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EDITORIAL

Academia–pharma partnerships for novel drug discovery: *essential or nice to have?*

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1. Introduction

The pharmaceutical industry continues to be challenged by skyrocketing costs and plummeting productivity in R&D, while many key products are facing patent expiration. Early discovery research from target validation through lead selection is costly, time consuming, and unlikely to yield a novel drug. The pharma industry reports that it takes well over a decade to develop a drug, and that there is a failure rate of more than 95%. This unsustainable model has led to a growing acceptance of a drug discovery process that incorporates open science thus paving the way to stronger collaboration between pharma and academia [1]. Pharma's academic funding focus in recent years has moved from handpicked, curiosity-driven, disease biology projects to large integrated programs with a strong emphasis on therapy development. Pharmaceutical companies have also initiated regional/global 'science hubs' in key academic centers to inspire biomedical innovation. Depending on the particular needs of the institution or the collaborative enterprise, a diverse array of innovation models have been implemented using grant- or contract-based agreements, with a tie to publications, royalty payments, or intellectual property rights.

Yet, the academic scientist, wary that the private sector sponsored research is market driven and is at the cost of basic science and academic freedom, views this shift with mixed feelings of appreciation and apprehension. Misalignment of the scientific value for a given research program versus its market value to a commercial partner is a constant sore point for the academic scientist. Nevertheless, open innovation has taken a strong hold within the last few years in reinvigorating pharmaceutical R&D endeavors. This is a shift from the concept of 'innovation within the corporate walls' to the acquisition of new intellectual property from outside to advance therapeutic strategies, a concept that advocates the fact that *a problem shared is a problem solved*.

1.1. Paradigm shift

It may seem at times that we are losing the battle against many of the diseases that ravage humanity; in reality we made great strides. We now live longer, with a life expectancy that has almost doubled over the last 150 years. Improvements in nutrition, sanitation, and housing combined with advancements in public health including the use of prophylactic vaccines and antibiotics have eradicated the deadly diseases that claimed millions of lives across the globe. However, with changing lifestyles, new diseases are emerging, age associated co-morbidities are increasing, and many old diseases still remain incurable. There are ~36 million deaths worldwide attributable to noncommunicable diseases.

Our knowledge of disease modalities is expanding. Over the last decade researchers, primarily academia and supported by public funds, have identified more than 1000 new biological changes that could translate to new targets or biomarkers of disease and its progression. Cancer is a premier example. It is not a single disease. To date, the research community has identified over 177 different types of cancer, and the number is growing. Genome-wide association studies have uncovered a multitude of gene variants that may be contributing to complex diseases, such a schizophrenia, coronary artery disease, and diabetes [2–4]. The power of sequencing and new chemistry has led to the identification of novel targets in infectious disease. Unfortunately, the translation of many of these discoveries into therapeutics has not been realized. Limitations in capacity, funding, and even culture in an industrial setting make the selection of the best new therapeutic targets from the overwhelmingly large list unlikely. Unlike their industry counterparts, academics have neither the experience nor the same incentives to take their discoveries to the patient. A new discovery model that can build an effective collaboration between academic experts and pharmaceutical industry partners with drug development experience could be transformative [5], resulting in greater access to novel disease targets while reducing costs and risk in the development of therapeutics. These types of collaborations have been executed with various levels of success. The power of public–private collaborations is the closer integration of subject matter experts with the drug development expertise and the resources to translate these novel findings to drugs. The shared goal of improving human health and realizing the potential of the research motivates these collaborations, but reaching a success milestone requires building of trust, open-minded debate, and incentives appropriate to each environment.

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1.2. Evolution of academic drug research

Academia has evolved in recent years from its traditional role of target identification and validation to probing for tool molecules (probes) against disease targets to explore their therapeutic relevance. This new focus in academia is a welcome change. Over the last 15 years, high throughput screening and translational research centers have come in to existence at many academic institutions worldwide. Although novel targets and drug leads have been sourced from academia prior to this investment, the expanded access has allowed for many more disease hypotheses to be tested. Not all sites are created equal with respect to capabilities, but many have capitalized on the downsizing of pharmaceutical research by recruiting experienced staff, acquiring cutting edge tools and technologies, and chemical libraries. The funding model under which these sites operate varies widely. The National Institutes of Health Molecular Libraries Program was instrumental in building state-of-the-art screening and chemistry centers that supported more than a 1000 early drug discovery programs and yielded hundreds of useful chemical probes some of which progressed to drug development in collaboration with private industry [6]. This program operated within the academic environment, but its success relied on building successful collaboration with multiple stakeholders. Project managers, an industry standard, were integral to projects' success. Regular review of progress by a governance body kept the focus on timelines. The requirement that the project began with the development of a written team agreement on the goals, decision criteria, roles and responsibilities, budget, and timelines fostered success. This level of transparency broke down barriers and built trust. A number of these projects are now the testament to academic entrepreneurship: spin out companies and pharmaceutical collaborations. For example, Receptos licensed intellectual property (IP) from the Scripps Institute for S1P1 agonists [7]. Positive Phase II data from Receptos led to its purchase by Celgene in 2015, and now a Phase III trial in multiple sclerosis is yielding positive results.

2. Pharma's realigned focus

Pharma's funding focus has also shifted in recent years. It has initiated regional/global 'science hubs' with academia to regain and reignite biomedical innovation. The options range from joint ownership of laboratories to open access to industry resources and facilities. Representative examples of early discovery programs include Pfizer's Centers for Therapeutic Innovation, GSK's Tres Cantos Open Lab Foundation, Lilly's Phenotypic Drug Discovery Initiative, Merck's SAGE Bionetworks and Clinical and Translational Science Awards Program ().

Academia in turn has reciprocated with translational research centers to help in reducing academic discoveries to practice: Stanford's SPARK; Harvard's Catalyst program; UPenn's Institute for Translational Medicine and Therapeutics; and University of California-San Francisco's QB3 (University of California-Berkeley, Southern California and San Francisco). This concept has now been extended to the drug safety, drug development, and bio manufacturing space through public–private consortia such as the Translational Center of Tissue Chip Technologies at MIT, Advanced Mammalian Biomanufacturing Innovation Center, and NIIMBL (National Institute for Innovation in Manufacturing). The recently formed Academic Drug Discovery Consortium hopes to build a collaborative network among the growing number of university-led drug discovery centers and aims to facilitate an avenue for academic researchers to exchange technical expertise as well as form partnerships with each other, biopharma companies, and drug discovery-focused contract service organizations and consultants [8]. An up-to-date listing of groundbreaking collaborative projects can also be readily accessed to gain a full scope of ongoing academia–pharma partnerships.

3. Are academia–pharma partnerships working?

Pharma has provided millions of dollars in recent years supporting innovative projects at academia, for example: GSK–Harvard, AstraZeneca–Columbia, Pfizer–University of California, Monsanto–University of Washington, and Hoechst–Massachusetts General Hospital. While these partnerships garnered wide public press coverage upon initiation, the outcome of joint success is not widely known. The best example of successful partnerships is in the area of infectious diseases. New treatments such as malaria drug combinations [9] and meningitis A vaccine [10] are examples. In an environment where many pharmaceutical companies had deprioritized infectious disease research, the formation of partnerships such as Drugs for Neglected Diseases Initiative, Medicine for Malaria Venture, TB Alliance, Global Health Innovative Technology Fund, and International AIDS Vaccine Initiative brought new focus to the problem. Funding mechanisms such as the Gates Foundation were instrumental in providing adequate resources to tackle the problem effectively. Formation of a partnership was a requirement of funding, and a project plan that all partners agreed to was needed to initiate the program. Many of these programs began with public organizations, but their progression required involvement of biotech and pharmaceutical companies to ultimately bring a drug to the market. The cost benefit of derisking a program through the use of public funds is an attractive business model where the cost of the drug must remain low. Involvement of private entities in these programs may have been driven more by public perception than profit, but further development of the drug would not have been possible if the foundation of work was not strong. Aligned behind a solid plan, real results and the proper incentives development of a novel drug could be achieved.

Extending this model to therapeutic areas beyond neglected diseases would seem simple, but additional challenges arise. How to define what is precompetitive and how to protect intellectual property may be perceived as some of the greatest challenges, but the incentives for the team members is a topic that is often overlooked. The reward systems in the public and private environments are not well aligned, but common ground can be achieved. A scientist in any organization is happy to see their work published, and public

organizations could find creative mechanisms to share in the financial reward of licensing. The bright young minds encountered in an academic setting are an excellent source of innovation, but due to their focus on completing their thesis and publishing the data, they may not be the ideal partnership team members. Funding professional staff to execute the project may avoid priority conflicts, but carving out a precompetitive aspect of the project taps into the innovative space that attracted the collaboration initially.

3.1. Gap assessment

These partnerships should not be one-sided with all information flowing in one direction. Academic colleagues can learn much from their pharmaceutical counterparts. Sharing experiences around technologies, knowledge management, operational excellence, and project management could bring benefit to most academic centers. Pharma should find mechanisms for academia to tap in to its vast chemical libraries, proprietary data sets, innovative tools and technology platforms. Early exposure of young scientists to translation of basic science to therapeutic applications fuels further innovation and entrepreneurship. In turn, academia must try to understand the business objectives of the organization and not assume that pharma has unlimited budget and timelines.

Technology transfer (TT) from academia to pharmaceutical partners is not a trivial task. Many academic TT offices are novices in the art of licensing, and most are intimidated by the sheer size of the pharmaceutical companies. While publications are important for the academic, as they are one of the most important barometers for measuring academic excellence and criteria for advancement, they can become a point of disagreement as to what and when to publish. Monetizing academic discoveries by pharma requires ownership of the intellectual property rights. Pharma has made big strides in this arena by settling for the 'right of first refusal' over outright ownership of patents until critical development decisions. This continues to be a key stumbling block and an area for further improvements in business models.

Another area of significant mistrust between the public and private institutions is the issue of data reproducibility. Public–private collaborations are often initiated when a researcher presents interesting data with a small molecule or a novel therapeutic target in established or unexplored disease models identified from a publically funded project. The cost-saving benefit of grant funded assay development, screening, and even some early medicinal chemistry needs to be weighed against the quality of the small molecule. The researchers' belief that a screening hit is a drug, a promiscuous molecule is specific for its target, or an insoluble molecule can be tested in an animal model is often encountered but despite this real potential can be found. Since the foundation for successful collaboration is based on mutual trust, all partners, especially the academic scientist, must work harder to rebuild and regain this confidence [11]. Independent verification of their results by a third party sounds ideal but this is costly and time consuming. Multidisciplinary teams that share best practices, get involved early in assay development, assay validation, and in hit selection experience greater success.

3.2. Finding common ground

Keeping pace with the rapid rate of new discoveries and harnessing the potential of new targets or biomarkers of disease can only be realized through strategic, collaborative innovation in biomedicine. Pharma's current business models rely on obtaining clinical candidates through acquisition, alliances, and mergers. Active partnerships with academia to address key scientific questions and translate new targets into therapeutic programs are essential to filling the future drug pipeline with innovative medicines. Transparency in data sharing, professional project resource management, and team-member-specific incentives would go a long way in improving these partnerships. Like any positive human interaction, mutual respect, trust, and accommodating the viewpoint of others are essential for success.

4. Expert opinion

Academia–pharma partnerships: are they essential, cosmetic, or are they just nice to have? We believe they are *critical* to overcoming the pharmaceutical innovation deficit and bringing publicly funded novel discoveries to the patient [12,13]. The rate of discovery of new therapeutic mechanisms, enabling technologies, and novel translational models are increasing year over year. Pharmaceutical research siloed within a company, the norm of yesteryears, is no longer the case anymore. Likewise, drug discovery in an academic setting has also evolved significantly in recent years, and the value of partnering with private industry has increased. The value is not solely monetary. These diverse partnerships bring together the best ideas and approaches for identifying novel therapeutic targets, address translational chemical biology deficits [13], and develop new technologies and chemistry to advance the utility of these public-funded discoveries. Transformation of academic discoveries for common good can only be achieved through the involvement of 'industry.' The high cost of establishing resources to support drug development and fund clinical trials is beyond the scope of any academic institution. Pharmaceutical expertise and resources are required to guarantee the therapeutic relevance, translational potential, and facilitate path to development. To harness the best avenues possible in the most cost-effective way, pharma now outsources many of its activities, and academic partnerships have become a key element of early pipeline strategies. It is time for the academic and industry partners to whole-heartedly embrace these partnerships and solve remaining stumbling blocks. Academic TT offices need to align licensing terms with pharmaceutical program stage gates. Harmonization of definitions of program stage with industry standards could be taken on by open source efforts to bring the broadest dissemination. A single collaboration model, of course, will not fit all, but by driving innovation in the partnership model as well as the research, the challenges can be overcome. The model can be a community-driven 'Wikipedia' or 'Waze'-type shared knowledge, openly accessible innovation model to harvest data, a crowd-sourced path to data (information) sharing, or a more traditional program-focused collaboration [11]. The broader

issue of reproducibility of data in academic research will continue to seed mistrust and hinder expansion of private funding. The academic community and public funding agencies need address this in earnest and increase the visibility around their efforts to overcome this mistrust. For example, the NIH has incorporated new requirements around scientific rigor and sharing of key reagents and data as a prerequisite to funding. The partnerships must foster a culture of the collaboration and embrace a shared project timeline, teamwork, trust, and certainly a share in the rewards. Private companies should be willing to provide greater transparency into the structure, scope, and outcomes of public–private collaborations through publication of successful models and the lessons learned. Broader knowledge of challenges in these collaboration models will bring forth new ideas and avoid repetition of mistakes. Public funding of research will continue to be constrained, and private funding is critical to keeping up the pace of new discoveries. These two entities are better together, and this new paradigm provides a viable means to bridge the pharmaceutical valley of death.

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Declaration of Interest

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