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Collaborative practices for medicinal chemistry research across the big pharma and not-for-profit interface

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In response to the dual challenges of increasingly risky target portfolios and realignment of traditional pharmaceutical company resources away from early-phase research and development (R&D), research groups have sought to engage across the industrial and not-for-profit divide, resulting in the emergence of many different collaborative models. Here, we describe two successful collaborations based upon shared commitment and risk. The risks and complexities of external collaboration can be mitigated by appropriate agreements and tools, but we found that it remains essential that the collaborating scientists adopt a collaborative mindset and embrace the diverse ways of working of partner organizations.

The challenges of discovering and developing novel therapeutics in the 21st century have been well documented [1], but as the 'low-hanging fruit' of drug targets have been picked off [2], the challenge to maintain the pace of new discovery has led to an increase in the complexity of targets and disease pathways in discovery portfolios. The economics of the pharmaceutical industry has forced a realignment of resources away from early R&D [3], in turn making industry more reliant on the discovery and early validation efforts taking place in academic settings [4]. The challenge has become how to connect the pharmaceutical discovery machine of industry with a more diverse and diffuse source of new targets, and to do so in such a way that both academic researchers and the pharmaceutical industry benefit. The validation of new targets cannot truly be completed without reaching the stage of Phase 2 studies in humans [5], a stage well beyond the reach of most academic research environments; thus, translational groups with research capabilities of their own have emerged to help bridge the gap [6]. Although our perspectives on the changes in discovery philosophy and strategies for both pharma and translational research groups are the subject of a future paper, here we describe how new collaborative practices, built around shared risk and commitment, can enhance the discovery of new medicines.

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The development of industry–academic collaborative models

Much has been written on the principles and practice of collaboration [7] and connections between academic research and industrial pharmaceutical discovery are not new. To illustrate collaborative arrangements between UK-based pharmaceutical companies and the UK academic sector, direct funding of post-doctoral researchers in academic settings, and joint supervision of PhD studentships through UK research council-funded schemes have been a component of drug discovery research for at least 40 years. Larger targeted schemes have been developed between the research funding bodies and industry; historically, the LINK schemes targeting particular scientific challenges or the more recent doctoral training schemes (http://www.bbsrc.ac.uk/dtp and http://www.epsrc.ac.uk/skills/students/centres/) are just two examples of such approaches. On a more global scale, examples include the Structural Genomics Consortium (http://www.thesgc.org/), established to focus academic structural biology on challenges identified by pharmaceutical companies, and Medicines for Malaria Venture (http://www.mmv.org/), which supports both early academic research as well as industrial partners in developing novel therapeutics as antimalarial drugs.

With the exception of direct research funding by companies, one significant factor of these examples is the component of public disclosure. Funded (at least in part) by research councils

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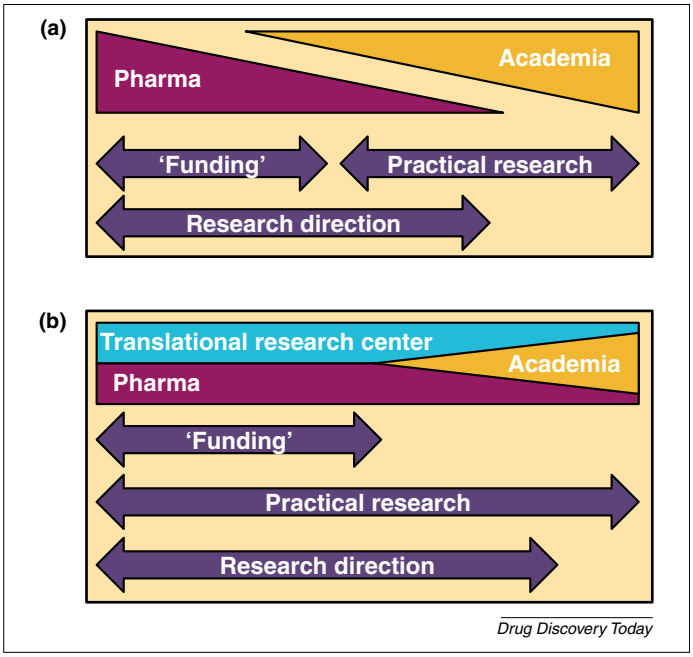

FIGURE 1

(a) Example of a traditional academic–pharma funding and research model. **(b)** Example of a translational research center–pharma–academic funding and research model.

or charitable foundations, there is an expectation that results will reside in the public domain, which can often be counter to commercial needs for intellectual property (IP) protection. In addition, the contribution of each party tends to reflect their position in the structure; industrial partners (which typically equates to funders) define the direction, whereas academics perform the experimentation (Fig. 1a). This runs the risk of different levels of commitment, which *in extremis* could divide between disinterested industrialist (we have told them what to do, get on with it) and disaffected academic (my academic freedom is being compromised) [8].

The collaborations described herein between AstraZeneca (AZ) and either Cancer Research Technology (CRT) or Medical Research Council Technology (MRCT) have been structured to address the concerns discussed above by being based upon shared commitment and risk. Active practical research is undertaken at both AZ and the partner Translational Research Center; moreover, any additional academic involvement is maintained through the already existing close relations between the Translational Research Center and its academic principal investigators (Fig. 1b). Appropriately structured collaborative models can incentivize all parties to invest in novel therapeutic approaches over the longer term [9]. The partners need to 'see it through' despite scientific challenges; the fact that they are tied in for the long term means greater commitment than if they were going it alone. A final benefit of the sort of strategic collaborations described is that they enable transferable learning from one project to another. We faced steep learning curves to improve the efficiency of some aspects of our early efforts to collaborate. However, the fact that we have prosecuted multiple targets together has informed effective ways of working, some of which we share herein.

Setting up the collaboration and creating an effective project team: best working practices

As has already been described, several collaborative models are being explored to promote innovation in drug discovery [10–15]. The distinguishing feature of the projects described herein is that, unlike other collaborations explicitly described in the literature, the boundary of collaboration has been extended beyond compound collection sharing (hit-seeking) to the collaborative design–make–test–analyze phase. The specific challenge for us was how to create a research agreement that gave the chemists the maximum freedom to work innovatively and synergistically, whilst controlling the risk of inadvertent reach-through into the broader proprietary information and know how that existed in the separate non-alliance parts of AZ, CRT and MRCT.

The complexity and potentially conflicting demands identified were tackled by ensuring that senior chemists from each organization were involved in the drafting of the research agreements. To make a meaningful contribution, the individuals drew upon a sound knowledge of intellectual property constraints and opportunities, business acumen, strong collaborative working skills and a willingness to work in external partnerships. The crucial step in drafting the agreements was the inclusion of mutually agreed definitions and nomenclature to describe key project milestones and progression (vide infra). This provided a precise set of ground rules for the chemists, in turn allowing maximum opportunity for creativity and innovation within defined boundaries. Additionally, when the strategic alliances deliver their goals or move into new collaborative phases, all parties will be clear about the extent to which compounds and know how are co-owned and restricted to the originating projects. Conversely, freedom-to-use outside of the original targets is also clear.

Between us the authors, we have over 60 years of medicinal chemistry experience, working in several organizations both large and small. Experience has taught us that lead discovery and optimization chemistry is a fairly uniform scientific process (albeit with several nuances dependent on target and therapeutic area), and that using widely available chemical structure and structure–activity relations (SAR)-based communication tools, medicinal chemists can readily agree and debate strategies for optimization of particular chemical series. This common experience of compound identifier + chemical structure + biological data allows immediate shared understanding, ideas and direction; however, many aspects of project collaboration across organizational boundaries have the potential to disrupt significantly the effectiveness of this core understanding. With this in mind, we invested time at the initiation of our shared programs to ensure as much common understanding as possible.

Project mind-set at the outset will be heavily influenced by the management of each party involved in the research project. From the very beginning, it should be understood by all that, for any particular program, there is one project and one project team, with membership from all parties; management commitment to supporting this is crucial to the success of any joint research project. This has to be extended to additional groups brought into any program; for example, in one AZ–MRCT project, key pharmacodynamic studies were performed by the US AZ research site. However, the management of the study and the consideration of the outcomes were managed at the combined AZ–MRCT project