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Academic and charitable drug discovery enterprises face common challenges, such as hit finding and target identification. Herein, we describe our own creative solutions to these issues.

Rethinking 'academic' drug discovery: the Manchester Institute perspective

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The contraction in research within pharma has seen a renaissance in drug discovery within the academic setting. Often, groups grow organically from academic research laboratories, exploiting a particular area of novel biology or new technology. However, increasingly, new groups driven by industrial staff are emerging with demonstrable expertise in the delivery of medicines. As part of a strategic review by Cancer Research UK (CR-UK), the drug discovery team at the Manchester Institute was established to translate novel research from the Manchester cancer research community into drug discovery programmes. From a standing start, we have taken innovative approaches to solve key issues faced by similar groups, such as hit finding and target identification. Herein, we share our lessons learnt and successful strategies.

Introduction

Q2 CR-UK is the largest single-disease charity in the world and annually commits over £300 million on basic and translational research, with the specific aim of improving the lives of patients with cancer. Although the charity has had a continuing presence in drug discovery, much of its funding has been dedicated to the fundamental understanding of cancer biology.

Following a strategic review of activities, the 5-year research plan of the charity from 2009 set the goal, by 2020, of delivering accurately targeted treatments with fewer adverse effects to at least half of all patients with cancer (http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@abt/@gen/documents/generalcontent/cr_043314.pdf). However, the review acknowledged that the charity had a relatively low presence in small-molecule drug discovery and that this was limiting the potential to exploit the groundbreaking biology emerging from its laboratories. Given that this limitation impinged on the ability to deliver the primary goal, a decision was taken to establish two new centres of drug discovery, closely aligned with core-funded research institutions and clinical centres of excellence, at the Beatson Institute in Glasgow and the Cancer Research UK Manchester Institute.

Herein, we describe the philosophies we have used in the establishment of the Manchester Institute Drug Discovery Unit (DDU) and the resultant capabilities established; we also discuss the

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Allan Jordan joined the Drug Discovery Centre in July 2009 as head of chemistry. After gaining a BSc in Chemistry from UMIST in 1993 and a short spell as a teaching assistant in Arizona, he returned to UMIST to conduct postgraduate research into anticancer natural products. After postdoctoral work at the University of Reading, he joined RiboTargets in Cambridge (now Vernalis), where he worked on several therapeutic areas at various stages of the research pipeline. Alongside involvement in several oncology programmes, ultimately leading to the clinical evaluation of heat-shock protein (Hsp)90 inhibitors in conjunction with Novartis, he became involved in central nervous system (CNS) research programmes, where he was a project leader on a G protein-coupled receptor (GPCR) drug discovery programme and was also involved in the management of clinical programme of Vernalis for Parkinson's disease.

Ian Waddell joined the Drug Discovery Centre in June 2011 as head of biology. He gained a BSc and PhD in biochemistry at the University of Dundee. After a short spell as a postdoc, he spent 5 years as a lecturer in molecular medicine in the Department of Child Health at Ninewells Hospital and Medical school before joining Zeneca in 1994. His interest in oncology began when he led the Cachexia team looking at preventing skeletal muscle wasting associated with pancreatic cancer. Following the merger with Astra in 2000, he returned to the diabetes and obesity team as a project and line manager and was directly involved in several projects that have subsequently progressed to late-stage clinical trials. In 2005, he moved into the oncology group at Alderley Park as director of bioscience where, among other things, he led the HTS, lead identification, and lead optimisation groups (including the integrative pharmacology group). In his last 3 years at AstraZeneca, Ian was the oncology director of discovery medicine at Alderley Park and was responsible for the preclinical translational science aspects of all development compounds emerging from that site.

Donal Ogilvie heads the Drug Discovery Centre and joined the CRUK Manchester Institute as a senior group leader in February 2009 after a 20-year career in the pharmaceutical industry. Donald obtained an MA in biochemistry at Oxford University in 1980 before working at the John Radcliffe Hospital for 8 years on the role of proteases in breast cancer and inherited connective tissue disorders. The latter was the basis of his DPhil degree. In 1988, he joined ICI, which subsequently became Zeneca and then AstraZeneca. For most of his industrial career, he worked on cancer drug discovery and early clinical development. He was directly responsible for the delivery of ten novel cancer development compounds, four of which have progressed to Phase II & III clinical trials and one, so far, to US Food and Drug Administration approval.

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lessons we have learnt along the way toward delivering what we believe to be an unusual and highly efficient, patient-driven drug discovery enterprise, embedded within an academic institution. These capabilities are discussed in terms of our infrastructure and facilities, our people, our philosophies around target selection, triage and prosecution, and our innovative approaches to overcome the day-to-day and strategic challenges faced by many DDUs of our size.

Infrastructure

Starting from a 'clean sheet' with no existing infrastructure was both an opportunity and a challenge, compared with many new DDUs that have tended to grow organically to exploit a fundamental new discovery emerging from an existing research centre [1,2]. With no facilities to grow from and no clear therapeutic targets to prosecute from the beginning, the task of delivering a fully functional and usefully occupied drug discovery unit was formidable. However, this challenge also presented an unusual opportunity to reflect upon the lessons of both pharma and pre-existing academic and/or non-for-profit DDUs and to plan in detail precisely how we would wish the unit to function, without the need to incorporate pre-existing infrastructure, protocols, or philosophies. Time was spent carefully analysing all the required steps in the drug discovery value chain, to determine where we would build core competencies and where we would rely on external expertise. Although outsourcing has become an unpopular phrase in the industry and is often synonymous with 'downsizing', in our situation it offered a cost-effective approach to access complementary crucial skills and technologies, such as *in vitro* drug metabolism and pharmacokinetics (DMPK) and crystallography, without costly investments in the requisite infrastructure and technology. This enabled us to focus building our core team to deliver aspects over which we desired to retain internal, dynamic control, namely high-quality synthetic and medicinal chemistry, *in vitro* biochemistry and cellular biology, and computational science, both in terms of chemistry and biological informatics. As described in more detail below, the DDU is currently limited to 30 members of staff and, given a team of limited size and scope, we felt that this strategy was vital to allow effective, flexible, and efficient delivery.

To ensure that our most promising projects progress as efficiently as possible, we acknowledged that we would need to generate highest quality data as efficiently as possible with small (<5 mg) amounts of compound and we resolved from the outset to build our laboratory workflow around acoustic dispensing. This single strategic decision shaped the entirety of our process design, but we felt that the accuracy, reproducibility, and parsimonious nature of compound handling was crucial to deliver the meaningful decisions on our projects in the most appropriate timeframe [3,4].

Once synthesised, these compounds need to be stored in a way as to preserve their longevity. Many similar groups to ours have invested heavily in storage systems that place sealed plates under a nitrogen atmosphere to prevent dimethyl sulfoxide (DMSO) hydration and compound degradation. However, our own investigations led us to question the necessity of this approach, given the use of 'off-the-shelf' DMSO for compound dissolution, the rapidity of DMSO hydration upon desealing, and the paucity of evidence supporting dehumidification of sealed plates under such conditions. Instead, we simply and pragmatically resolved to store capped working plates in desiccators at ambient temperature until foil sealed, at which point the plates are snap frozen. Indeed, our informal discussions with other organisations have suggested that this step is the single most crucial one for compound quality; the often-used slow freezing of master and screening plates in a refrigerator (2–4°C) increases the likelihood of DMSO-specific freezing and concentration of the compound itself into the residual water present in the DMSO. Ultimately, this can result in compound precipitation and, upon thawing, incomplete dissolution leading to meaningless data points because of incorrect compound concentrations. This simple, scalable, and pragmatic approach is easily implemented and considerably reduces the required infrastructure for compound storage of the 1000–2000 solid samples we prepare internally each year. To date, this workflow has served us well and we have not seen any noticeable variability in assay data from historical samples.

From this outline, we then worked backward to envision how best to deliver compounds for evaluation into the workflow, and forwards to plan the more detailed pharmacological evaluations of these derivatives. These approaches led to considerable investment in technology, more common in biotech or pharma than the academic sector, but we felt that this investment was crucial to deliver the ability to generate project decisions based on robust data. These data, of course, were meaningless without the ability to capture, retrieve, and interrogate them in a timely and integrated manner. Therefore, we have spent much time implementing a fully integrated chemoinformatics platform that captures data from point of chemical and biological reagent acquisition, through molecular design, synthesis, analysis, *in vitro*, and *in vivo* testing through to data evaluation, all within a single environment. This environment is largely based on the Dotmatics suite of applications (http://www.dotmatics.com) and encapsulates electronic lab notebooks across all our disciplines, assay data-processing tools, searchable storage, and data visualisation. This platform is closely linked to our computational chemistry tools, such as the Schrodinger Suite (http://www.schrodinger.com/), Cresset BioMolecular Design (http://www.cresset-group.com/), ACD/Labs (http://www.acdlabs.com/products/percepta/) and Pipeline Pilot (http://accelrys.com/products/pipeline-pilot/) and this detailed integration enables all the team to capture, process, and interrogate knowledge and data in a transparent and seamless manner, to deliver project decisions that are timely and informed (Fig. 1). Q3

To further facilitate these crucial project discussions and decisions, and in a step change away from most drug discovery environments, we took the decision during the laboratory design phase to colocate our chemists and biochemists in the same physical space, with no divide between the disciplines. Although some concerns were raised initially regarding cross-contamination, we found not only that these fears were wholly unfounded, but also that this setup delivered a dynamic and vibrant laboratory environment, where regular open cross-discipline debate ensues at the bench, which in turn enriches and advances our portfolio. Through careful air handling and prudent lab design, we have yet to find any impediment to this colocation of differing scientific disciplines. On the basis of our experiences, we believe that disrupting the traditional divide between the two teams delivers a more streamlined workflow, resulting in a more efficient and

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