



feature

Collaborative approaches to anticancer drug discovery and development: a Cancer Research UK perspective

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The pharmaceutical industry is under huge pressure to overhaul what is currently viewed as a highly inefficient operating model. Unacceptable levels of late-stage failure in clinical development remain a fundamental problem for the sector. Lack of efficacy is a major reason for candidate failure and a lack of understanding of disease biology is considered to be a key issue underpinning this problem. There has been a recent upsurge in interest from pharmaceutical and biotechnology companies to collaborate with academic institutions, with the latter viewed as being home to research teams with in-depth biological knowledge and translational research expertise. This article outlines models for collaboration in drug discovery and development being pursued by the research-based charity Cancer Research UK (CR-UK).

The discovery and development of new therapeutic options to address the currently unmet medical needs of society is the overarching mission for research-driven pharmaceutical and biotechnology companies. However, despite investing, on average, more than US\$50 billion per annum in research and development (R&D) over the past decade [1], productivity is in decline [2] and pharmaceutical companies have not been able to bring sufficient numbers of novel and effective drugs to market to deliver the levels of profitability demanded by the financial markets [3]. The industry also faces additional challenges as key patents expire, generic competition increases, healthcare budgets become increasingly constrained and positive health technology assessments become a requirement for reimbursement. As a consequence, share prices for the sector have generally fallen or stagnated over the past decade

[4] and the industry has, perhaps understandably, responded to these challenges by cutting R&D budgets and terminating drug development projects [5,6]. Attrition in drug development has long been recognised as a crucial issue, with a clinical development failure rate as high as 95% being reported for anticancer drugs [7–9]. The greatest cost to the industry comes with failure in late-stage, large-scale clinical trials, and recent studies indicate that despite massive R&D investments, the situation appears to be worsening with increased late-stage failure rates being reported [2,10].

Industry engagement with academia

The direction that the pharmaceutical industry has taken in seeking to develop innovative drugs targeting unexplored biological mechanisms implicated in the pathogenesis of chronic diseases is to be applauded, but the risk has proven

too much to bear alone. Lack of efficacy in clinical trials is the single most-cited reason for compound attrition [10,11]. A lack of understanding of biological mechanisms allied with the profiling of candidate drugs in models that display a pathophysiology that is poorly representative of the human disease condition has been cited as a major factor contributing to clinical failures [12]. These shortcomings have been further compounded by the application of suboptimal clinical trial designs; in the era of molecularly targeted agents, it is increasingly recognised that a new paradigm for clinical development needs to be adopted [13].

On a more positive note, having analysed reasons for clinical failure, the research-based pharmaceutical industry is now seeking to pursue new innovative ways of discovering and developing novel therapeutic agents. A central theme to the new thinking of the industry

around how to best pursue drug discovery and development is collaboration with the academic sector [14]. A key factor driving this trend is recognition that the real in-depth understanding of disease biology resides in academic groups, who often spend years focused on specific research areas. Furthermore, academic centres are also increasingly home to expert translational and clinical research teams focused on the design of hypothesis-testing, early-phase clinical trials. The current industry view seems to be that by accessing the academic knowledge base, more informed drug discovery and development strategies can be adopted that might mitigate against the costly risk of failure in late-stage clinical trials.

CR-UK drug discovery and development activities

Cancer Research UK (CR-UK) is the leading cancer charity in the world, whose activities include conducting basic research into understanding cancer biology and supporting translational and clinical science. The charity is funded entirely by public donations and raised nearly £500 million in 2010–2011. This money funds research activity carried out in institutes, universities and hospitals throughout the UK. Approximately 40% of research expenditure supports basic biology teams researching the molecular basis of cancer to understand how the disease develops. Understanding the biology of cancer is, however, by no means the sole focus of CR-UK, and the charity has for many years had an active role in the discovery and development of new cancer drugs. Notable successes emanating from CR-UK-funded activities in these areas include the discovery of temozolamide, an alkylating agent used for the treatment of glioblastoma multiforme, and conducting the early development of abiraterone, an inhibitor of 17 α -hydroxylase/C17,20 lyase, recently approved by the US Food and Drug Administration (FDA) for the treatment of castration-resistant prostate cancer [15]. Furthermore, CR-UK has contributed to the discovery or development of over 30 drugs currently in preclinical or clinical development with commercial partners. Cancer Research Technology (CRT, <http://www.cancertechnology.com>), the technology development and commercialisation company of the charity is responsible for protecting and commercialising intellectual property arising from charity-funded research and has also been involved in the establishment of over 20 companies active in cancer drug discovery and related areas.

CR-UK has provided long-standing support for the drug discovery groups at the Institute for

Cancer Research (Sutton, UK) and the Northern Institute for Cancer Research (Newcastle, UK) and has recently significantly increased its funding for research in this area. The CRT Discovery Laboratories were established to translate academic ideas into new drug candidates and are home to a multidisciplinary team of over 80 scientists (http://www.cancertechnology.com/discovery/discovery_laboratories). In addition, drug discovery teams have been established at the Beatson Institute (Glasgow, UK) and the Paterson Institute for Cancer Research (Manchester, UK). The charity also provides grant funding for several small molecule and biotherapeutic drug discovery programmes running in universities across the UK. Overall, CR-UK and CRT are currently supporting approximately 100 drug discovery projects.

In addition to activities in drug discovery, the charity also has a considerable track record in preclinical and early clinical development. The Drug Development Office of CR-UK (DDO, <http://science.cancerresearchuk.org/research/drug-development/scientists>) was established during the early 1980s and has taken over 120 agents into early-phase clinical development, including conducting the first-in-human trials of abiraterone [16]. The CR-UK DDO is home to a team of scientific and clinical operations staff currently managing a portfolio of over 35 projects in the space from preclinical candidate to phase II clinical trials. The DDO portfolio has a broad range of therapeutic modalities, including cell and gene therapies, antibodies, vaccines and radiotherapies, in addition to more conventional small molecule drugs. Several imaging agents are also being developed. Supporting the DDO is the CR-UK Formulation Unit based at Strathclyde University (Glasgow, UK), which undertakes the formulation development and good manufacturing practice (GMP) manufacturing of small-molecule investigational medicinal products (IMPs) for DDO-sponsored clinical trials. In addition, the charity has also recently made a further major investment in drug development with the opening of an £18 million state-of-the-art Biotherapeutic Development Unit in Potters Bar, UK. This facility undertakes process development and GMP manufacture of biological IMPs. The early-phase clinical trials of CR-UK are delivered through a UK-wide network of Experimental Cancer Medicine Centres (ECMCs; <http://www.ecmcnetwork.org.uk/>) that are home to translational research teams with expertise in pre- and early-clinical cancer drug development. These centres are supported jointly by CR-UK and the Departments of Health for England, Scotland, Wales and Northern Ireland.

Developing new collaborative models

As well as having a long-standing role in translating academic discoveries, CR-UK and CRT have been responding to the rapidly changing global landscape in pharmaceutical R&D by developing new business models and ways of collaborative working. In December 2009, CRT signed a 3-year multi-project alliance with AstraZeneca to discover novel drugs modulating cancer cell metabolism. The ideas for targets come from the in-depth biological expertise in tumour cell metabolism of CR-UK-funded investigators. If agreed by a joint steering committee, drug discovery projects are jointly resourced by CRT and AstraZeneca, with continuing involvement in the project from the biology experts from CR-UK. Any intellectual property (IP) generated by the alliance is jointly owned. In addition, both parties have co-exclusivity on targets brought into the alliance and receive non-exclusive rights to the use of biomarker IP. Drug candidates emanating from these collaborative projects will be taken through preclinical and clinical development by AstraZeneca, with CRT receiving milestone payments and royalties on projects as they progress. Four projects have been initiated since the inception of the alliance. A second model developed by CRT in the drug discovery space is to bring together hand-picked teams of academic scientists with common biological interests into scientifically themed consortia. The first example of this is Senectus Therapeutics Ltd (<http://www.senectustherapeutics.com/>), a virtual drug discovery company focused on identifying novel therapeutics targeting cellular senescence. The company, founded around a consortium of scientists with research expertise in telomere biology, autophagy and tumour suppression, aims to develop a suite of assays to deconvolute senescence signalling pathways and build a network of genes for target and biomarker discovery. Senectus has secured £1 million of translational research funding from the Discovery Committee of CR-UK and is currently seeking further investment. CRT are actively working with CR-UK scientists to establish further consortia in several areas, including epigenetics, the ubiquitin-protease system, tumour microenvironment, cancer stem cells, lipid metabolism and early diagnosis (http://www.cancertechnology.com/discovery/partnerships/academic_consortia/).

In the drug development area, CR-UK and CRT jointly launched a Clinical Development Partnerships (CDP) initiative in 2006. Under this initiative, the DDO of CR-UK takes on the pre-clinical and/or early-clinical development of selected projects that have been deprioritised by

TABLE 1
The CR-UK CDP pipeline

Agent name	Classification	Disease setting	Stage of development	Originating company
GSK1070916A	Aurora kinase inhibitor	Solid tumour, FIH trial	Phase 1 study-open	GlaxoSmithKline
IMA950	Multi-peptide cancer vaccine	Glioblastoma, FIH trial in combination with GM-CSF	Phase I study-open	immatics Biotechnologies
AZD3965	Monocarboxylase transporter 1 inhibitor	Solid tumour, FIH trial	Phase 1 preparation	AstraZeneca
DI-B4	Anti CD-19 monoclonal antibody	Haematological malignancies, FIH trial	Pre-clinical	Merck KGaA
AZD0424	Src/Abl inhibitor	Solid tumour, FIH trial	Pre-clinical	AstraZeneca
AT13148	PKB/Akt inhibitor	Solid tumour, FIH trial	Pre-clinical	Astex Therapeutics
CEN-209	Hypoxia targeted agent	Solid tumour, FIH trial in combination with radiotherapy	Pre-clinical	Centella Therapeutics

pharma and biotech but which the charity believes still might have the potential to deliver patient benefit. All projects undergo peer-review before commitment of charity resources. Under this initiative, the cost of early development is borne by the charity and the originator company has the option to licence preclinical and clinical data and continue development of the project following the conclusion of early-phase trials. If the originator company does not wish to pursue further development, rights to the therapeutic agent are passed to CRT for further development and commercialisation. In a recently published analysis of pharma industry R&D performance, Paul *et al.* [4] proposed that companies could increase overall R&D efficiency by shifting resources to focus on undertaking more early-stage proof-of-concept (POC) studies. However, a recent report [6] clearly indicates that this is not happening, with 47% less drugs entering phase I trials in 2010 compared with 2007. This underscores the importance of collaborative initiatives, such as CDP, in maintaining a route for the investigation of more 'high-risk' approaches in early-phase POC trials. The current CDP pipeline is shown in Table 1.

It is widely appreciated that the development of many cancers is driven through multiple pathways and that combinations of drugs will be required to control disease progression effectively [17]. Individual companies only have the internal resources to explore a small set of 'high-priority' combination trials with drugs in development and are dependent on harnessing additional resources to explore areas outside of the core development plan. A second recently launched initiative in the drug development

space is the ECMC combinations alliance. Again, the first deal of the charity in this area is with AstraZeneca. In this model, CR-UK investigators can propose combination trials with molecularly targeted agents from the development pipeline of AstraZeneca, to be delivered through the ECMC network. AstraZeneca provide drugs and financial support with management of the programme overseen by the DDO of CR-UK. The charity is currently seeking similar alliances with other pharma companies and also looking to facilitate cross-company collaborations.

Concluding remarks

Academia and pharma bring distinct but complementary expertise and thinking to the understanding of disease processes, the discovery and development of candidate therapeutics and the introduction of new medicines into clinical practice. As an independent, research-based charity, CR-UK is committed to working with industrial and academic partners to develop new innovative and collaborative models that best serve the needs of patients with cancer.

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