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Leading Edge
Commentary

Partnering with Big Pharma—What Academics Need to Know

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Knowledge of the parameters of drug development can greatly aid academic scientists hoping to partner with pharmaceutical companies. Here, we discuss the three major pillars of drug development—pharmacodynamics, pharmacokinetics, and toxicity studies—which, in addition to pre-clinical efficacy, are critical for partnering with Big Pharma to produce novel therapeutics.

Academic institutions are playing an increasingly large role in developing both new and repurposed drugs. The creativity and the discovery process, which is the tenant of basic science, can lead to the recognition of new drug targets involved in pathways associated with a disease process. Some academic and not-for-profit institutions are investing in the infrastructure for high-throughput screening of chemical libraries, optimization of "hits" to "leads" with medicinal chemistry, pre-clinical safety and efficacy testing, and early human clinical studies to aid the development of drugs for targets identified in basic science labs. Other universities have chosen to outsource these processes either to the academic institutions with these facilities or by using Contract Research Organizations (CROs) that have specialized equipment and personnel dedicated to drug discovery. Spinout companies formed by academic scientists also often serve this purpose. However, partnering with a large pharmaceutical company (so-called "Big Pharma") becomes critical in this effort, as drugs move into larger, multi-centered advanced human clinical trials. Such partnering provides additional expertise in a particular area of drug development, considerably more resources, and, importantly, both knowledge and funding for large human clinical trials. This piece outlines what an academic scientist needs to know and what to do in order to approach Big Pharma with a new chemical entity (NCE). We describe the three pillars of drug development, dealing with drug pharmacology and host action, plus a fourth pillar of socio-economic importance, namely, drug affordability.

Clinical Pharmacology: A Primer

A compound developed by academic scientists can enter a pharmaceutical pipeline at different stages of its development. Take for instance the following scenario: a small molecule displays potent effects on a signaling pathway in cell culture, and there is an understanding of the molecular mechanisms underpinning these effects. The excitement in the lab is brewing, but is this knowledge sufficient to partner with Big Pharma? This may be the case if the identified compound or target molecule is of high interest, but it is often just a first step in a long process that will determine the potential of this compound or a related congener to be developed into an actual FDA-approved drug. Hence, finding a compound that is efficacious is just one of several steps that must be undertaken prior to discussions with companies. Box 1 provides a summary of the requirements for partnering with pharma, as well as the knowledge that needs to be in place for drug development. This knowledge of critical parameters of clinical pharmacology will be described in detail in the upcoming sections.

The major branches of clinical pharmacology, which represent two of the pillars for drug development, are pharmacodynamics (PD) and pharmacokinetics (PK). An understanding of how a candidate drug molecule affects these parameters is critical in determining if the drug can move forward in the U.S. Food and Drug Administration (FDA) regulatory pathway toward development as a human therapeutic. Just because a drug appears effective in a dish or in an animal model does not mean that the compound will be "druggable" in humans. A detailed knowledge of the PD and PK will help determine if this is the case and, hence, help you speak the language of pharma; it will also allow you to understand whether pharma will want to partner with you for further drug optimization and development of your discovery. Similarly, understanding these concepts will help the academic scientist comprehend when an efficacious compound ends up being rejected because of a deficit in druggability and hence as a potential human therapy.

The Three Classical Pillars of Drug Development

I. Pharmacodynamics

Pharmacodynamics concerns the study of the biologic effect of a drug with regard to concentration and time and represents the first pillar of drug development. In brief, pharmacodynamics describes "what the drug does to the body." Generally, it is important to understand the mechanism and site of action of a drug, as well as its target in the tissue or organ of interest. The authors' expertise is in development of drugs targeting brain function, and our experience has taught us that the mechanism of action of a compound is critical for its ability to be clinically tolerated. Therefore, understanding

Box 1. Steps in Partnering with Big Pharma

1. Identify a target, pathway, or platform for looking for a potential new (or repurposed) drug.
2. Screen or otherwise pick and optimize your candidate molecule (sometimes you can do this with a pharma partner if you have identified a novel, interesting target that will appeal to them).
3. Perform preliminary efficacy studies in appropriate animal models.
4. File IP/patents for protection.
5. Perform early PD and PK/ADME/toxicity testing.
6. Perform preclinical IND-enabling studies with cGMP compound under GLP conditions (usually, for academics, this is performed in collaboration with a CRO).
7. Network and present your findings to Big Pharma or smaller biotechs (occasionally this can be attempted at an earlier stage—see above—but, in general, the later the stage the better, as this de-risks the deal for pharma).
8. Formulate a compound development or licensing deal.

Abbreviations: IP, intellectual property; PD, pharmacodynamics; PK, pharmacokinetics; ADME, absorption, distribution, metabolism, excretion; tox, toxicity; IND, investigational new drug application; cGMP, current good manufacturing process for clinical-grade material; GLP, good laboratory practice (a certification for qualified laboratories); CRO, contract research organization.

the target and drug action at biochemical, molecular, and even atomic levels is often necessary in developing a "hit" molecule from an initial screen (which must be verified in counter screens) toward a lead compound that is suitable for entering the clinic. A detailed understanding of the structure-activity relationship (SAR), which describes how a 3D structure of the molecule affects its biological function, is also necessary for medicinal chemists to be able to further optimize a compound toward a lead candidate.

Critically important to future human clinical trials is the development of an assay that will allow drug-target engagement to be judged in vivo in a manner that is relevant to the disease process. While drug levels in blood or another relevant compartment should be monitored, it is also important to have an indication of drug action and efficacy that can be used as a surrogate readout in human clinical trials. For instance, implementation of a direct biochemical, imaging, or molecular assay that can be used as a biomarker relevant to the disease process to complement human behavioral data, such as improved survival for a cancer drug or better memory function for an Alzheimer's disease drug, has become a critical criterion of Big Pharma for future drug development.

Beware that nearly every drug manifests multiple effects, and the only time that an NCE is considered "specific" is the day it is first found to interact with a target of interest (meaning that, as a drug is studied more, additional effects on other targets are invariably encountered). Along these lines, most drugs affect multiple organ systems and thus may exert unwanted and untoward effects on cells or tissues. It is also important to consider that, in addition to the intrinsic properties of the drug and its concentration (dose-response), many other factors can affect both therapeutic and undesirable (side) effects, including patient gender/pregnancy status, age, race, weight, diet, allergies or sensitivities, concurrent medical conditions, inflammation, trauma, and other concomitant drug intake.

II. Pharmacokinetics

Pharmacokinetics represents the study of how the body handles the drug and how the resultant drug concentration in the relevant compartment varies with time after administration. This entails not only drug measurement but also a detailed investigation of drug absorption, distribution, metabolism, and excretion (ADME). In brief, this is the study of "what the body does to the drug" and constitutes the second pillar of drug development.

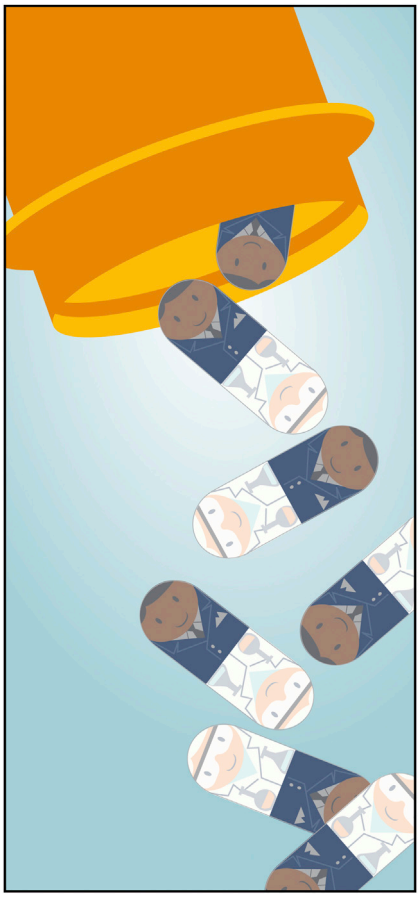
These parameters are of critical importance for drug action because the drug must be present at an appropriate concentration and site in the body in order to manifest a beneficial effect. For this to occur, a series of events must proceed that involve its absorption and distribution to the appropriate tissue or cell type. During this process, non-specific binding to serum or other proteins in addition to the target protein may occur. Biotransformation to an active form (if a pro-drug is administered) or to an inactive form as the drug is metabolized can also occur and must be carefully studied. Finally, the route and rate of excretion of the drug will affect its concentration. Thus, pharmacokinetic attributes of drug handling must be thoroughly understood in order to determine the optimal route, dose, and timing of drug administration. The influence of a patient's disease on drug levels must also be ascertained, in addition to the possible effects of patient gender/pregnancy status, age, and other concurrent drug administration. Finally, potential drug toxicity on all organ systems in the body must be studied in a dose-dependent manner. Thus, the pharmacokinetic properties of a drug involve the study of the following parameters:

- Absorption (oral, parenteral, and transnasal/intranasal routes)
- Distribution (in blood [and/or binding to plasma proteins], total body water, fat, extracellular fluid, and cerebrospinal fluid)
- Metabolism (conjugation, hydrolysis, redox posttranslational modifications; site of modification, e.g., liver or other local tissue metabolism)
- Excretion (kidney via urine, gastrointestinal via feces [either of unabsorbed drug or drug excreted in the bile], lungs via air, and skin via sweat elimination)

The overall effect of the PK profile will affect the bioavailability of the drug. This constitutes the fraction of drug administered that is actually absorbed into the compartment where the target resides and is available for interaction with that target. Other components in drug formulation and manufacture—e.g., chemical stabilizers, which can differ among various drug manufacturers—can exert a dramatic effect on bioavailability and thus on drug efficacy.

III. Toxicity versus Safety

A critical factor in determining the eventual approval or disapproval of a New Drug Application (NDA) submitted to the FDA concerns its safety prolife, not only at the desired therapeutic concentration



but also at other doses, hence defining the therapeutic index (TI) or the ratio of efficacious dose to toxic dose. The TI for preclinical animal studies is defined as TI = LD_{50}/ED_{50} (ratio of the lethal dose at which 50% of the animals die versus the minimum effective dose at which 50% of the animals are significantly improved). For human clinical trials, TI = TD_{50}/ED_{50}, where TD_{50} represents the maximally tolerated dose for 50% of the population tested.

Additionally, it is critical to determine the maximal tolerated dose (MTD) or maximal feasible dose (MFD) by performing preclinical, dose-escalation safety studies in at least two animal species (in most cases) and also in human phase 1 clinical trials. Subsequent clinical testing will determine both minimal and maximal efficacious dosing. Initially, these studies can be performed with research-grade materials, but for investigational new drug (IND) approval from the FDA, which will be necessary in order to perform a human clinical trial, both safety and efficacy studies need to be performed using clinical grade product (made with current good manufacturing processes [cGMP] under good laboratory practice [GLP] conditions). Often, such IND-enabling preclinical studies are performed in concert with other institutions offering these specialized services.

For example, since many academic institutions are not equipped for these purely clinical pharmacological studies involving PD/PK (ADME)/toxicity, they can often be accomplished in collaboration with contract research organizations (CRO) that are very experienced in these procedures.

IV. The Fourth Pillar: Drug Affordability and Ethical Drug Development

With increasing pressure on the budgets for drug development and healthcare expenditure, there is a need to look for novel approaches to drug discovery. Hence, much more work by academic scientists and small biotechnology companies, as well as Big Pharma, is needed to find new targets to treat a wide variety of disorders. Given the current climate, the importance of R&D investment by drug companies in collaboration with academic institutions and their scientists cannot be overemphasized. Compared to the more directed research of most biopharmaceutical companies, the wide-ranging approach to scientific discovery taken by academic principal investigators can potentially lead to the discovery of novel targets important in disease or even to new types of compounds that interact with these targets. Moreover, an academic center may be able to carry out these initial studies in a more cost-effective manner. Thus, these academic efforts are can be very valuable for drug development by Big Pharma (see Box 2).

When considering cost containment, it is equally important to know when to "kill" a drug candidate (for example, because of a deficit in efficacy, ADME, PK or its toxicity) as it is to know when to take a drug forward into advanced clinical trials, which can cost many millions of dollars. Hence, academic scientists should not be disappointed when pharma turns down a seemingly efficacious compound for a partnering opportunity, as this may happen for a number of reasons that may not always be obvious—for instance, if an experienced medicinal chemist at the company has determined that this kind of compound cannot be synthesized cheaply or may have expected toxicity, thus making it a poor candidate to take forward.

A disturbing trend in pharma is the buyout of ethical drug companies by large generic houses whose primary goal is marketing of existing drugs with a paucity of new research and development (R&D). This, coupled with rising prices, and in some cases frank price gouging for drugs used by specialized audiences (e.g., rare diseases or AIDS patients), has resulted in our politicians calling for price restrictions on drugs. One side effect of this series of events has been to send stock prices of smaller biotechnology companies into a tailspin. What we feel is needed is a commitment by pharma, large and small alike, to set a percentage of its budget for R&D. Further partnering of pharma with the NIH and other federal agencies for drug development, in order to support academic forays into this area, might also be beneficial in today's environment. We need to agree on a fair economic profit margin for the pharmaceutical industry, coupled with reasonable investment in R&D. Price gouging, in contrast, should in our view be discouraged.

One formidable impediment to new drug development is the length of time required to secure an NDA from regulatory bodies such as the FDA, which can often take 15 to 20 years from the start of the research. Although the exact number remains contentious, ~350 validated drug targets have been reported, and new targets are desperately needed in order to treat additional maladies; this is one area where academic researchers have the potential to make great contributions. Another approach taken by a number of academic scientists is the repurposing of existing drugs for a new indication, which can shave many years off of the developmental timeline since safety and tolerability studies, as well as other PK and PD analyses, are already completed. However, the lack of patentability of repurposed drugs for another indication can prove to be an economic deterrent to companies. In the case of repurposing drugs, therefore, financial support for these studies to academic institutions

Box 2. Finding a Pharma Partner

The R&D function in an innovation-driven pharma company has two separate but highly interdependent roles. The first—and most obvious—is to invent, evaluate, and later develop the molecules that eventually lead to products on the market. The second—and less obvious—is to provide scientific expertise capable of identifying and evaluating external opportunities. These can be specific molecules at various stages in the value chain. It can also be technologies or ideas that can be directly developed into new molecules or contribute to other projects.

All Big Pharma companies scout for new exciting opportunities externally. These may come from the academic world, biotech, and—more recently—other Big Pharma companies. This recruitment of new intellectual property takes place though different processes. Traditionally, informal contacts between scientific colleagues have been dominating. Recently, however, we see more formalized approaches, such as the establishment of big conferences, where "speed dating" between pharma companies, biotech, and academic institutions occurs.

After the initial contact, a due diligence process is started, which can be more or less formal. The more advanced the project, the more formal and strict the process becomes, reflecting the large financial stakes at this stage. The molecule is evaluated with regard to its chemical and biological properties. Does it cross the blood-brain barrier to reach its target in adequate amounts and with appropriate pharmacokinetics to be a useful drug? Can it be produced in the large quantities? What are the safety aspects? What are the pharmacological properties in man and so on? Usually, only a small fraction of all projects that have reached this due diligence step eventually results in an agreement to further develop the compound.

If partnering with Big Pharma is the eventual goal, getting your compound into people, at least in early stage (phase 1 or 2) clinical trials, will greatly increase its monetary value and the likelihood of such partnering. However, if a compound is in an early stage of development, a smaller biotech partner, a niche pharmaceutical company, or even a virtual start-up, spun-out of an academic laboratory, may be a more reasonable option. The possibility of partnering with Big Pharma for drug development increases if protection of the intellectual property (IP) by patents, trade secrets, and such is in place and if the product fits into the company's existing pipeline.

from governmental agencies or private foundations will be critical.

To summarize, the more insight an academic scientist can bring to bear, at least in preclinical animal models, not only on efficacy but also into PD, PK, and toxicity profiles of a compound, the more likely the possibility of partnering with Big Pharma becomes. If early human toxicity studies (e.g., a dose-escalation phase 1 clinical safety trial) can be initiated, this will further enhance partnering opportunities and increase your value. There is a great need for drugs to treat rare and neglected diseases, as well as disorders of aging, such as Alzheimer's and Parkinson's diseases. With the aging demographic of our population, these pathologies could consume a large portion of our gross domestic product (GDP) by mid-century and are thus of great socioeconomic concern. On the other hand, ethical drug development requires that drugs are affordable to a large number of people. This represents a conundrum in our society, as drug development is expensive. However, we feel that it is critical for Big Pharma to continue to contribute their share to drug development, not only by in-house research but also via partnering with academic scientists and by participating in NIH initiatives to foster such collaborations. For further reading please, consult the following sources: Dahlin et al. (2015), Hall et al. (2015), and Rosier et al. (2014).

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This article is dedicated to the memory of the late Eugene Step, former President of the Pharmaceutical Division of Eli Lilly and Company. S.A.L. characterized the mechanism of action, spearheaded clinical trials, and helped commercialize the drug memantine (marketed as Namenda), an NMDA type of glutamate receptor antagonist. This work contributed to FDA approval of memantine for moderate-to-severe Alzheimer's disease. For licensing the drug to Forest Labs/Allergan, S.A.L. participates in a royalty sharing agreement with his former institutions Harvard Medical School/Boston Children's Hospital under the guidelines of Harvard University intellectual property rules. He is also the co-founder of Adamas Pharmaceuticals, Inc., which co-developed NamendaXR and Namzeric with Forest Labs. S.A.L. is a member of the Neuroscience SAB at Eli Lilly and Company and holds the Hannah and Eugene Step Distinguished Professorship and Chair, named after the late President of the Pharmaceutical Division of Eli Lilly. C.N. is Vice President, Neuroscience Discovery Research and Clinical Investigation at Eli Lilly and Company, overseeing Lilly's global neuroscience drug discovery and early clinical development. He has worked in the CNS area in Big Pharma at Roche, AstraZeneca, and Lilly for over 20 years.

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