SPECIAL ARTICLE

Symposium Review: Drug Discovery, Development and Clinical Research in Academia

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The development of new drugs for the pharmacological treatment of diseases is a costly and time-consuming process. The pharmaceutical industry has traditionally played the main role in the discovery, development, manufacturing and marketing of new drugs. However, in recent years, the role of academia in the process of drug discovery and development, and its eventual translation into clinical applications has steadily increased. At the occasion of their 95th anniversary, the School of Pharmacy at the University of Puerto Rico organized a symposium titled "Drug Discovery, Development and Clinical Research in Academia". This article presents a summary of the symposium presentations and the potential role of academic drug discovery and development as a complement to the pharmaceutical manufacturing industry in Puerto Rico.

The pharmaceutical industry has had a longtime presence in Puerto Rico. Currently, it contributes to one-third of the Gross Domestic Product of Puerto Rico and provides employment to 120,000 highly trained and qualified workers. However, its main focus thus far has been in the area of manufacturing of drug substances (the active ingredients of a drug) and drug products (the vehicle, i.e. tablets, creams, injectable solutions). The patent-expiration of high-volume drugs, the decline of the introduction of new products in the drug development pipeline, combined with recent competition with countries with lower production costs, provide a challenge for Puerto Rico to maintain its attractiveness for new investments. However, its highly trained workforce and experience in the pharmaceutical industry remains an important asset, especially with the introduction of new, advanced manufacturing technologies. Even though in recent years considerable investments have been made in the Biotechnology manufacturing industry in Puerto Rico, an area of opportunity still remains in another aspect of the “Biotech” industry that include the development of both new large biological as well as new small chemical drugs. An important complementary opportunity to the pharmaceutical manufacturing industry will arise when researchers in academia are able to translate their current research into clinical applications, and eventually into commercial applications. Academic investigators at Puerto Rican universities have been successful in attracting federal and private funding in order to support the advancement of their research projects. However, few projects have led to products that directly benefit patients, and thus, that eventually could be brought to market. New discoveries in the area of drug development could lead to such products and, combined with appropriate patent protection, attract new investments in start-up “Biotech” companies. In addition, the local government currently has a major interest in promoting Puerto Rico as a “Bio-Island” and in stimulating investment in “Research and Development”. A review of the factors that determine success in the area of drug development, therefore, warranted the organization of a symposium in this area.

On September 18-19, 2008, the School of Pharmacy of the University of Puerto Rico, on the occasion of its 95th anniversary, held a symposium titled “Drug Discovery, Development and Clinical Research in Academia”. As later described in this symposium review, the discovery and development of new drug therapies for the treatment of diseases, requires a multidisciplinary effort from investigators in basic, applied and clinical sciences. Therefore, one of the main goals of the symposium was to foster relationships between investigators, present examples of successful drug development projects and provide investigators with opportunities to establish new collaborations. An integrative approach towards drug development, its clinical applications, and eventual commercialization was followed throughout the symposium. Topics included the description of the relevance of traditional medicine, natural products, chemical synthesis, activity screening, biochemical and
pharmacological implications, animal studies, clinical research and relevance for patients, patent opportunities and venture capital investments, all of which, eventually, could lead to the introduction of new drugs to the market for the benefit of patients.

**The drug discovery process**

The path towards the discovery, development, and eventual marketing of a new drug is generally represented as in Figure 1 (1) and has been further detailed in the “critical path” initiative as outlined by the U.S. Food and Drug Administration (FDA) (2).

**Target identification:** In target identification, a biological process is identified that is associated with the disease of interest. Traditional biochemical methodology, as well as modern proteomics and genomics approaches can determine if a certain target is implicated in the progression of disease. Selective interference of this target with biological or small chemical molecules can potentially be developed into novel drugs, and eventually can lead to improved health outcomes.

**Assay development:** In order to identify these novel molecules, an assay procedure needs to be developed, which determines the extent of interference of these molecules of interest with the target.

**Screening:** “Lead” compounds that selectively bind to the target can be identified via high-throughput screening procedures, (in some cases more than 100,000 compounds are tested).

**Lead development:** In subsequent lead development, the compounds are modified in order to optimize the binding for better activity, and their effects in animal models of the disease are investigated.

**Preclinical studies:** In preclinical studies, required before submission of an Investigational New Drug (IND) application to regulatory agencies, the pharmacokinetic and pharmacodynamic parameters of the new compound, as well as the potential for metabolism and toxicity are determined in suitable animal systems. Furthermore, a drug dosage form is developed for administration of the drug to patients. During the above-described process preceding a Phase I clinical study, there are multiple factors that determine whether further development can be successful, i.e. the compounds does not demonstrate the expected efficacy, the compound is not reaching its in vivo target, the compound shows toxicity, etcetera. Opportunities exist for academic institutions and its researchers to play a role in all steps of the development process described so far. Due to the exponentially increasing costs, later stage clinical trials are prohibitive for academic research. However, after the academic institution licenses patents related to the drug, venture capitalists interested in starting a small biotech company, or major pharmaceutical companies, may be attracted in sponsoring further development of the drug. Nevertheless, these clinical trials are frequently carried out in academic medical centers via collaboration with academic physicians interested in clinical investigations.

**Phase I clinical trials:** In general, in a phase I clinical trial, a few dozen healthy volunteers are administered the new drug in order to assist in the determination of the optimal dosing amount, and to study potential side effects. Exceptions are terminal diseases such as cancer, in which patients for whom no other medications have proven effective are enrolled.

**Phase II clinical trials:** In a phase II clinical trial, several hundred patients with the disease to be treated, are administered the novel drug. The efficacy of the drug in treating the disease is monitored, as well as side effects.

**Phase III clinical trials:** When the results of these investigations are successful and correlate with the expected outcomes, a larger phase III clinical trial with thousands of patients is carried out. Upon successful demonstration that the drug is useful for the treatment of the disease, a New Drug Application (NDA) is submitted to regulatory agencies requesting approval of the drug for marketing. Disappointingly, despite considerable investments of time and resources, the success-rate of compounds entering clinical trials is only about 11% (3).

**Marketing-Phase IV:** In phase IV studies, the safety of the drug in the larger general population is monitored, as well as the potential of the drug in the treatment of diseases not included in the original approval.

**The pharmaceutical industry in Puerto Rico**

In the first presentation, Dr. Sigfredo García, vice-president of Pfizer Puerto Rico and president of INDUNI (Industry and University collaboration with Government support) emphasized the importance of the symposium as a contribution to the development
of an “innovation eco-system”. Currently, with 89 manufacturing plants from 29 different companies in the biopharmaceutical and pharmaceutical industry, the importance for further development of this industry in Puerto Rico cannot be underestimated. Not only do 19 of the 33 largest pharmaceutical companies have a presence in Puerto Rico, but also 13 of the 20 top-selling drugs are manufactured here. However, as Dr. Garcia indicated, the industry is under pressure to bring new drugs to market, even though estimated costs for the development of a new drug are $800,000,000 to $1,000,000,000 (4). At the same time, the amount of new drugs with different mechanisms of action entering the market has shown a significant reduction. Therefore, “Big Pharma” is interested in new ventures with academia, and several collaborations between Pfizer and academic institutions in the US in this area of drug discovery and development were explained. He also indicated that similar collaborations with academic institutions in Puerto Rico could be advantageous due to the beneficial tax law for Research & Development investments and the fact that many pharmaceutical companies already have a presence on the island.

Nature as a source or as an inspiration for drugs

Nature has been an important resource for the discovery of new drugs. Of the drugs brought to market in the last twenty-five years, 34% are natural products or have been directly derived from natural products (5). A particular field in natural product drug discovery is ethnobotany, in which the use of plants in traditional medicine is investigated. Dr. Michael Balick, vice-president for Botanical Science, Research and Training, and Director and Phylecological Curator of the Institute of Economic Botany of the New York Botanical Garden, presented several aspects of his research in the area of ethnobotany. From investigations into the use of medicinal plants in traditional use by healers or by the general population in Belize (6-7), Micronesia and in the Dominican Republic and the Dominican population in Manhattan (8-9), several interesting applications of plants or plant extracts for disease treatments have been identified. Potentially, these plants could lead to novel drug therapies to be implemented in modern Western medicine. Moreover, Dr. Balick emphasized that in ethnobotany it is important to consider the comprehensive aspects of ‘Plants – People – Tradition’. Unfortunately, modernization leads to the disappearance of ancient cultures, and as a consequence, their extremely valuable knowledge of traditional medicine is on the verge of extinction. An example of the importance of studying traditional methods can be seen in the use of Cinnamomum carolinense bark shavings as a medicinal tea on the island of Pohnpepi in Micronesia (10). While ethanolic extracts of the bark contain saffrole, a known carcinogenic compound, a special preparation procedure utilized by the native residents eliminates saffrole from the tea. It should be mentioned that Puerto Rico, with its tropical climate, has a large diversity of plant species, some of which have been used traditionally for treatment of a variety of ailments or diseases. A newly remodeled Medicinal Plants Garden is located within the University of Puerto Rico’s Botanical Garden. Therefore, the opportunity exists for an ethnobotanical investigation in the island which, together with identification of the active substances in specific plants, could eventually lead to novel drugs.

Chemistry-inspired drug discovery

An example of a successful account of drug discovery in academia was presented by Dr. Waldemar Priebe, Professor of Medicinal Chemistry, MD Anderson Cancer Center. Dr. Priebe presented his research based on chemistry-inspired drug discovery and development of novel anti-cancer drugs. His approach to drug discovery is to prepare novel chemical entities, based on molecular “LEGO®” blocks. Each Lego-block represents a small specific chemical structure designed for its ability to interact with biologically relevant macromolecules. By connecting and combining the Lego-blocks with each other, a large variety of combinations of drug-like molecules can be prepared. The newly prepared compounds are then tested for their biological activity. Depending on the target for the (potential) drug, this could be the extent to which the new molecules interact with DNA, or their ability to inhibit enzymes known to be involved in disease processes. Several of the compounds synthesized in his laboratory have been successfully brought into Phase I clinical trials for ‘first-in-man’ testing. One example of a potential new drug that is currently in clinical trials is identified as WP744 (also known as RTA744) (11). This doxorubicin-derivative was designed to be active against multidrug resistant tumor cell lines and, even more interestingly, was shown to be able to cross the blood brain barrier (12). This new molecule, therefore, offers promise as a new drug in the treatment of glioblastoma multiforme, a highly malignant form of brain cancer for which treatment options are very limited. However, in order to comply with regulatory requirements of an IND-submission for clinical testing, an extensive evaluation of its pharmacological properties and potential toxicity had to be carried out. As described below, the “Pharmaceutical Development Center” at M.D. Anderson has proven to be invaluable in providing the required support and pharmacological data necessary in this process.
Preclinical studies

Before a compound can enter clinical trials, pre-clinical studies are required since these ultimately determine whether the compound is safe for administration to humans. Via pharmacokinetics (PK), pharmacodynamics (PD) and ADME-Tox (Absorption-Distribution-Metabolism-Excretion-Toxicology) studies, a safe starting dose for clinical trials can be established. At MD Anderson, these studies are carried out in the “Pharmaceutical Development Center” (PDC), which provides these services to its investigators with promising drug candidates in development. One of the compounds that was studied in the PDC and was able to advance into phase I clinical trials was the above-described WP744.

The Director of the PDC, Dr. Timothy Madden, MD Anderson Cancer Center, described his experiences during the five years the center has been in existence. The goal of this center is to facilitate the availability and testing of novel, promising therapies for patients. The center supports pre-clinical to Phase I studies, including safety testing. The testing procedures for qualified projects, as determined by an internal advisory board, provides researchers all needed data required by government regulations in order to commence clinical trials. These testing procedures include analytical assay validation, mechanism based experiments, proof of concept studies and in vitro metabolism studies. In addition, pharmacokinetic studies for ADME-Tox data are performed. Also, support is provided in the area of dosage form development for pharmaceutical production, including drug solubility and stability studies. During the last five years, more than 40 projects have utilized the services of the center, leading to 23 patent filings, 37 publications and 11 projects for which an IND application (Investigational New Drug), required by the FDA to start a clinical trial have been submitted. At present, clinical trials are in progress for nine projects supported by the PDC.

Advancing to Phase I clinical trials

Dr. Charles Conrad, MD Anderson Cancer Center, presented his clinical research in the area of brain cancer treatments. As one of the examples, he described his successful collaboration with Dr. Walter Priebe, in which WP744, synthesized in Dr. Priebe’s laboratory was brought into clinical trials as a potential treatment for glioblastoma multiforme. Because surgery and radiation are frequently not an option for the treatment of glial tumors, it was decided to investigate this novel compound as a potential therapeutic alternative for this disease. It was observed, from clinical studies under the direction of Dr. Conrad, that WP744 showed clinical activity in patients with brain tumor; the activity ranged from stabilization of the disease to a complete response, thus providing the promise of a novel treatment for this devastating disease. Other compounds, several of which were also developed in collaboration with Dr. Priebe are in different stages of development (13-14). As was emphasized by Dr. Conrad, the success in developing new drugs and the development of other novel clinical candidates would not be possible without the collaboration of researchers from various disciplines. As exemplified in Figure 2, the interdisciplinary collaboration of scientists from various disciplines is extremely important in order to translate discoveries made in the laboratory to clinically relevant applications.

Neglected diseases

An especially relevant opportunity for drug discovery and development in academia is in the area of diseases with unmet needs (15-16). Typically, diseases that only affect a relatively small part of the population, or diseases primarily occurring in developing countries such as malaria or tuberculosis, are not of primary interest to large pharmaceutical companies. Dr. Scott Franzblau, Director Institute for Tuberculosis Research, College of Pharmacy, University of Illinois, presented his work on the establishment of a research center dedicated to the development of novel anti-tubercular therapies. The center has developed methodology that allows the high-throughput screening of compounds for their ability to inhibit the growth of Mycobacterium tuberculosis, the causative microbe of tuberculosis (17). Thus far, 50,000 chemical compounds and 60,000 natural product extracts from investigators worldwide have been tested for activity. From these experiments, several dozen “hits” have been obtained that potentially could be further developed into clinically useful drugs.
Drug discovery and development at the University of Puerto Rico

The symposium provided a forum for a dozen University of Puerto Rico faculty researchers to present their work in the area of drug discovery and development. Even though many more researchers on the island are active in this area, the presentations varied from topics of the pharmacologic effects of plant extracts to methods for quantification of active plant constituents, the development and evaluation of new targets, the chemical or biochemical synthesis of new compounds that can interfere with disease-related enzymes or DNA, nanotechnological approaches via self-assembly as well as the development of methodology for drug delivery of siRNAs's to the brain. A remaining challenge, one of the reasons in organizing this symposium, is to increase the potential to translate the ongoing research projects into clinical applications via multidisciplinary collaborations.

Commercialization and intellectual property of innovations

The industry, academic and government perspectives of the value of intellectual property based on inventions related to novel drugs and their potential for commercialization were discussed in a round-table discussion. Ms. Véronique Riethuisen, Director Worldwide Business Development of Pfizer, indicated that, on average, it takes approximately thirteen years for an idea to develop into a drug. This leaves only a limited amount of time for a compound to be marketed with patent protection before generic manufacturers can market the drug without the high investments in research and development that the originator company has committed. Importantly, in order for the pharmaceutical industry to become interested in potentially licensing patents based on inventions originated in academic institutions or in other types of industry-academic partnerships (18-19) the intellectual property rights must be well-defined. Dr. Emma Fernández, vice-President of Research of the University of Puerto Rico, described the potential role of the recently established “Fideicomiso de Ciencia, Tecnología e Investigación” (Science, Technology and Research Trust), which supports the promotion and financing of projects that strengthen research and development of science and technology in Puerto Rico, and promotes the commercialization of products resulting from local inventions. Dr. Roberto Rodríguez from the Puerto Rico Industrial Development Company (PRIDCO), a government-owned corporation responsible for attracting investors, highlighted examples of infrastructural investments made with this aim such as a new Molecular Sciences Complex with eight floors and 120,000 square feet of research space currently under construction in Río Piedras, as well as the Bioprocess Development & Training Center, recently inaugurated in Mayagüez.

Funding opportunities

As was mentioned above, the discovery and development of new drugs is a costly enterprise. In a second round-table discussion, several potential sources for financial support for drug discovery and development projects were presented. Besides investments by academic institutions, frequently via their own trust funds, the US National Institute of Health (NIH), with its recent focus on translating laboratory discoveries into clinical applications via the NIH roadmap initiative, could provide a potential resource for funding (20-21). As was further explained by Dr. Franzblau, more recently, non-profit “public-private partnerships” have been established such as the “Global Alliance for TB Drug Development” (22) and the “Medicines for Malaria Venture” (MMV) (23). These partnerships support research in their respective disease areas. Ms. Kate Carr, president and chief executive officer of Accelerate Brain Cancer Cure (Washington), presented her experiences as representative of various “venture philanthropy” organizations. These organizations are interested in sponsoring research in a very specific interest area as determined by the organization and could be a valuable option for obtaining financial resources for investigators. Finally, Dr. Maribelis Ruiz, Venture Capital Group Advent-Morro, pointed out the existing interest of venture capital groups in investing in promising research projects. However, the presence of intellectual property and the potential for commercialization are still the main considerations before venture capitalist funds finance possible projects.

Clinical studies and translational research

In a last round-table, Dr. José Carlo, Chancellor Medical Sciences Campus UPR, described the establishment of the Comprehensive Cancer Center at the campus, a shared effort between the government and MD Anderson Cancer Center. The facility is soon to be opened and will have 20,000 sq. ft. of research laboratories dedicated to basic and translational cancer research. A related new clinical building for cancer research and treatment is in the design phase. In addition, the Medical Sciences Campus houses the Clinical Research Center, in which various clinical trials, some in collaboration with major pharmaceutical companies, are currently ongoing. Dr. Carlo stated the strong commitment of the Medical Sciences Campus to advancing the progress of translational research, in harmony with the priorities of the NIH roadmap.
Conclusions

The “Drug Discovery, Development and Clinical Research in Academia” symposium highlighted the importance of integrative and interdisciplinary research collaborations between basic research scientists and clinical scientists in the process of drug discovery and development. The increasing availability of freely accessible resources such as the Protein Database, PubChem and others, increase the access of academic researchers to valuable information (24-25). Discoveries of novel compounds for the treatment of diseases in academia can lead to intellectual property, which could attract new investments, either via venture capital funds for small biotech (start-up) companies, or via collaborative agreements with big pharma. The development and investments in Research and Development facilities in Puerto Rico are an important step in complementing the current emphasis on pharmaceutical manufacturing on the island. An expanded academic research base that connects the biomolecular, pharmaceutical and clinical sciences will not only provide the foundation to attract new investments, but it will also provide newly trained graduates a multi-disciplinary education, allowing a smooth transitioning into employment in the pharmaceutical industry. Most importantly however, is that the development of new drugs and pharmacological treatments will extend the lives and improve the quality of life of those suffering from one of the many diseases prevalent worldwide.

References