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Making the most of academic drug target discoveries

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The explosion of new technologies and research techniques, and encouragement from funding agencies for academic institutions to undertake more translational research, has led universities to devote greater resources towards applied drug discovery activity. Universities and academic institutes are therefore now discovering an increasing number of 'drug targets'. These are molecules, often proteins (such as enzymes or cell surface receptors), that could potentially be manipulated by chemical or biological entities to treat disease. Arguably, universities now lead companies in discovering novel drug targets. Two key problems are encountered by many research intensive universities and their technology transfer offices in relation to such activities. The first is whether there is value in filing patents on novel drug targets. The second is how to progress the development of new drugs against such targets in order to best position them for licensing to pharma and biotech companies. Although these novel target discoveries may ostensibly be of interest to industry, it can be difficult for universities to secure commercial investment and translate them into fully-fledged drug discovery programmes, particularly in the absence of further validation.

In certain unique cases, such as the output from the Structural Genomics Consortium at Oxford, the target structures and associated probes generated are all deliberately made open access and it is a policy not to file any related patents[1]. The rationale is that industry will, in the absence of any IP barriers to entry, step in early and use these results as a basis for downstream screening activities and identification of patentable chemical series. However, as will be outlined below, in situations where no open access policies exist, patenting drug targets remains fraught with difficulty, and in many cases alternative approaches to support commercialisation are more viable. We examine the strategic options for managing and protecting IP associated with new targets, and discuss a range of approaches to help universities make the most of such early stage discoveries, and ultimately position them favourably for the large-scale external investment required to develop new therapeutic products. These strategies have the potential to lead to more effective outcomes for universities, technology transfer offices, and industry.

The challenges of patenting drug targets

Researchers generating new insights into disease processes will often discover a particular protein or other molecule that is important in the disease, and thus a potential target for therapeutic intervention via a drug. The most common approach to commercialising this type of discovery in a university environment is to file a patent application claiming the novel and inventive aspects of the discovery, and then seek to license this and any accompanying knowhow or data to a commercial partner for further development. However, there are various difficulties with this model when it comes to patenting drug targets.

Due to the limitations of the university environment, and the pressure to conduct novel research, in most cases university researchers will not be able to fully validate the target nor develop any form of new chemical entity (NCE; a novel chemical compound which has activity against the target) or biologicals (antibodies, or small protein molecules called peptides which are engineered to have activity against the target molecule) to increase or decrease the activity of the target for therapeutic effect.

Researchers will generally seek to demonstrate the function of the target by knocking out the gene involved using RNAi (RNA interference, a method for down-regulating the activity of a gene), by mutagenesis (disrupting the function of the gene in an animal model), or by gain of function approaches, whether in cell culture or animal models such as mice. However, the lack of novel chemical entities or biologicals rules out the possibility of gaining the most valuable type of patent protection, the so-called 'composition of matter' patent application. Composition of matter patent applications seek to claim the production and use of a novel and inventive NCE, class of NCEs, or particular antibody clone for use against any target in any disease – a very strong form of patent protection, and an attractive commercial proposition. This type of patent is very attractive to industry, as it enables them to, at least partially, exclude competitors from the same space.

In cases where NCEs or biologicals are not available, it is not possible to get composition of matter claims, and it is therefore necessary to consider other types of claims. One alternative is to file a patent application against the drug target itself. Patents against drug targets commonly include two major types of claim – the use of an agonist (a molecule that increases the activity of a target)/antagonist (a molecule that decreases the activity of the target) of target *x* to treat disease *y* (commonly known as 'method of treatment' or 'reach-through' claims), and a method of screening for molecules that agonise/antagonise target *x* (screening/assay claims). Such patents can also include biomarker-type claims, which for example, claim the presence or level of the target molecule as an indicator of a particular disease or disease sub-type.

Unfortunately, such patents often have limited commercial value and appeal. The main reason for this is that courts in the US and Europe have generally ruled against the more valuable 'reach-through claims' i.e. ones which claim the use of any possible hypothetical drugs/antibodies against the discovered target (for a review of this see[2]). Unless evidence is included in the patent that particular chemical entities will work against the target, patent examiners will not grant such claims (and if NCEs are included in the claims, granted claims will relate only to that class of drugs and not to all possible drug molecules). This stems in part from a famous legal case in the USA[3], where the University of Rochester sued Searle (now Pfizer) claiming that Searle's Cox-2 inhibitors infringed the reach-through claims in the university's Cox-2 target patent. The courts found that, as the University of Rochester had not provided any compounds to exemplify its claims for Cox-2 inhibitors, the claims were invalid.

In many ways, this decision was entirely understandable, as otherwise a single party could 'lock-up' a whole field with very limited data, by claiming all entities against a particular target. This could then discourage other companies from investing in developing drugs against the target, and thus hinder innovation and patient benefit.

Unlike 'method of treatment' claims, screening assay claims are more likely to be granted by patent examiners, as academics will often have developed a screening assay of some kind during their research, which can be included in the patent to exemplify the claims. Unfortunately, however, these claims may also have little value. By the time any patent is issued, companies will, based on their prior review of any published academic paper on the target, have developed lead compounds – and will therefore not infringe the now issued screening claims. Notwithstanding the fact that companies will often have generated lead compounds by the time screening assay patents are issued, due to the confidential nature of companies' screening activities, it is in any case extremely difficult to determine whether they might be infringing a screening patent.

Pharmaceutical and biotechnology companies generally do not file target patents for the reasons described above, but instead seek to keep their research confidential until they have developed lead drug candidates. At this point they will file composition of matter patents, possibly including some claims to the particular drug target. Universities, however, are in a trickier position, as academics generally need to publish their work rapidly, and may also not have the capability to discover drugs against a target (though this is changing in some cases with the establishment of internal drug discovery institutes, as discussed later).

Due to the difficulties in gaining any value from the commercialisation of target patents, university technology transfer offices have become much more cautious about filing patents against drug targets (for example see this interesting web article by the former Director of Technology Transfer at UCSF[4]). Universities therefore need to be creative in generating value (both commercial and clinical) from their discovery of novel, scientifically interesting drug targets, and some strategies for doing this are described below. In the next section, however, we first outline the limited scenarios in which it may still be worth filing patent applications against a novel drug target.

Exceptions to the rule

In some cases it may be worthwhile to file a target patent application. Example scenarios are listed below:

1) If the drug target and disease is amenable to being treated by RNAi, then if the academic researcher has RNAi probes available, it may be worth claiming the use of these probes against the target for the particular disease. However, it should be noted, that the RNAi treatment field is very new, and it is therefore unlikely that the patent application itself will be of commercial interest unless there is substantial, and well validated work in an animal model to demonstrate both the validity of the target, and the utility of RNAi as a therapeutic strategy. In addition, claiming specific RNAi probes may be difficult in the US, as case law is unclear on whether these will be granted or not.

2) When a target is amenable to treatment by an antibody (e.g. an extracellular receptor), and knockdown or mutant data is available, then it may be worth filing a target patent claiming antibodies against the target. As it is now well known how to generate antibodies by scientists 'skilled in the art', patent examiners may grant claims to antibodies against a drug target even if the antibody does not yet exist, and is not described in the patent specification. This is by no means guaranteed however, and depends on the quality of the data and the vagaries of the patenting process. In addition, commercial partners may not be interested in licensing such a patent if the antibody does not exist and has not at a minimum been tested in animal models.

3) Where novel small molecules, peptides or antibodies are not available at the time of filing but may be generated within the first year, it can be worth filing a patent application, as the supporting data can be added into the patent before the end of the first year, at entry into the international PCT stage.

4) Method of screening claims may have some value if the target is of exceptional scientific and commercial interest. For example, the company Euroscreen claims to have successfully

licensed patents for the CCR5 receptor, and states that its target patents contain claims for the receptor sequence, for antibodies against the receptor, and how to generate and purify the receptor for use in ligand screening assays[5]. This patent family appears to have been commercially successful because of the importance of the CCR5 receptor in HIV treatment. Unlike most universities however, Euroscreen has been prepared to commit the significant financial resources needed to enter into expensive patent litigation to defend the patent against challenges brought by other companies, such as Progenics Pharmaceuticals Inc, who launched an opposition against the patent in Europe[6].

In all cases, projects will be much more likely to represent attractive licensing prospects to industry if there is a detailed package of data available, ideally including validation in animal models.

Getting the most out of new drug targets

In recent times, there has been a growing recognition of the need to try and bridge the gap between where university research ends, and clinical drug development in the pharmaceutical industry begins. The effort to bridge this gap has resulted in the development of a range of different public-private partnership models, which are well-summarised in a report by the Tufts Institute for Drug Discovery[7].These models have proved relatively successful in maintaining rapid progress in medical research and development, by bringing together the strengths of academia, industry, and independent research entities.

Some of these models represent useful ways in which new drug target discoveries could be advanced. There are also other ways that universities and academic institutions can take early stage target discoveries and build value around them in order to create licensing packages that are attractive to acquisitive pharmaceutical and biotech companies. This section lists a selection of these options.

1. <u>In-house drug discovery using translational funding</u>

Some larger universities, such as Oxford, are now developing resources – financial and infrastructure - to allow them to validate novel targets, develop NCEs and other potential therapeutics in-house, and to conduct their own clinical trials on resulting molecules. For example, Oxford has created the Target Discovery Institute (TDI)[8], a new facility which aims to link recent advances in genetics, genomics, and cell and chemical biology for improved drug target discovery and validation. It is intended that a more specific focus for refining and validating new targets will provide a better link between the traditional "open-ended" academic approach to biomedical research, and the need of the pharmaceutical industry for accurately defined targets for drug development. In addition, with the support of industrial funding, Oxford has developed and launched the 'Oxford Targets' programme, which provides internal translational funds for Oxford academics to develop and validate molecules against new drug targets, and an established mechanism through which pharmaceutical companies can engage to manage funding calls in specific therapeutic areas.

These types of initiatives, coupled with an increased ability to develop appropriate assays to screen compound libraries, allow university TTOs to file stronger, more commercially valuable composition of matter patents, and to take projects forward to a stage at which they are more likely to be licensed by industry, namely robust preclinical or (in smaller numbers) clinical efficacy proof of

concept. This strategy bridges the classic gap between academic research and projects of value to industry. It also enables universities to progress projects that may be of limited interest to industry, but have important public health benefits, such as drugs to treat diseases of the developing world.

However, this approach is expensive, both in terms of initial capital costs, and funding for specific projects. It also requires a substantial effort to set up the facility space, equipment, and to hire suitably qualified staff. Not all universities may therefore be able to pursue this route. In the UK, relevant translational funding to support drug discovery projects is available from external funding agencies such as the Wellcome Trust (e.g. the Seeding Drug Discovery scheme[9]) and Cancer Research UK (e.g. the Drug Discovery Project Awards scheme[10]). In the US, support for drug discovery activities may be obtained from a range of government organisations, charities, and philanthropic entities such as the Harrington Discovery Institute at University Hospitals in Cleveland, Ohio. The Harrington Discovery Institute[11] is the non-profit arm of The Harrington Project for Discovery & Development, a national initiative supporting breakthrough research by physician-scientists which provides financial and nonfinancial support through programs like the Harrington Scholar-Innovator Grant, the Foundation Scholar award, and the Harrington Prize to physician-scientists specifically to advance translational research addressing unmet clinical needs. In addition, it has an aligned for-profit commercial development/investment arm called BioMotiv[12] which seeks to develop promising new projects coming out of The Harrington Project, along with other selected opportunities sourced from universities and SMEs. The Harrington Project for Discovery & Development has historically focused on US academic institutions, but has recently entered into a first collaborative project with Oxford and plans exist to expand its activities further in Europe.

Although this section lists a range of ways in which universities can enhance their internal target validation and drug discovery abilities, academic institutions are unlikely to be able to match the discovery chemistry resources of a major pharmaceutical company. Using an in-house approach to address a very popular target could therefore be unsuccessful, as companies may already have more advanced programmes in-house. Instead, universities may be better focusing on their own novel target projects that require the kind of innovation and blue skies thinking for which academics are renowned.

2. Collaborative target development with external agencies, investors or CROs

An increasing number of organisations will work with universities to provide the resources and expertise to develop drug targets to a point at which they can be licensed to industry. For example, the Centre for Drug Research and Development (CDRD; http://www.cdrd.ca/) is a Canadian, government-funded institute which performs this activity, and which has an end-to-end capability to take targets through hit and lead generation to early stage clinical trials. Projects are selected by an experienced CDRD panel, which includes former industry executives. Another similar organisation is the IME Screening Port (formerly known as the European Screening Port)[13] within the Fraunhofer Institute for Molecular Biology and Applied Ecology (IME) in Germany. This organisation specialises in providing CRO-type services to academia, both to help validate drug targets, and to generate lead compounds and biologicals.

The resources provided by such organisations are useful as they allow university researchers to concentrate only on the research questions of interest to them, whilst outsourcing drug development and testing to an experienced partner. The partner and the university can then seek to

file composition of matter patents if appropriate, and once suitable proof of concept has been achieved, license these out to industry.

An alternative model is the European Lead Factory (ELF)[14], which is an open-innovation platform for drug discovery managed by a public-private partnership between a number of academic institutions, large pharmaceutical companies, and Small/Medium Enterprises (SMEs), and funded under the European Innovative Medicines Initiative (IMI)[15]. Academics and SMEs are invited to submit novel targets for screening against an existing library of 300,000 drug-like compounds which have been sourced mainly from large pharmaceutical companies. They are then offered various options to gain rights to exploit these compounds commercially under defined terms, or to file new composition of matter patents around derived compounds. This exciting initiative gives universities access to the kind of large-scale chemistry libraries, and high-throughput screening resources normally only available to large pharmaceutical companies.

A further possibility is for the university to work with a commercial Contract Research Organisation (CRO) to develop a novel NCE against a particular target, if the university believes the target may be of particular value. This could be an expensive proposition if undertaken on a pure fee-for-service basis. However, CRO's are increasingly prepared to consider more flexible collaborative arrangements with academic centres, where early costs are minimised or deferred by means of risk-sharing mechanisms and success milestones. For example, initial screening work to identify some lead series from a CRO's library (and so generate more robustly patentable matter) may be undertaken free of charge but with the expectation that the CRO and the university will then jointly apply for public translational funding to optimise and further develop the leads, with the CRO performing the work under a normal fee structure.

Finally, another option is to seek funding from a commercial investor to develop early stage targets to the pre-clinical stage, although the number prepared to consider single asset projects at such an early stage is limited. One example is Canada's Amorchem, whose business model involves 'financing research-stage projects to enable them to reach pre-clinical proof-of-concept' (Amorchem, http://www.amorchem.com/). Another example is BioMotiv, described earlier.

3. Research collaborations with industry

Industry may wish to collaborate directly with academics that discover a novel drug target, if it is of high therapeutic relevance, because the scientific lead that the academic may have can result in a competitive advantage for the company. Such collaborations can be a useful source of research funding for academic labs, and may allow them access to some of the resources that are available in-house at pharmaceutical companies. Many universities now have business development teams that seek to build research relationships with leading companies on a wider scale than with individual laboratories. These relationships can help fund a range of projects at the university, or may even fund facilities. Careful thought needs to be given to the intellectual property terms associated with these contracts, to ensure that the university receives appropriate commercial benefit if any data generated proves valuable, or amenable to patent protection. In addition to these more direct benefits, building research collaborations may lead to enhanced recruitment of students, licensing of other intellectual property marketed by the university's technology transfer office, and the broadening of the relationship into a more strategic arrangement.

Conclusions

Although patenting drug targets discovered in academic labs may not always be appropriate, there are other ways of generating and capturing value for the university from these discoveries – beyond simply the dissemination of knowledge to the wider world – and of developing these nascent discoveries into more fully formed drug discovery packages with sufficient data and robust IP protection to be attractive licensing propositions for commercial partners. This article has outlined several of these possibilities, which represent part of a growing toolbox of options that can be used as appropriate, according to the size and resources of the university and its technology transfer office, and the needs of the particular project. Universities may also wish to formulate internal strategies on how to maximise their ability to capitalise on the discovery of drug targets, and also produce guidance for their academics on why it may not be appropriate to file patents on targets without accompanying molecules. On a larger scale, collaboration between universities on costly resources like drug development institutes may also be a good way of maximising the benefit from useful discoveries, whilst avoiding unnecessary duplication. Finally, industry players interested in benefitting from this type of research need to keep in mind that universities (and their funders) wish to share in the value generated by their discoveries of novel drug targets, despite the difficulties in patenting them, and that this may require creative solutions.

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