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The emerging academic drug-discovery sector

“The development of integrated drug-discovery groups in universities has the opportunity to revolutionize the early phase of drug discovery and support our ailing biopharma industry...”

The short history of drug discovery has been one of constant scientific and structural change. In the early days of academic biology and pharmacology, discoveries such as those of Paul Ehrlich in the late 1800s identified interactions between compounds and protein receptors and laid the foundations of modern drug discovery. Such advances, coupled with expansion of the understanding of chemistry to a level that could support the concept of a pharmaceutical industry, led directly to the emergence of blockbuster drugs and the large multinationals of today. The 1970–1980s saw the rise of the biotech industry, where many companies were launched as spin-outs from universities. Although many have struggled to make any impact, there have been significant exceptions, such as Genentech. More recently, there has been a growing movement within the more forward-thinking universities not just to spin-out individual business opportunities, but also to develop basic research by creating drug-discovery capabilities in-house. In recent years, a number of such centers have been established worldwide. For example, in Europe at the Katholieke Universiteit Leuven (Belgium), Actar, Karolinska Institute (Sweden), the Drug Discovery Unit, University of Dundee (UK), The Drug Discovery Centre, Imperial College (UK), and, in the USA, at the Translational Research Institute, Scripps Florida, and the Center for Chemical Diversity (CA, USA). Centers such as these are operating under very diverse models from totally virtual organizations with only project management in-house, to organizations that run most of the predevelopment studies in-house and from loose collaborations to fully integrated groups under one management structure. These centers mirror developments in established organizations within the public and charitable sectors, such as the Institute of Cancer Research, Medical Research Council

Technology or Cancer Research Technology, which have emerged to exploit their fundamental research. All such organizations are distinguished by their nature from the more usual industry–academic partnerships.

This article will concentrate on the opportunities and benefits offered by the establishment of such an academic drug-discovery sector. It will cover only drug discovery *per se* rather than the field of chemical biology, which represents the major associated activity in academia.

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There are significant opportunities for university-based drug-discovery and development centers, provided they are not seduced by the large sums paid for the inlicensing of promising drug-development candidates and, thus, end up competing with biopharma or merely replicating biopharma in another setting. Non-biopharma drug-discovery and development centers need to find ways of developing activities complementary to the biopharma industry that can provide value to patients. An organized and well-funded academic drug-discovery sector could develop such a complementary approach and make a significant impact in five major areas:

- Partially de-risking novel drug-discovery targets;
- Tackling neglected and orphan diseases, whose patient base demographics or numbers are not suitable to generate sufficient income to offset the cost of drug development in a commercial setting;



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- As a test bed for the development of new paradigms for drug discovery, within an environment carrying out drug-discovery projects;
- Training young scientists in the practice of drug discovery and educating basic scientists in the requirements for the translation of fundamental research into drug discovery;
- Efficient use of grant funding.

At the same time, the emerging academic drug-discovery industry must be alert to the pitfalls that may prevent it from achieving its potential. I will deal with these areas in turn.

De-risking novel drug-discovery targets

Despite further advances in our understanding of diseases via information on the human genome, this wealth of information has not eliminated the bottleneck in the identification and validation of therapeutic targets, something that has been one limiting factor in the rate of therapeutic discovery. In fact, while we might imagine that all the new technological and biological information might expand the potential for new drugs and free this bottleneck, experience has shown that ‘new targets’ as opposed to ‘established targets’ are, in general, more prone to drug-discovery project failure. This experience has driven a trend, beginning at the turn of the 21st Century and continuing today, of increased risk aversion in target selection among pharmaceutical companies.

Although the discovery of ‘me too’ compounds has supported the industry for some time, diminishing opportunities and greater pressure from regulatory authorities have started to limit the returns from this approach. To survive, therefore, the traditional drug-discovery industry will have to address the more difficult area of novel targets as a means of freeing the current bottleneck. This is one area where academic research and drug discovery can, and are, making a significant impact.

For the foreseeable future, while new target validation methodologies are developed, the attrition rates of these risky projects will be high. However, limited successful outcomes in a drug discovery sense can be offset in an academic setting by the additional end products used to measure success in this sector. These measures of success include the advancement of basic science and its reporting through high-quality publications, the training of scientists and the

development of novel techniques and methods. Since making money and satisfying shareholders is not the measure of success in the academic drug-discovery sector, it enables the very risk taking that will expand opportunities for taking advantage of technological developments and enhanced understanding of biological systems.

There must be a principled approach to risky projects, however, to ensure that the research is driven by patient need as well as to maintain the genuine drug-discovery ethos. In this way, the paradigm of drug discovery within the academic setting can make a significant contribution, through the parallel running of true milestone-driven drug-discovery projects alongside academically driven projects that develop the underpinning biology of the target or indication under consideration. If carried out by open-minded individuals, this cross-fertilization approach can have many benefits. These will include: the development of screens and secondary screens to identify lead and drug-like compounds suitable for use in cell and *in vivo* studies, robust assays to confirm on-target action of the compounds in cellular or animal models of disease, improved models of disease either in animals or by the use of patient-derived tissue (the latter not often available to biopharma organizations) and biomarkers to aid translation into clinical trials. Although some of the techniques mentioned above are expertly developed by biopharma, the depth of these studies can be limited by the tight timelines of critical path-driven projects. Universities have the added advantage that the range of expertise available is extremely broad, a breadth not available within the biopharma industry.

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Successful projects will lead through to high-quality data packages suitable to support further grant applications to enable additional optimization in-house or selective licensing out to external partners, such as biopharma or public-private product-development partnerships.

Currently, there are significant out-licensing opportunities due to the need of the biopharma industry to in-license projects at all points of the drug-discovery and -development process, due to empty pipelines. In a few cases, successful

projects, developed in academic drug discovery, could act as a source of revenue, through the licensing of targets and chemical matter.

Although biopharma is seeking to engage with academic groups, the industry continues to be highly reluctant to release tools and knowledge, such as proprietary compounds to help accelerate progress. Possible gains from such extended collaborations are lost due to fear of missing intellectual property rights on compounds that might be screened many years in the future. Building successful and professional academic drug-discovery centers with a track record of success should help to redress the balance in favor of the release of proprietary compounds and technology to develop new targets and assets now, rather than holding on for an imaginary future.

Tackling neglected & orphan diseases

Academic drug discovery is an ideal setting to tackle noncommercially viable diseases, such as neglected and orphan diseases, where the final market is not sufficiently large or wealthy to recoup the massive costs of drug development. The early discovery phase can be carried out using charitable or traditional modes of academic funding and then projects can be passed on, either during lead optimization or at the pre-clinical stage, for further development by dedicated not-for-profit development organizations, which themselves are funded by governmental or charitable donations.

In the case of neglected diseases, development is carried out by organizations such as the Drugs for Neglected Diseases initiative, Medicines for Malaria Venture or TB Alliance. For orphan diseases, a level of target de-risking could be undertaken to a point where it becomes commercially attractive or could be funded by a disease-focused charitable group (e.g., the Michael J Fox Foundation for Parkinson Disease and Cystic Fibrosis Foundation Therapeutics). Already, more biopharma companies are becoming involved in neglected or orphan disease drug discovery and see academic groups as attractive partners to contribute expertise as well as hit and lead generation capabilities, thereby allowing the commercial partners to focus their resources on areas of core expertise, such as lead optimization.

Test bed for development of new paradigms for drug discovery

There have been significant advances in the last 20 years in underpinning technologies and our understanding of biological systems. Together

with advances in synthetic chemistry technology and the ability to develop more sophisticated animal models of diseases, the outlook for the discovery of novel therapies should be bright. However, drug discovery remains a long process, with high rates of attrition at all stages and a correspondingly low rate of new drug registrations. This has led to the much-discussed lack of success of biopharma in translating the ever-rising expenditure in drug R&D into registered drugs and therefore highlights the need for new paradigms of drug discovery.

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The mixed model of academic drug discovery allows the opportunity to develop new drug-discovery methodologies within live, truly integrated drug-discovery programs, to feed into the biopharma sector. The broad range of research over many disciplines within universities opens up the possibility of establishing many collaborations to develop new methods and approaches in areas such as data mining, informatics, computational chemistry, compound library selection and design, synthetic organic chemistry methodology, parallel synthetic and purification technology, *in silico* pharmacokinetics and toxicity predictions and animal models for efficacy and toxicity. The true expansion of this area would need a relaxation of the tight timelines imposed on projects by funding agencies, which drive the use of tried and tested methods and discourage risk taking, through the introduction of additional measures of success outside just drug candidate delivery.

Training young scientists in the practice of drug discovery

There is a rare opportunity to build an academic drug-discovery sector with an unprecedented pool of talent and experience leaving biopharma due to shrinkage of the sector in America and Europe. This talent needs to be engaged before their expertise is lost to other sectors.

In parallel, there is across the world a vast amount of basic research that could be exploited to tackle unmet medical need. It is essential that embedded drug-discovery groups in the academic sector develop strong ties with basic researchers to ensure existing and potential new

targets are taken into drug discovery where possible and when appropriate. This can be achieved through informing those carrying out fundamental research about the additional studies required to validate targets and develop assay formats to a stage where they are suitable for drug discovery. Embedding drug-discovery groups within universities improves and makes the most of the links between fundamental research and drug discovery as well as associated organizations, while also allowing people to focus on their key areas of expertise.

The presence of the experienced drug discoverers from industry allows the direct and indirect transfer of knowledge into both the undergraduate teaching and postgraduate research of university departments in areas such as assay development, medicinal chemistry and pharmacokinetics. This kind of training is not normally available to scientists who have only taken the academic research route.

The addition of experienced drug discoverers, as high-quality scientists, into academic research departments can also bring many positive attributes from the mainstream industry. This encompasses industrial good practices, such as robust quality control, outcome-driven project management, the understanding of target drug-gability and compound lead and drug likeness and the ability to operate across the many disciplines needed to successfully carry out drug-discovery projects. While such considerations may seem obvious, they are not always of primary importance in a pure academic context, which has very different drivers and measures of success. Many academic chemical biology projects, though aimed at identifying biochemical target inhibitors, operate according to different measures of success and, thus, frequently identify compounds that are not suitable even for cell-based assays, let alone *in vivo* testing.

Efficient use of funding

The establishment of drug-discovery groups within universities has significant potential benefits for funding bodies interested in achieving their missions of improving human health. Indeed, studies have shown financial return on pharma industry investment in academia through both licensing and funding basic research can be similar to that of investments in their own internal research programs.

Although all universities could seek to establish a drug-discovery group, few would have the infrastructure and critical mass of fundamental

research to support one long term. Even with a significant number of historically accumulated projects, a significant future pipeline of suitable new projects would be required to support drug-discovery activities. Therefore, a more realistic model is the establishment of a limited number of fully functional drug-discovery centers, which would contain compound libraries and the robotics to efficiently screen them with associated medicinal and computational chemistry in addition to drug metabolism and pharmacokinetics groups to develop hits into leads. These centers could be accessed for support and resources by smaller discipline-focused groups.

This model would represent an efficient use of resources on a number of levels. The establishment of central screening centers with accompanying compound screening sets would reduce redundancy and allow the compilation of larger sets, rather than duplication of the same compounds in multiple centers.

Running a portfolio of projects within a core drug-discovery group rather than as standalone projects, or spinning out companies, has efficiencies as the per-project running costs will be substantially lower than running standalone biotechnology companies, due to ready access to a substantial levels of expertise, equipment and infrastructure within the university.

In addition, concentration of a number of projects within an expert group allows the implementation of portfolio-based project management and funding that can provide both financial and scientific efficiencies and synergies. Portfolio-based project management has the benefit of encouraging critical assessment of projects as individual closures would not result in withdrawal of funding. This also reduces the need to constantly build teams to work on individual projects, resulting in increased job security and aiding recruitment. People employed in this way can readily work across projects, thereby increasing both productivity and effective use of expertise and funding. This model fits well with current funding trends, such as the Medical Research Council Pathway Funding Scheme.

Portfolio-based funding allows the risk of funding early-phase projects, which could fail very early and rapidly, to be spread across multiple projects. These projects could score very poorly during the established process of seeking funding for each individual project, resulting in their never being funded and stifling the very innovation scientists, industrialists and governments are seeking. Other advantages are

possible, such as reduced timelines for projects going from idea to funding approval, the reduction of redundancy of funding, where the normal mode of funding could be for 1–3 years, although a project might in reality fail after 6 months. Although this model would see many projects halted within the drug-discovery paradigm, this would not necessarily spell the end for the fundamental research. In fact, the drug-discovery project would, in most cases, present a new series of questions to be answered and, in many instances, supply tools, including compounds, to answer them. Once issues have been addressed, there will be the potential to bring projects back onto the drug-discovery radar.

Concluding remarks

In summary, the development of integrated drug-discovery groups in universities has the opportunity to revolutionize the early phase of drug discovery and support our ailing biopharma industry. The current turmoil within the biopharma industry opens up a wealth of opportunities to develop this new drug-discovery sector. The establishment of dedicated drug-discovery centers has the potential to deliver benefits to both patients and to the biopharma industry through the partial de-risking of new targets and the identification of lead compounds. The introduction of biopharma-experienced drug discoverers to universities will bring all the benefits previously outlined.

Academic drug-discovery organizations should be more than screening centers, as much of the information generated will be lost without downstream optimization and exploitation of the hits generated. However, they will need to be realistic about which aspects of the drug-discovery process they seek to address and will need to ensure sufficient resource is available at each stage to make sufficient progress.

Like all new endeavors, this paradigm needs to be given time and funding to reach its full potential and seek alternative ways of doing drug discovery. Both universities and funding

bodies need to bear in mind that, although these groups have the possibility to generate funds from the commercialization of successes, to become self-supporting, commercially viable successes will be sporadic and take significant time to deliver.

The next 5 years will be a crucial time for this sector, with the establishment of new groups and the continuing success of established groups consolidating the sector at the forefront of global early-stage drug discovery. What the sector needs to do now is to continue the battle for suitable funding, deliver high-quality outcomes and continue to carve its niche alongside the pharma and biotech industries.

Disclaimer

The opinions expressed in this editorial are entirely personal and do not reflect those of the University of Dundee, The Wellcome Trust or any other organization.

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