intensified its activities in the isolation and development of natural products as drugs while at the same time it began to exploit the increasing power of organic synthesis to design, synthesize, and test small organic molecules as potential drug candidates through what became known as medicinal chemistry. The process of rational drug design based on the identification and validation of a biological target followed by medicinal chemistry to find small molecules that would bind and modulate the function of the biological target became the standard paradigm for the drug discovery and development process during the last decades of the twentieth century. At the same time, chemists and biologists in academia began to recognize and appreciate the importance and potential impact of merging their efforts toward the elucidation of biological pathways and disease pathogenesis.

This drive toward merging chemistry and biology gave birth to chemical biology (Schreiber and Nicolaou, 1994a, 1994b), an umbrella scientific discipline; one of the main areas of investigation of this domain is the synthesis and use of small organic molecules of natural or designed origins to probe human biology as a means to gain new fundamental knowledge and pave the way for drug discovery and development (Nicolaou, 2013, 2014b; Nicolaou and Montagnon, 2008; Schreiber, 2011; Wetzel et al., 2011). Tools to elucidate biological pathways and lead compounds for drug discovery are two of the most important objectives of organic synthesis and chemical biology today. The merging of chemistry and biology in academia is now expanding to include drug discovery and development (Waldmann, 2012), often in collaboration with industry. Indeed, during the last 25 years or so a number of lead compounds and drug candidates were developed into approved clinical drugs through partnerships with pharmaceutical and biotechnology companies. Notable examples of such successes include pemetrexed (Alimta, approved 2004) (Taylor, 2011), emtricitabine (Emtriva, approved 2003) (Furman et al., 1992; Saag, 2006), vorinostat (Zolinza, approved 2006) (Marks and Breslow, 2007), pregabalin (Lyrica, approved 2004) (Silverman, 2008), and eribulin (Halaven, approved 2010) (Towle et al., 2001; Yu et al., 2005) (Figure 1). Currently, collaborative research programs between academic and industrial partners are on the increase, leading to the new paradigm of drug discovery and development through academic-industrial (or private-public) partnerships (Nicolaou, 2014a). An example of this is the Accelerating Medicines Partnership between the National Institutes of Health (USA) and ten biopharmaceutical companies and various nonprofit organizations to tackle Alzheimer's, type II diabetes, lupus, and rheumatoid arthritis.

The chemistry-biology-medicine paradigm in academia parallels the traditional drug discovery and development process practiced in the pharmaceutical and biotechnology sectors but differs in some respects and should differ from it in a number of important ways. The chemistry-biology-medicine continuum of research in academia may cover the entire spectrum of activities of the drug discovery and development process (Figure 2) (Nicolaou, 2014b) from pathogenesis of the disease and target identification and validation to lead discovery and optimization and clinical trials, although the latter most likely will need industrial partnerships for technical and financial support. Given the mission of academia, these research and development activities ought to be focused on different or modified

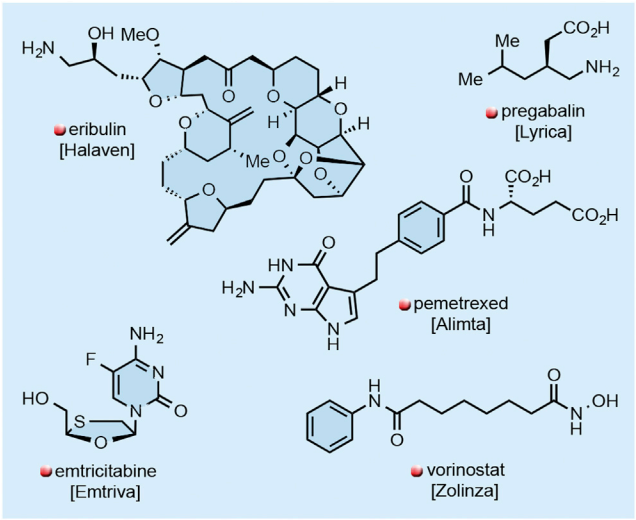

Figure 1. Examples of Drugs Discovered and Developed through Academic-Industrial Partnerships

objectives than those in industry with regards to (1) potential to advance the core sciences involved, (2) potential to lead to new principles and paradigms for the drug discovery and development process, and (3) potential to maximize and balance the high risk/high impact relationship. Due to their complexity and resource demanding nature, these partnerships are almost always obligatory and could include transdisciplinary academic-academic and academic-industrial partnerships among chemists, biologists, computational scientists, and clinicians, and more broadly patients, patient group advocates, policy makers, regulators, and the general public. These initiatives should be undertaken with great wisdom in order to create opportunities that encourage and maintain academic freedom to discover and disseminate scientific knowledge, result in educationally and scientifically challenging and meaningful programs and benefit and reward all participants and stakeholders (Nicolaou, 2014a).

Making Transdisciplinary Research at the Chemistry-Biology-Medicine Continuum a Reality

Although interdisciplinary research at the interface of chemistry and biology in academia has been a tradition for some time, such programs are still on the rise. They are becoming more crucial for success due to the increasing complexity of biomedical research and the new trends and emerging paradigms within the drug discovery and development process, such as:

- Increasing academic-industrial partnerships
- Renaissance in natural product chemistry, biology, and medicine
- Antibody-drug conjugates
- Involvement of clinicians in the early stages of drug discovery and development
- Patient-derived xenografts (PDXs)
- Cancer stem cell biology and targeting for chemotherapy purposes
- Phenotypic screening
- Synthetic method development, novel structural motifs, and drug design synergies
- Rare diseases
- Biomarkers
- Introducing fluorine ^{19}F and ^{18}F into drug candidates and imaging agents, respectively
- Computational and cognitive sciences

These endeavors are becoming more multidisciplinary and transdisciplinary, meaning that more disciplines and closer interactions and exchanges among the participants are required to solve newly defined challenges and exploit the opportunities they present. Such transdisciplinary research may include not only chemistry and biology but also new disciplines, such as bioengineering, nanotechnology, and computational sciences whose potential to contribute to and benefit from such endeavors are becoming evident. Prominent among them are computational science and drug discovery and development, the latter being the ultimate goal of biomedical research (Nicolaou, 2014b).

The reliance of the pharmaceutical enterprise on fundamental discoveries in chemistry and biology provides enormous dividends to society. While the majority of these basic discoveries were made in academia, a good number of them resulted from research in pharmaceutical and biotechnology companies. Pressures in industry in recent years, however, led to shifting priorities and decreasing support for internal basic research, compelling pharmaceutical and biotechnology companies to rely more on academic discoveries to provide the foundations for their research directions and drug discovery efforts. This paradigm necessitates strategic collaborations between academia and industry, which are currently on the rise and in flux. There are a number of strengths and benefits of academic-industrial partnerships, for example:

- Complementarity of academic and industrial expertise
- New funding opportunities for academics
- Potential financial benefits for academic investigators and institutions
- Acceleration of translational research
- Enhancement of multi- and transdisciplinary research
- Enrichment of education and training
- Bridging the gap between discovery and clinical development

However, there are also challenging issues of academic-industrial partnerships as illustrated by the following points:

- Timely dissemination of results in lectures and publications
- Less fundamental and curiosity-driven research
- Issues with career development and job hunting for students due to confidentiality restrictions
- Differences in culture, mission, and operation
- Potential negative impact on academic freedom
- Licensing and royalties
- Time pressures and deliverables

Thus, for such partnerships to be successful, a number of criteria have to be fulfilled and their specific aims carefully defined. The first issue is how to bring the two cultures together

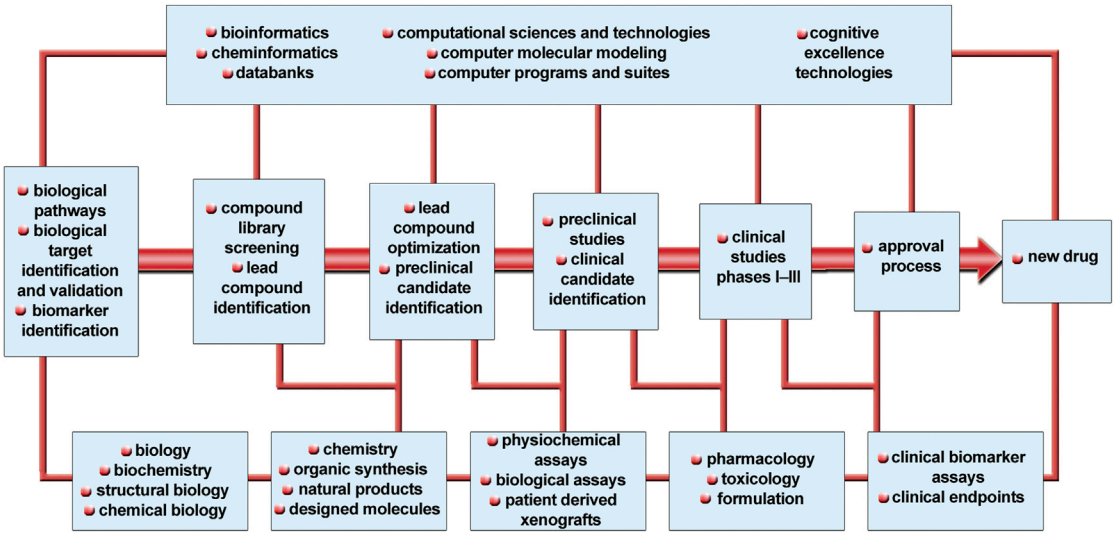

Figure 2. The Modern Drug Discovery and Development Process

The current paradigm of the process (main pipeline, center) begins with the pathogenesis of the disease and identification and validation of the biological target(s) associated with it as well as the identification of biomarkers which become indispensable in personalized medicine (first box, center, from left to right). Screening of compound libraries against the target(s) to identify lead compounds (second box, center) is followed by optimization and selection of preclinical candidates (third box, center) and subsequent preclinical studies that lead to the identification of clinical candidates (fourth box, center). Alternatively, phenotypic screening of compound libraries in biological and pharmacological assays in cells, tissues, or whole organisms (third and fourth boxes, bottom) may precede target identification. Clinical trials phase I, II, and III (fifth box, center) then follow, and, if successful, a new drug application (NDA) is submitted (sixth box, center) to the appropriate agencies for approval as a clinical agent (seventh box, center). The boxes above and below the main drug pipeline (center) summarize the primary driver disciplines and useful technologies and assets deployed in the advancement of the process along the pathway from the identification and pathogenesis of the disease to approval. The current average rate of success of small molecule drug candidates is in the single digits (modified from Nicolaou, 2014b).

with optimal benefits to both. Academics cherish their freedom of thought and enjoy the privilege of curiosity-driven research, as opposed to scientists in industry who are constrained by timelines and other pressures that limit their pursuits to highly focused, streamlined, and mission-oriented discovery programs. The latter are also restricted by intellectual property considerations that compromise the timely dissemination of their findings while the former are under pressure to disclose their discoveries on basic research to the scientific community at large as quickly as possible. On the other hand, scientists in industry often have access to more resources and support facilities and staff to their disposal as compared to academic investigators. The issue of intellectual property (IP) and royalties are often thorny and require patience for resolution. Facing these challenges and balancing the benefits versus the disadvantages is not always an easy task. Bridging the differences, however, is a priority and should be based on mutual respect of the cultures and interests of each side and, above all, trust. The gap may seem wide, but once the specific goals and missions for each side are clearly defined, the parties can settle on a structure that provides the necessary incentives and enthusiasm for success as appropriate in each case (Nicolaou, 2014a).

The emerging chemistry-biology-medicine research paradigm in academia may manifest itself in a variety of ways in an increasing number of areas. Thus, for example, chemistry-driven research programs may be initiated by academic investigators in collaborations with biologists and clinicians that involve chemical synthesis of natural or designed molecules for evaluations as potential biological tools, lead compounds or drug candidates. Strongly supported along the drug discovery and development pathway by experts from each domain at each stage, such partnerships could become powerful vehicles for advancing the sciences of chemistry and biology, improving the drug discovery and development process, facilitating diagnosis of disease, and delivering new drugs. Another emerging paradigm that may involve chemists and clinicians is the design, synthesis and evaluation/utilization of imaging agents such as compounds containing ^{18}F, the latter being suitable for positron emission topography (PET), a highly desirable imaging clinical technique (Kamlet et al., 2013; Tredwell and Gouverneur, 2012). The advantages of PET, however, are compromised by the half-life of ^{18}F that requires short reaction times and rapid transfer to the patient, necessitating special innovations in chemistry and direct interactions of the chemists with clinicians who have access to the patients. The continuously emerging new synthetic technologies for introducing fluorine residues in organic molecules for drug discovery purposes in general, are providing crucial support to these programs.

Other paradigms of particular relevance to the chemistry-biology-medicine continuum include orphan or rare diseases (Jarvis, 2013; Klein, 2009) and cancer (Williams et al., 2013). Attending the bedside of the patient, clinicians can play major roles in the diagnosis and etiology of rare diseases (Jarvis, 2013; Klein, 2009) and deciphering the pathogenesis of newly identified ones. Further biological studies may then be undertaken to fully understand the human biology involved in these diseases with the goal of identifying and validating the relevant biological target(s), at which point chemists can step in to discover enabling biological tools and drug candidates for development as therapeutic agents to complement any cell, enzyme

or gene therapies that may have been developed in the meantime. These academic-medical collaborations may benefit by partnerships with pharmaceutical and biotechnology companies that can bridge the gap between academia and the clinic in terms of preclinical studies of discovered drug candidates. These drug candidates can then be tested for their efficacy and safety by these same physicians who may have initiated the programs in the first place.

The advents of cancer stem cells (CSCs) and patient-derived xenografts (PDXs) (Williams et al., 2013) provide further opportunities to expand the chemistry-biology axis to include the clinic into the biomedical research continuum and extend the traditional role of clinicians in carrying out the clinical phase of drug development by engaging them in the earlier stages of the drug discovery process. Recent discoveries in cancer biology place cancer stem cells on center stage as drivers for cancer growth, proliferation, drug resistance and recurrence. It is, therefore, of paramount importance not only to categorize cancer patients at the personal level but also to define their cancer stem cells at the molecular level through biomarker identification in order to provide guidance for the development of personalized and effective medicines to treat and cure their cancers. PDXs have recently emerged as superior models for evaluating the efficacy of cancer drug candidates because of their closer simulation of human clinical conditions. Pathologists, oncologists, and surgeons are positioned to assist in bringing such cells and tissue specimens into the drug discovery and development process by virtue of their expertise and proximity to patients, thus making the academic chemistry-biology-medicine alliance a forceful new paradigm in biomedical research. To be sure, patients and their advocates will provide their support for this involvement. The various institutions involved should also move decisively toward resolving the remaining challenges and issues as they position themselves to support these collaborations and partnerships (Williams et al., 2013).

Biological Target Identification and Validation

The process of target identification and validation is of extreme importance to the drug discovery and development process (Benjamin et al., 2012; Cong et al., 2012; Futamura et al., 2013; Moellering and Cravatt, 2012; Prinz et al., 2011; Schenone et al., 2013). It often defines not only the start of the process but also the end, given that clinical success of a drug candidate hinges heavily on the full understanding and relevance of the biological target to the intended disease. Indeed, ill-defined and partially validated targets have been increasingly associated with the high attrition rates of drug candidates as their modulation does not lead to the expected efficacy in treating the disease or may result in side effects. The previously adopted and currently widely used paradigm of identifying a biological target against which compound libraries are screened in order to discover lead compounds for optimization serves well in the early stages of the drug discovery and development process but often fails to predict pharmacological properties and clinical efficacy. It has recently been argued that phenotypic and pharmacological testing in cells, tissues and whole organisms of compound libraries may have certain advantages over screening against the biological target in that it increases predictivity of pharmacological success in the latter stages of the process (Cong et al., 2012; Futamura et al., 2013; Moellering and Cravatt, 2012; Schenone et al., 2013; Swinney and Anthony, 2011). This so-called chemical genomics paradigm, however, requires identification of the biological target once active compounds are discovered. Irrespective of which paradigm is employed, the two approaches should merge as soon as possible so as to proceed to the validation stage with parallel and simultaneous efforts involving molecular target screening and pharmacological testing in order to avoid surprises at the later stages of development. Target identification remains a challenging task requiring new tools, methods, and strategies. Thus, the traditional direct biochemical methods involving affinity chromatography are continuously augmented and improved by the development of new techniques. Genetic and genomic methods using knockout animal species, RNAi profiling, and small molecules with well-defined mechanisms of action are routinely employed to identify biological targets, especially after phenotype observations. Combined with bioinformatics and computational inference methods, these approaches are poised to sharpen our ability to identify and validate biological targets. Chemical genomics, employing phenotype screening followed by target identification and validation requires continuous build-up of high quality compound libraries enriched with novel molecular structures and new reagents and methods for chemical proteomics and imaging studies, all presenting challenges and opportunities for synthetic organic chemists. The Chemical Genomics Center at the National Institutes of Health (USA) provides an example of how these technologies are enabling chemical biology studies and, potentially, drug discovery efforts.

Disease-associated biomarkers are of great importance to drug discovery, clinical development, and prescription, especially as we move into the era of personalized medicine (Armitage and Barbas, 2014; Henry and Hayes, 2012; Williams et al., 2013). For example, and as mentioned above, cancer stem cells (CSCs) and their biomarkers are increasingly recognized as a new paradigm for targeted chemotherapy due to their link to the genesis, evolution, and heterogeneity of cancer (Williams et al., 2013). Investigations directed toward elucidating such complex biological systems can be greatly facilitated further by increased collaborations and alliances among academic and industrial groups. Such partnerships are indeed essential for accelerating the drug discovery and development process and lowering its attrition rates. In this context, chemistry can facilitate endeavors in target and biomarker identification through the development of new and improved analytical and synthetic techniques.

Exploration of Nature's Molecular Diversity

Exploring nature's molecular diversity and understanding its biology continues to be enormously valuable for advancements in chemistry, physiology, and medicine (Newman and Cragg, 2012; Nicolaou et al., 2012). Whereas nucleic acids and proteins can serve as biological targets, secondary metabolites (i.e., natural products) are valuable ligands as biological probes, lead compounds, and drug candidates. In addition, natural products provide inspiration and challenges for organic synthesis, chemical biology, and biosynthesis research efforts. The discoveries of aspirin, penicillin, and taxol are exemplary in that respect, for they not only provided lasting medications for people but also advanced the sciences of chemistry, biology, and medicine

in terms of synthetic strategies and technologies, elucidation of biological pathways, and novel treatments of disease (Nicolaou and Montagnon, 2008). The fact that the majority of biodiversity around the world remains unexplored coupled with the impressive record of success of natural products provides a compelling case for continued explorations of the forests, soil, and oceans for further clues to be discovered, translated, and developed into new science and medicines. Unfortunately, the pharmaceutical industry has disinvested considerably from the natural products field in recent years primarily due to the required long term commitment to such projects and the organic synthesis-driven ease of access to small molecules as lead compounds and drug candidates. The present trend toward transdisciplinary partnerships between academia and industry provides new opportunities and dictates renewed initiatives supported by both industrial and government institutions. Augmented by new analytical techniques, modern instrumentation and high tech exploration vehicles and equipment, such explorations of the unknown parts of the Earth may reveal untold treasures for chemistry, biology and medicine. Biosynthetic techniques relying on genetic engineering and synthetic biology offer an alternative and complementary approach to the production of natural products and their analogs. These objectives required, however, long term vision, appreciation of the importance and value of fundamental research, and new resources.

Synthesis and Biological Evaluation of Natural Products and Other Molecules Like Them

Scarce bioactive naturally occurring substances are of special interest because they are likely to remain unexplored unless they become readily available through laboratory techniques. Such compounds are ideal targets for total chemical synthesis (Nicolaou et al., 2012), or synthetic biology (Carothers et al., 2009; Weeks and Chang, 2011) (once their biosynthesis is elucidated). Either or both practices may render them readily available in sufficient quantities for further biological investigations, which may, in turn, justify further studies to determine their pharmacological profiles that may lead to their clinical development and medical applications. Most importantly, employing the developed synthetic technologies, designed and otherwise inaccessible analogs of these molecules may be synthesized and tested for optimization purposes. The numerous examples of successful efforts in this arena over the years should serve as the motivation for intensifying such research programs, whose successes hinge decisively on fueling both the discovery of new natural products and their total synthesis (Newman and Cragg, 2012; Nicolaou et al., 2012) and biosynthesis (Walsh and Fischbach, 2010; Weeks and Chang, 2011).

The relatively recent advent of antibody drug conjugates (ADCs) (Chari et al., 2014; Dosio et al., 2014; Gerber et al., 2013; Perez et al., 2014; Sapra and Shor, 2013; Sievers and Senter, 2013) provides special impetus to natural products isolation, synthesis, and structural modification. Applied primarily in targeted cancer chemotherapy, ADCs require the development of specific antibodies (Hoogenboom, 2005) onto which highly cytotoxic compounds (often rare naturally occurring substances or their analogs) are attached as payloads through chemical linkers. Projects to develop such sophisticated drugs demand a wide spectrum of research activities and expertise along the chemistry-biology-medicine continuum ranging from biological target identification and validation, biomarker identification, cancer stem cell isolation and understanding and antibody development to chemical synthesis, pharmacology, and clinical trials. Such multitask projects demand multidisciplinary structures and serve as drivers for academic-industrial-medical collaborations and partnerships. The discoveries of calicheamicin γ_1^I, maytansine, and dolostatin and their synthesis and modification allowed the development of the ADC drugs Mylotarg (Lederle Laboratories/Wyeth/Pfizer, approved 2000, withdrawn 2010), Kadcyla (Genentech/Roche, approved 2013), and Adcetris (Seattle Genetics and Millenium/Takeda, approved 2011), respectively), demonstrating this new paradigm and providing inspiration and confidence for further investment in the field. Indeed, numerous ADCs are currently in clinical development and many more are in earlier stages of discovery and development (America's Biopharmaceutical Research Companies, 2013a, 2013b). In addition to the payloads, linker technologies (Chari et al., 2014; Perez et al., 2014; Sievers and Senter, 2013) for ADCs are also in demand and present their own challenges and opportunities. One of the most successful linkers to be developed thus far is the enzymatically cleavable (by cathepsin) valine-citrulline peptide moiety, which proved its value in the success of Adcetris. The discovery and development of other cleavable (chemically or enzymatically) linkers possessing the required balance of robustness prior to entrance into the targeted cells and cleavability within these cells would be another important area of interface in chemistry, biology, and medicine. Noncleavable linkers are also applicable provided their remnants do not affect the bioactivity of the payload upon degradation of the carrier antibody within the targeted cell. In addition to the high potency required for the drug, molecular scaffolds, and synthetic technologies are also needed to allow attachment of the payload onto the antibody without compromising the cell recognition ability of the latter, with the minimum number of payload molecules per antibody molecule preferred. Similarly, biomarker research (Armitage and Barbas, 2014; Henry and Hayes, 2012; Williams et al., 2013) straddles the disciplines of chemistry, biology, and medicine and is important for developing cell-specific antibodies, recognizing the targeted cells, and identifying patient populations for specific treatments. The advent of personalized medicine and the realization of its importance is a strong driver for such interface programs and multidisciplinary collaborations, especially in the area of cancer chemotherapy and cancer stem cell biology as mentioned above (Williams et al., 2013).

Synthetic Methods, Structural Motifs, and Molecular Diversity

Although the domain of synthetic method development has traditionally been, for the most part, a thematic area of research, this discipline has recently been widened to include addressing the needs of other areas such as total synthesis, medicinal chemistry, and chemical biology. The emergence of the chemistry-biology-medicine continuum as a unified paradigm cemented by the overarching domain of biomedical research and drug discovery and development provides new challenges and opportunities for the synthetic method development field and its practitioners. Thus, the discovery and development

of synthetic methods and strategies could encompass exploration of the scope and generality of the new reactions with compounds relevant to biology and medicine, especially if the method leads to new structural motifs and molecular diversity or provides more efficient, practical, and cost effective routes to compounds useful for biological and pharmaceutical purposes (Dai et al., 2011). Collaborative efforts at these interfaces involving academic-academic and academic-industrial partnerships should be encouraged and fueled by industry, start-up companies, and Federal and State funding agencies. An example of the latter is the Cancer Prevention and Research Institute of Texas (CPRIT), which funds academic cancer research and industrial commercialization of products for cancer prevention and treatment. Such transdisciplinary research efforts would increase the awareness of the needs and capabilities of the various disciplines, thereby inspiring, driving, and focusing research on important problems to be solved and powerful methods to be applied in the various areas of science and technology covered by the collaborations and partnerships. Such research programs would also promote the use of hitherto neglected chemical reactions that form the huge armamentarium of organic synthesis and have been underutilized due to various reasons, including, to a considerable measure, lack of awareness of the needs of biology and medicine in terms of sharper tools and improved drug candidates (Nicolaou, 2014b). Lying between organic synthesis and drug discovery, chemical biology relies heavily on selective molecular probes for its discoveries. Prudent designs of synthetic strategies and method development to match molecular designs for chemical biology studies are highly fruitful and productive in terms of delivering, in addition to new molecular space for further biological investigations and screening, useful chemistry, and novel lead compounds for drug discovery and development purposes (Schreiber, 2011; Wetzel et al., 2011).

Computational Sciences, Chemistry and Biology, and the Drug Discovery and Development Process

Advances in computational (Sliwoski et al., 2014) and cognitive sciences (Parmenides Foundation, 2014) combined with bio- and cheminformatics could provide important auxiliary tools for chemists and biologists as they attempt to navigate their efforts in chemical biology and the drug discovery and development process (Figure 2, top). Collaborative research at these interfaces involving chemists, biologists, computational scientists, and logicians, among others, could have enormous consequences in ligand matching with biological receptors and for drug design purposes. The dream of biologists and drug designers of being able to design a molecule that would bind selectively to a given biological target and possess the proper biological and pharmacological properties can only come true through such partnerships working in a transdisciplinary manner. Coupled with equally valuable developments in automation in preparative organic chemistry driven by collaborative efforts among synthetic organic chemists, computer scientists, and engineers, such successes in computational drug design have the potential to revolutionize organic synthesis, chemical biology and the drug discovery and development process in terms of speed, reproducibility, predictivity, and efficiency.

Conclusion and Future Perspectives

What started in academia as a shy and reserved interface of chemistry and biology in the last century is now in full throttle and moving to embrace the clinic as well. What is driving this movement is the grand challenge of advancing and accelerating the drug discovery and development process (Figure 2) (Nicolaou, 2014b). Indeed, the chemistry-biology-medicine continuum presents a view of the broader activities and objectives of these disciplines, defines the capabilities and limitations of the drug discovery and development process, and offers a vision for its future. The condition and capabilities and productivity of the biomedical enterprise and drug discovery and development process can only be improved and advanced through the merger and synergy of these sciences. Amalgamated research programs within this expanded scientific landscape should, therefore, be encouraged and nourished. Education and training of young scientists along the same spectrum of scientific disciplines should also be established and advanced in academic institutions through appropriate curricula and research programs to provide the essential talent and expertise. The overarching objectives should be directed toward pushing the frontiers of fundamental science in chemistry, biology, and medicine, expediting translation of fundamental discoveries into new and better drugs, especially for currently untreated and uncurable conditions, and advancing the overall drug discovery and development process to higher levels of efficiency and productivity.

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