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Playing Well with Others! Initiating and sustaining successful collaborations between Industry, Academia and Government

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It was the best of times and the worst of times; conducting the science and business of drug discovery through unprecedented funding and regulatory challenges is now the unfortunate normal for industrial and academic/non-profit/government research labs. These challenges come at a time featuring extraordinary opportunities as new scientific discoveries and technologies are revealing ideas and techniques that are ripe for rapid development into novel therapeutics. Facing difficult realities imposed by diminishing resources, traditional barriers within drug discovery are being broken with increased frequency. The conventional and often enigmatic road toward clinical approval is giving way to a more open approach where the complimenting strengths of pharma/biotechs and academic/government labs are being leveraged to hasten the translation of new discoveries into new drugs.

The topic of ‘best practices’ for conducting drug discovery is one that elicits strong opinions from scientists in all domains of research. Pharma researchers correctly point out that the plurality of drugs are the result of painstaking efforts at large and small pharmaceutical and biotechnology companies [1]. Academics fittingly counter that much of the basic research that justifies new programs within pharma are conducted at the world’s universities and research institutions [2]. These debates often cloud the reality that complex endeavors, including drug discovery, are nearly always the result of a rich tapestry of interconnected discoveries and inventions rooted in both public and private research efforts. In recent years, a multitude of organizations and individuals have increasingly embraced this fact and, by accepting fully the premise that one organization can’t do it all, are pursuing new collaborative efforts in hopes of finding more fertile ground.

Collaboration, of course, is not a requirement for success. Drug discovery efforts confined within the walls of one organization are still a major source of new chemical entities entering clinical trials. Successes of this nature are often the result of a vast institutional knowledge in a disease state. Eli Lilly, for instance, introduced pharmaceutical grade insulin in 1928 and the success of this drug has led to a nearly century long commitment to diabetes research and drug discovery at this organization [3]. Not-to-be outdone, academia can claim several impressive discoveries including block-buster successes such as pregabalin (Lyrica™; Silverman lab, Northwestern), emtricitabine (Emtriva™; Liotta lab, Emory) and

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pemetrexed (Alimta™; Taylor lab, Princeton)[4–6]. Achievements such as these will continue to materialize to the delight of the people and organizations that spearhead the efforts. In light of declining success rates, however, collaborative efforts between industry and academia are on the rise.

Collaborations can come in many shapes and forms. Traditionally, start-up companies pioneered by university professors have been supported by venture capitalists. Genentech, founded by UCSF professor Herbert Boyer and venture capitalist Robert Swanson, being among the great success stories that will undoubtedly spur the continued practice of VC supported-academic pioneered startups [7]. Additionally, through internal venture capital units and licensing agreements, major pharmaceutical companies have enabling academic principle investigators with key expertise's and/or strong track-records of success to start and/or expand for-profit organizations. Notable examples include start-ups pioneered by Professor Kevan Shokat and colleagues (Intellikine, Araxes Pharma), Professor Lew Cantley and colleagues (Agiros Pharma), Professor Robert Langer and colleagues (Blend Therapeutics, Pulmatrix), Professor Stuart Schreiber and colleagues (Vertex, Infinity, H3 Biosciences) and Professor Ben Cravatt and colleagues (ActivX Biosciences).

Several pharmaceutical companies have taken the additional step of establishing research institutions with affiliations to academic centers of excellence in hopes of blending the academic culture of innovation with expertise rarely found outside of big pharma. Prominent examples include the Genomics Institute of the Novartis Research Foundation (GNF) that is geographically located near strong academic sites including the Scripps Research Institute (TSRI), UCSD and the Salk Institute for Biological Studies [8]. GNF was originally founded and directed by TSRI Professor Peter Schultz. Another example of the strong ties between highly innovative academic researchers and major pharmaceutical enterprises is the California Institute for Biomedical Research (Calibr) which was launched in 2012 via a partnership between Merck and Professor Schultz [9].

Direct partnerships between pharma/biotechs and academic centers are also becoming more common. Recently, Boehringer Ingelheim established a wide-ranging collaboration with the Harvard Medical School's ICCB-Longwood Screening Facility to initiate multiple RNAi screening programs surrounding research questions of mutual interest to both organizations. Leo Pharma has partnered with Professor Phil Baran (TSRI) to leverage that lab's expertise in natural product synthesis. Genentech and the UCSF School of Pharmacy have established research partnerships based upon mutual interest and complementary expertise within the general field of neurodegenerative disease. Indeed, collaborations between pharma and major research institutions are growing in popularity. High-profile pharma/academia collaborations include efforts at TSRI (Takeda, Merck, Pfizer, Janssen), Harvard (Ipsen, Pfizer, Roche, Sanofi), UCSF (GE Healthcare, Pfizer, Sanofi, Bayer), MIT (Novartis, Sanofi, Pfizer, Merck), The Broad Institute of Harvard and MIT (AstraZeneca, Roche, Novartis) and Vanderbilt (GlaxoSmithKline, Janssen, Bristol-Myers Squibb, AstraZeneca). A recently started syndicate of academics engaged in drug discovery [the Academic Drug Discovery Consortium (ADDC)] maintains an up-to-date cataloguing of major pharma/academia collaborations [10].

Many pharma/biotechs have opened their doors for collaborative enterprises through open-source competition and the submission of idea's and potential research tools. Eli Lilly and company has established an Open Innovation Drug Discovery platform (OIDD) that includes phenotypic and target drug discovery units (PD² and TargetD²) that allows submission of candidate small molecules which, if approved, are entered into a series of phenotypic and target-based assays conducted by Lilly scientists [11]. Agents with biological activity of mutual interest can be licensed and advanced through more rigorous preclinical studies. Pharmaceutical firms are also taking advantage of crowd thinking by submitting problems ranging from scalable, efficient synthetic methods for key intermediates to predictive phenotypic outcomes in systems biology to open source programs like Innocentive® and the Dialogue for Reverse Engineering Assessments and Methods challenge program (DREAM)[12, 13]. Other open-source, pharma backed initiatives include the Merck backed SAGE Bionetwork and the Broad-Novartis Cancer Cell Line Encyclopedia (CCLE)[14, 15]. The rationales behind all of these endeavors stems from the belief that open-access scientific group-thinking will hasten novel discoveries and, ultimately, drugs.

Another source of indirect collaborations between pharma and academia is the increasing level of public disclosures from the private sector that historically blinded its IP positions. In particular, the release of small molecule structures through publication and the licensing of many of these agents to commercial suppliers like Sigma, Selleck and Tocris has given academics access to research tools that are then tested in a wide array of settings. The resulting publications often prove more beneficial to the organizations that hold composition of matter rights to the agents and, in selected cases, have provided the justification to reposition clinical agents versus new disease indications. There is still reluctance among much of pharma to release the structures of their painstakingly engineered and therefore precious clinical candidates. Much of this fear stems from the belief that adverse data may be generated in studies (appropriately or inappropriately conducted) outside the major stakeholders control. However, examples of this occurring are far outnumbered by the beneficial studies conducted when molecules are made publically accessible and the instances where a well-performed study does reveal a negative consequence for an agent offers an opportunity for the patent-holding organization to mitigate future losses. Some companies, including GlaxoSmithKline, have embrace this practice by providing academic partners access to proprietary small molecule libraries with the goal of discovering novel targets and molecular probes that may, in turn, spearhead new development programs [16].

Disease foundations are also playing an increasingly important role in the drug discovery process. Many organizations are shedding the label of uninvolved fund raisers and are getting more immersed in the research that their funds enable. One of the most important examples is the role that the Cystic Fibrosis Foundation (CFF) played in the development and approval of Kalydeco™ (VX-770)[17]. Here, the disease foundation took the relatively unprecedented step of funding research and development efforts at a for-profit organization (Vertex). Once a clinical candidate was identified the efforts of CFF shifted to using their vast social networking organization to help coordinate the clinical effort. Another Vertex drug (VX-809) whose discovery was partially funded by the CFF is involved in late-stage clinical trials. Inspired by these successes, many disease foundations are now actively

funding research within for-profit organizations including the Alzheimer's Drug Discovery Foundation and the Michael J. Fox Foundation. The movement, generally referred to as Venture Philanthropy, will undoubtedly continue to gain momentum.

Government support of industry/academic partnerships is also undergoing a renaissance. The National Center for Advancing Translational Sciences (NCATS) recently launched a drug repurposing program that allows academic researchers access to 58 investigational drugs that were deprioritized by pharma [18, 19]. The premise involves drugs with mechanisms of action that academics believe may make them appropriate for clinical indications not pursued during the initial clinical evaluations by the patent-holding organization. An example involves the use of saracatinib, a Src inhibitor pioneered by AstraZeneca for cancer indications, for the treatment of Alzheimers disease based upon its activity versus Fyn kinase. The UK's Medical Research Council (MRC) offers an Industry Collaboration Agreement (MICA) that facilitates academics/industry collaborations through funds and in-kind research in both basic and applied fields of study. A major aspect of this program is a pre-agreement of either a 'fully flexible' or 'gated contribution' IP policy that allows participants to avoid one of the major hurdles in setting up such collaborations.

Clearly the scope and style of collaborative efforts being explored by pharma, academia and government research organizations are impressive and growing. New drug approvals hit a 16 year high in 2012 (39 total new drugs) and new regulatory programs such as the FDA's 'breakthrough therapy designation' are revolutionizing clinical practices. Despite these exciting developments, its arguable that the most promising development in drug discovery is the current interest in collaboration, rather than isolation, being demonstrated by all invested parties. This issue of Current Topics in Medicinal Chemistry highlights several of the organizations and the intrepid researchers that are illuminating the process-of and benefits-to conducting research in this manner.

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