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Editorial

The Rise of Academia-Pharma Partnerships for Discovering New Chemical Matter for Future Drugs

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Amazing opportunities exist at the interface of academia and the pharmaceutical industry. However, partnering on critical projects has been relatively restrained due to distinct purposes and goals, along with differences in culture and potential issues such as patent rights. These barriers are now less onerous as both academia and pharma are undergoing core changes and the potential benefits of interacting are becoming more attractive [1-4].

To promote and properly manage these interactions, one should first better understand historical legacies. Over the last 25 years the pharmaceutical industry has experienced many trends and fads that have come, gone or evolved. Many have centered around new technologies and strategies such as high-throughput screening, combinatorial chemistry, PCR, computer- and structure-based drug design, biologic drugs and more recently CRISPR-Cas9, etc. In general, pharma invested in these technologies by bringing them in-house and enjoyed their benefits with full confidentiality. However, the changes experienced by pharma during the latter part of this decade has been profound and will likely have lasting impacts. The industry is undergoing dramatic and fundamental changes to its business model, which is due largely to multiple convergent sources. For example, the lucrative income provided by patents on many blockbuster drugs have recently or will soon expire (referred to as the "patent cliff"), and this has also helped spawn a significant rise in the marketing of competitive generic medications. As a result, pharma is experiencing serious losses in profits which has also been further exasperated by the, (i) endless rise in costs for research and development (R&D), (ii) few new blockbuster opportunities, (iii) changes in healthcare funding (pricing pressures), and (iv) the rise of cheaper pharma from Asia. Furthermore, the "hierarchal mentality" and "tunnel vision" of pharma has promoted a "conveyor-belt mentality" that contributed in part to lower innovation and productivity, which is often referred to as the "valley of death".

Pharma's business model is reacting to these convergent sources in perhaps a non-reversible manner. Company mergers and acquisitions have become common place strategies. Many therapeutic portfolios have been eliminated or refocused, and partnering has become more attractive. This has also been accompanied by some troubling consequences such as massive layoffs and the reduced commitment to less-profitable therapeutic targets. This is unfortunate for society given lowered competition can lead to reduced invention and innovation. Also, this results in smaller talent pools of scientists to mentor the next generation. Downsizing and the closure of R&D sites in western countries has become familiar as well as mass migration toward Asia. More recently, however, pharma has been adopting smart strategies. For example, they are downsizing and strategically establishing a strong core of scientists in-house that focus on critical projects and outsource as much as feasible. Another important trend has been the increase in academia-industry partnerships which have coincided with relocations of pharma to academic-rich centers such as Boston, San Francisco and San Diego. In short, there appears to be a conscience effort to alter the core business model toward outsourcing which effectively trims R&D costs and augments profitability. If managed well, then outsourcing to academia may also improve opportunities for inventions and innovations.

Academia is also experiencing economic and existentialist issues. Major reductions of government funding are currently stifling research, which is further exasperated by rising costs. Moreover, the current and future job markets are rapidly changing as a result of new and advancing technologies, which in turn are influencing the roles of academic institutions to quickly respond with appropriate refocusing in student education and training. It appears that applied science is taking more of a front seat with regard to funding opportunities, student interest and relevant training for the job market.

Perhaps the time is right for seizing the opportunities that exist at the interface of academia and pharma. Pharma needs to outsource and improve inventions and innovations to establish a steady and reliable pipeline of drug candidates. Core changes were imminent due to the downsizing trend described above, and catalyzed by the financial crisis of 2008. Rather than re-invest in infrastructure, pharma is looking to fill their pipelines by outsourcing, leaving the financial and research risks to biotech companies, contract research organizations, and academia. On the other hand, academia needs funding and practical training programs for students. Therefore, fruitful opportunities are available if appropriate relationships are developed that satisfy their distinct cultures and needs as partners. Below we describe one example where collaborations can be developed – the discovery of new chemical matter for future drugs.

Historically, there have been four principle avenues for identifying new chemical matter to initiate small-molecule discovery programs. (1) The "me too" strategy entailed copying literature and patent claims to find similar but sufficiently distinct compounds. (2) Natural substrates have also been a rich source for ideas to design active mimics of peptides, sugars and nucleosides. (3) High-throughput screening of large compound collections (e.g. 1 - 5 million compounds) has also been a profitable means of identifying new chemical matter. (4) Finally, fragment screening is becoming a valuable alternative and is discussed in more detail below.

Academic-industry partnerships can perhaps help to improve these avenues. The "me too" and substrate mimic strategies would have to be considered on a target-by-target basis. Novel ways of jumping from one chemical series to another could be attractive, and there are a multitude of potential ways to produce new substrate mimics. However, the transposition of high-throughput screening (HTS) will be difficult in an academic environment as the responsibility for the discovery of new chemical matter for initiating drug discovery programs will be falling more and more onto the shoulders of smaller institutions (e.g. biotechs, universities, non-profit institutions). Simply put, these smaller institutions lack the impressive infrastructure, large compound collections (e.g. > 1 million) and manpower traditionally employed by large pharma. Nonetheless, some institutions are mounting medium-sized collections of hundreds of thousands of compounds and implementing medium throughput screening platforms.

Fortunately, fragment-based screening provides a potential means for smaller institutions to identify drug seeds, as it is a validated strategy which has led to compounds to the clinic/market. Fragment-based lead discovery (FBLD) requires much smaller compound libraries (i.e. ~1,000 to 3,000 fragments), fewer personnel and minimal infrastructure. It involves the screening of small libraries of low molecular weight compounds called 'fragments' to search for new binders to target proteins. These binders can then be employed as scaffolds from which appendages can be systematically added to improve potency. This and other related strategies are used to "build drugs from scratch".

Overall, academic-industry partnerships can develop "win-win" opportunities that would provide access to translational research not readily available otherwise. Valuable services and partnerships could save time, reduce risk and result in significant savings. Intellectual property can be generated on a fee-for-service basis, eliminating major historical obstacles. Novel strategies can be continuously developed, improved and published. It may also allow academia to focus on intriguing observations as sources for important innovations, rather than set aside as non-target annoyances. Unique and pertinent educational programs will help train the next generation of skilled high-tech scientists and promote knowledge transfer. In short, these collaborations can help spawn education and training, invention and innovation, and foster new economic alternatives.

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