



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

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

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 Vernalis' clinical programme of Vemalis for Parkinson's disease.



Ian Waddell joined the Drug Discovery Unit 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.



Donald Ogilvie heads the Drug Discovery Unit 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 a 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 DDU 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.

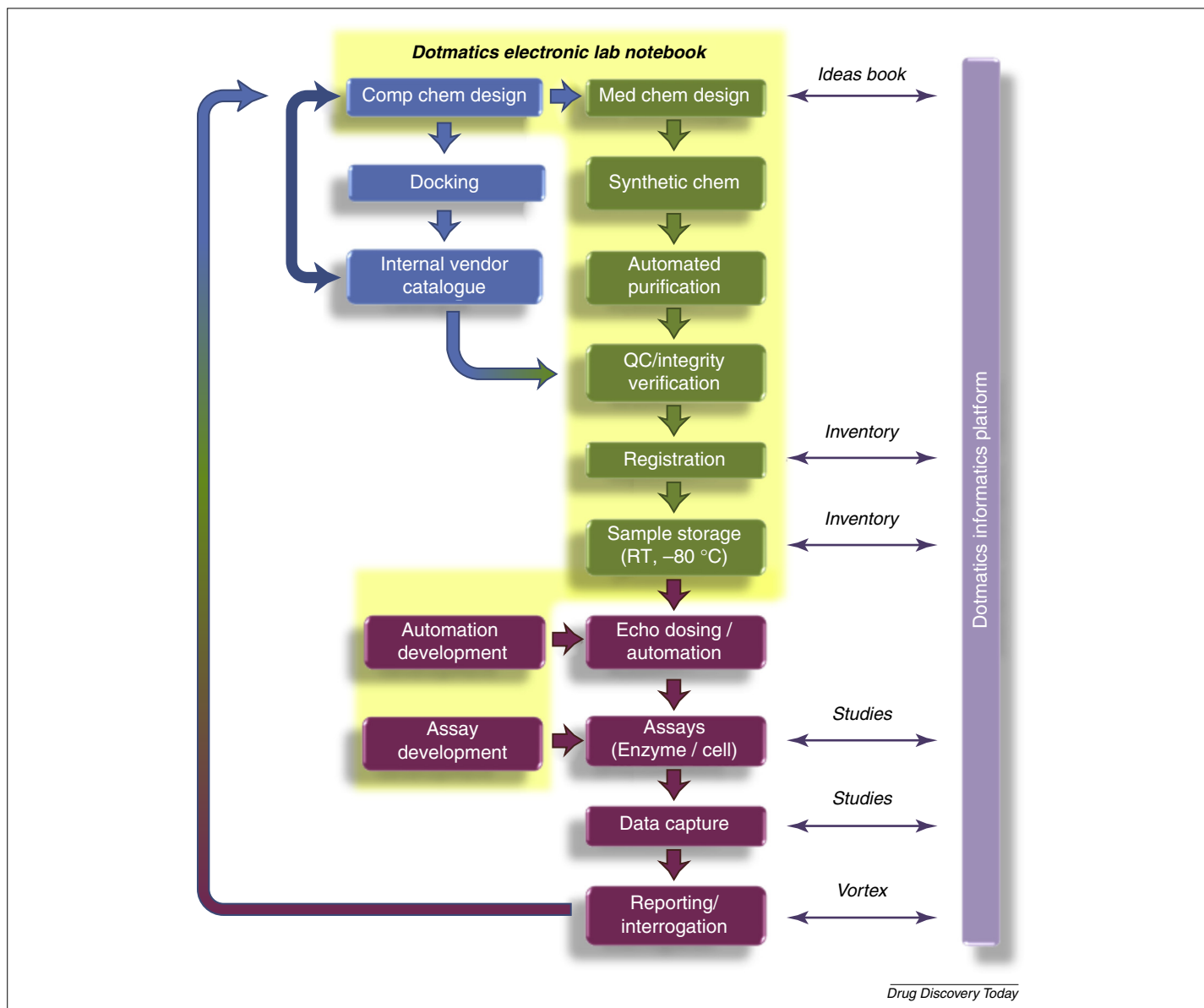
To ensure that our most promising projects progress as efficiently as possible, we acknowledged that we would need to generate the highest quality data as efficiently as possible with small (<5 mg) amounts of compound and we resolved from the outset to build our laboratory workflow around acoustic dispensing. 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 descaling, 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).

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 collocation of differing scientific disciplines. On the basis of our experiences, we strongly believe that disrupting the traditional divide between the two teams

**FIGURE 1**

Drug discovery unit (DDU) integrated informatics platform. *Abbreviations:* QC, quality control; RT, room temperature.

delivers a more streamlined workflow, resulting in a more efficient and enjoyable laboratory environment. Moreover, the substantially enhanced communication and dynamic interactions delivers real improvements to the quality and vibrancy of science that we undertake.

Important to our future success is our colocation with the largest single site oncology treatment centre in Europe, The Christie. Treating in excess of 40,000 patients with cancer every year, our location close to the hospital remains a considerable asset in terms of accessing clinical expertise and, ultimately, the evaluation of new medicines, being home to the largest oncology Phase I/II clinical trials unit in the world. Our ideal scenario would be to translate novel basic biological research from Manchester researchers into medicines that can be evaluated for the first time in the Christie Trials Unit, all on the same site. Facilitating this delivery, The Christie excels in two important regards. First, direct and facile access to clinical oncologists enables us to make project

and target decisions based upon clinical expertise and experience. Second, the considerable patient population offers unparalleled access to biobanks of patient materials, which can be used to help validate preclinical hypotheses. At present, the biobank collects samples from >100 patients each month and holds in excess of 5000 samples across a diverse range of tumour histologies. Through ethical approval, access to these valuable samples is already transforming our research and target validation across several disease areas, for example in haematological [5,6], and in lung and in breast cancers. The considerable size of the patient population implies that, even for more rare disease subtypes, such as some subtypes of leukaemia, relevant (and sometimes multiple, longitudinal) tissue samples are available to facilitate our early studies.

People

Inevitably, within an organisation such as the DDU, success is dependent on the quality, capabilities, and skills of its people and,



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FIGURE 2

The Drug Discovery Unit (DDU) team at the Manchester Institute.

in this regard, we have been exceptionally fortunate. Over recent years, industrial drug discovery research in the UK has experienced a considerable downturn in headcount. This has largely been driven by the contraction of early-stage pharma research activity; however, many biotech companies have also been forced to downsize research operations.

These pressures have dramatically increased the available 'talent pool' from which units such as ourselves are able to recruit, and this has presented an opportunity to gather together considerable expertise across the spectrum of drug discovery, bringing together learning from multiple organisations, cultures, therapeutic areas, and scientific disciplines, enabling us to assemble a stronger team than we had originally envisioned. Indeed, our small team of just 30 staff (Fig. 2) have a remarkable track record; across the team, we have delivered in excess of 340 publications on drug discovery and are named inventors on over 60 patents describing small-molecule therapeutics. More importantly, we have been involved in the delivery of over 50 candidate drugs, of which over 35 have entered clinical trials and two, so far, have gained marketing approval. We strongly feel that this combined experience and the amassed lessons learnt particularly from those projects that have not progressed as far, have added considerable additional value to our efforts to deliver drugs to the clinic, as we strive not to repeat the (often undisclosed) mistakes and blind alleys experienced across the sector.

However, we are acutely aware of our location in an academic environment and our previous time spent in this sector has also been invaluable. Our experiences strongly suggest that academics and industrialists often use the same words but speak a different dialect when discussing drug discovery topics. Our experience of both camps was vital to our efforts to provide an efficient and effective bridge between the two environments [7]. There is no question that this will be required to deliver truly meaningful translational research.

Being embedded in an academic environment, the group runs the risk of two key issues that, if not well managed, could have a detrimental impact on productive drug discovery, namely the requirement to publish and the drive to embed students within the team [2,8]. Although both of these aspects are important to us and can have considerable benefits, they also bring marked caveats if not appropriately tempered against the core goal of delivering new medicines.

The case regarding publications was straightforward; we cannot publish our best science until intellectual property (IP) concerns

are addressed and our ideas protected to facilitate later partnering and development. This strategy is commonplace across the sector and can be easily managed within the team, but requires more careful negotiation with those groups with which we interact, where pressures to publish are greater in terms of grant income and tenure review, to name but two. Ensuring that such discussions are conducted upfront and mutual expectations on timeframes are clear considerably reduces potential issues in this regard.

The case regarding students might seem somewhat minor; however, there are considerations here that in many ways reflect those discussed above. Although we see training as a key part of our operation, particularly as opportunities to gain this experience through industrial placements or PhD programmes continue to dwindle, we are also acutely aware that the nature of our work presents several conflicting demands that can severely compromise the value of the student in terms of their time in our laboratories.

Of most immediate concern, to facilitate the next step in their career progression, our trainees require the freedom to present their work and describe their experiences openly, and this conflicts with our requirement to retain confidentiality. Therefore, we feel that it is unethical to recruit, for example, PhD students, onto our active research programmes because their inability to discuss their activities openly would severely compromise their ability to secure future positions, at least in the near term until publications are forthcoming. Moreover, drug discovery is a fickle and fast-changing environment and we are required to adapt rapidly to these changing demands through flexible resource deployment and robust decision-making. We feel that it would be unfair to deploy students onto active programmes that might stop abruptly and force, potentially on multiple occasions, a complete change in focus of their thesis, leading to an incomplete, disjointed, and unsatisfying dissertation as a result.

It is with these concerns in minds that we have taken the conscious and largely unusual decision in an academic environment to employ most of our staff as tenured members of the team, rather than students and postdoctoral researchers on fixed-term contracts. We feel that this continuity and flexibility is vital to our chances of successful drug discovery. However, taking into account our unique setting, we have in exceptional circumstances offered PhD positions to exploit breaking science that is not directly connected to our core portfolio.

Choosing the right target

As was mentioned above, the DDU was founded as a result of a strategic research review in 2009 and was established with the remit of translating breaking biological research into clinically relevant, novel treatments for patients. From the outset, it was our clear intention not to compete with ‘big pharma’ because we felt that we could simply not contend in areas such as fast-follower medications or best-in-class agents. Rather, we strongly believed that our role was to ‘derisk’ novel, emerging biology through the discovery and development of pharmacologically active, drug-like small molecules that would serve both as tools to deliver robust target validation, perhaps confirming data obtained from genetic methods, and to deliver potential new therapeutic agents for preclinical and ultimately clinical evaluation [9].

This approach raises some challenges in our undertaking, particularly around the confirmation of early target validation studies and the assessment of technical challenge of the target of interest. Indeed, in many cases where we have access to prepublication data on emerging targets, this information simply does not exist at the outset of our interactions. Therefore, an important task from the outset was to offer some insight into the drug discovery process to our basic research colleagues, to highlight areas to which we would require answers before we embarked on the long road toward a drug. We have found this early outreach to deliver some very productive relations that have led to several potential drug discovery programmes. However, the early assessment of these programmes is often fraught with challenges when the targets under discussion are previously unknown. Among these are the technical challenges of measuring biological activity in a manner that has sufficient throughput and reproducibility to support drug discovery and evaluating the chemical tractability of novel biological target classes. We call these issues the ‘can we do it?’ challenge and this technical feasibility assessment is not unlike that used by almost every other drug discovery enterprise when evaluating a new target.

However, in this respect, we feel that our ethos is somewhat different in that the ‘can we do it?’ question is addressed later in our evaluation. Of more direct impetus is the strength of clinical line-of-sight in disease linkage to patient populations and it is here where our close proximity of the clinicians in The Christie is important. This interface enables us to directly question the patient focus of any putative new basic biology and to investigate, in some detail, how strongly we believe that chemical modulation of the target will result in patient benefit. Simply put, ‘if we deliver a drug, will it work, and can we test it clinically?’ (Fig. 3). We consider that this patient-centric approach, where clinical rationale outweighs technical feasibility, is crucial for long-term successful drug discovery, in that if we can overcome the inevitable technical hurdles of novel targets, we would anticipate a downstream reduction in clinical attrition compared with the more conventional model where the technical feasibility and pursuit of known ‘druggable’ targets is of prime concern and of lower perceived risk, at least in the early stages of a drug discovery programme.

This about-face in target selection delivers considerable hurdles that require addressing before a project enters our portfolio and often leads to spirited debate around target selection, both within and outside of our immediate team. However, we have found that

Will it work?	Clinical hypothesis	How clear is the path to clinical testing?
	Preclinical hypothesis	How strong is the preclinical target concept?
Can we do it?	Chemical feasibility	Can we deliver the required drug attributes in a molecule?
	Biological feasibility	Can we measure the desired biological profile?
	Competitive position	Can we compete in this area (or not)?

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FIGURE 3

Cancer Research UK MI drug discovery unit (DDU) target selection criteria.

this approach engenders highly productive debate with our basic biology colleagues who value the rigorous but constructive appraisal of their discoveries from a translational viewpoint and, importantly, a clear statement of what might be required to answer the questions arising from the ‘will it work?’ evaluation. This open debate enables us to share our opinions on which specific areas might need to be addressed to answer unresolved questions or to formulate hypotheses around patient benefit before an idea becomes ready, under our criteria, for portfolio entry. This iterative cycle of engagement allows access to early and relevant target validation experiments that help to derisk the pursuit of these novel targets. Moreover, these discussions help to inform principal investigators in the differing challenges and complexities of drug discovery and we have found a strong advocacy from those engaged in such debate, which has opened up unanticipated avenues of discussion with additional basic researchers. We believe that enhancing and expanding this wider understanding of the desirable attributes required of a novel drug discovery target is a prudent and valuable investment, helping to drive forward translational science, and ultimately deliver more ‘ready now’ early-stage drug discovery programmes into our portfolio.

Many of the very early programmes that we consider are validated in the first instance by the originating investigator through the use of genetic tools such as short interfering (si)- or short hairpin (sh)RNA depletion of the specific protein of interest. Although of undoubted value in investigative biology, such studies are often complex to reproduce in a manner reliable enough to support drug discovery target validation. The concerning pervasiveness of this issue has recently been reported by other groups [10]. Furthermore, readouts from such studies are complicated by factors such as the inability to dissect out the roles of, for example, functional inhibition of a specific enzymatic activity versus the removal of a key regulatory or scaffolding protein–protein interaction or the inability to rapidly reverse this inhibition of action.

However, these techniques remain crucial in several experiments, given the paucity of high-quality small-molecule research tools readily available to basic researchers, despite considerable and admirable efforts in this regard. However, to enter our drug discovery portfolio, we endeavour to carry out key target validation studies internally before chemistry resources are applied.

To help in this effort, and as part of our remit, we interact closely with local principal investigators to provide relevant and robust tool compounds, often identified from the biological literature, which might help facilitate their research and further strengthen target validation. In our experiences, many of the tool compounds used in the literature to demonstrate biological efficacy are not always the most appropriate for the experiment in question, perhaps being PAINS compounds [11,12], promiscuous, nonselective inhibitors [13–16], or simply overtly cytotoxic. Expert access to the chemical literature and medicinal chemistry evaluation of putative tool compounds is valuable to identify appropriate tools and highlight potential issues with these compounds that might confuse or confound the resultant biological readout [2]. Moreover, our ongoing discourse with the local academic community highlighted that lack of access to synthetic chemists who can deliver these compounds in a timely fashion limited the choice of tool compounds to readily available commercial tools that were often suboptimal for the experiment in question. The urgent requirement for such tools has been demonstrated by such groups as the Structural Genomics Consortium (SGC) (<http://www.thesgc.org/>). By addressing this need more locally with internal resources, after appropriate evaluation and triage, we are interactively and proactively supporting the research community in their quest to do more meaningful science and deliver more robust and reliable target validation data. In the short term, this builds strong and interactive relations with the academic community. More importantly, in the longer term, we expect that this will deliver emerging targets into the portfolio, based upon robust target validation obtained through both genetic and pharmacological investigations. Indeed, we are already seeing the benefits of this outreach approach where, through provision of tool compounds, exciting novel biology around the epigenetic regulator Lysine specific demethylase 1 (LSD1) has emerged from the Institute [5]. This biology has directly prompted rekindling of interest in compounds already under development and, through the connections we have facilitated, has recently delivered a first-in-man clinical trial to Manchester (<http://www.oryzon.com/en/news/oryzon-and-cancer-research-uk-s-paterson-institute-for-cancer-research-have-started-a-collaborative-research-project-on-therapeutic-uses-of-ld1-inhibitors-for-acute-leukaemia/148>). We feel that this is clear demonstration that this early interaction and facilitation of basic research can lead to marked changes in clinical practice and deliver real patient benefit. As such, this activity forms a key component of our philosophy and remit within the team.

Although these activities help in the key activity of target identification and validation and to address the ‘will it work?’ arm of our target triage process, it is apparent that they have little direct influence upon the assessment of technical feasibility and the ‘can we do it?’ conundrum of unprecedented targets. For these challenges, alternate and innovative approaches are required to deliver assessments of both chemical and biological risk, tractable

chemical start points, and reproducible, measurable biological readouts suitable for the support of a drug discovery programme. Whereas solutions for many of these challenges exist within larger organisations, these are not immediately accessible to a smaller enterprise such as our own and, thus, appropriate solutions require a different mind set to deliver a workable and pragmatic resolution.

Of particular note in our ongoing efforts in terms of target selection and validation is the use of bioinformatics at the core of everything we do. Perhaps the best example of this focus has been the use of the concept of Collateral Vulnerability to select new synthetic lethal targets. This concept first came to our notice in a report from the laboratory of Muller *et al.* [17], who proposed enolase 2 (ENO2) as a therapeutic target for a subpopulation of glioblastoma in which ENO1 was a ‘passenger deletion’, consequentially deleted alongside phosphatase and tensin homolog (PTEN). This concept was validated experimentally whereby ENO2 inhibition by small molecules or RNA knockdown was selectively toxic to ENO1-null cells. For several reasons, ENO2 did not fit our specific target selection criteria but we decided to apply this intriguing concept to non-small cell lung cancer (NSCLC), utilising publically available data such as the Cancer Genome Atlas. At the time, there were some 230 samples in TCGA with RNA-seq, copy number, and sequencing data and, from this data set, we identified 957 genes in 20 deleted regions from Tumourscape. Using the pipeline described below (Fig. 4), we quickly identified 67 genes that had an abundance of over 2%, had between one and four paralogues and were lethal in either *Drosophila* or nematodes. Following detailed Target Validation (TV) efforts, SWI/SNF-related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2 (SMARCA2) has emerged from this pipeline as a potential target in a SMARCA4-deficient population. Importantly, this work has subsequently been validated independently by other groups, confirming our belief in this pipeline [18].

These efforts have delivered a practical, validated, and functional bioinformatics pipeline that we have now applied to other cancer-specific disease areas, such as small cell lung cancer, liver and pancreatic cancer, and melanoma, in an effort to uncover additional novel synthetic lethal opportunities that fulfil our target selection criteria.

Overcoming the key technical challenges of drug discovery in smaller enterprises

In common with many groups of similar size, finding novel, tractable, and pharmacologically appropriate hit matter across diverse target classes is a challenge that the team has dedicated much effort toward solving. Moreover, many of the prepublication, emerging targets that we review are entirely unprecedented and this brings forth an additional challenge in that the druggability of the target is largely unknown. This is especially the case where the target arises from a protein family with little or no prior precedent. Such examples include kinases and epigenetic targets, both of which were, upon emergence, the subject of intense debate as to whether such targets were selectively druggable. Indeed, this question is only truly addressed once potent, selective, and pharmaceutically acceptable ligands have been identified and proven to display biological activity, in many cases several years after the

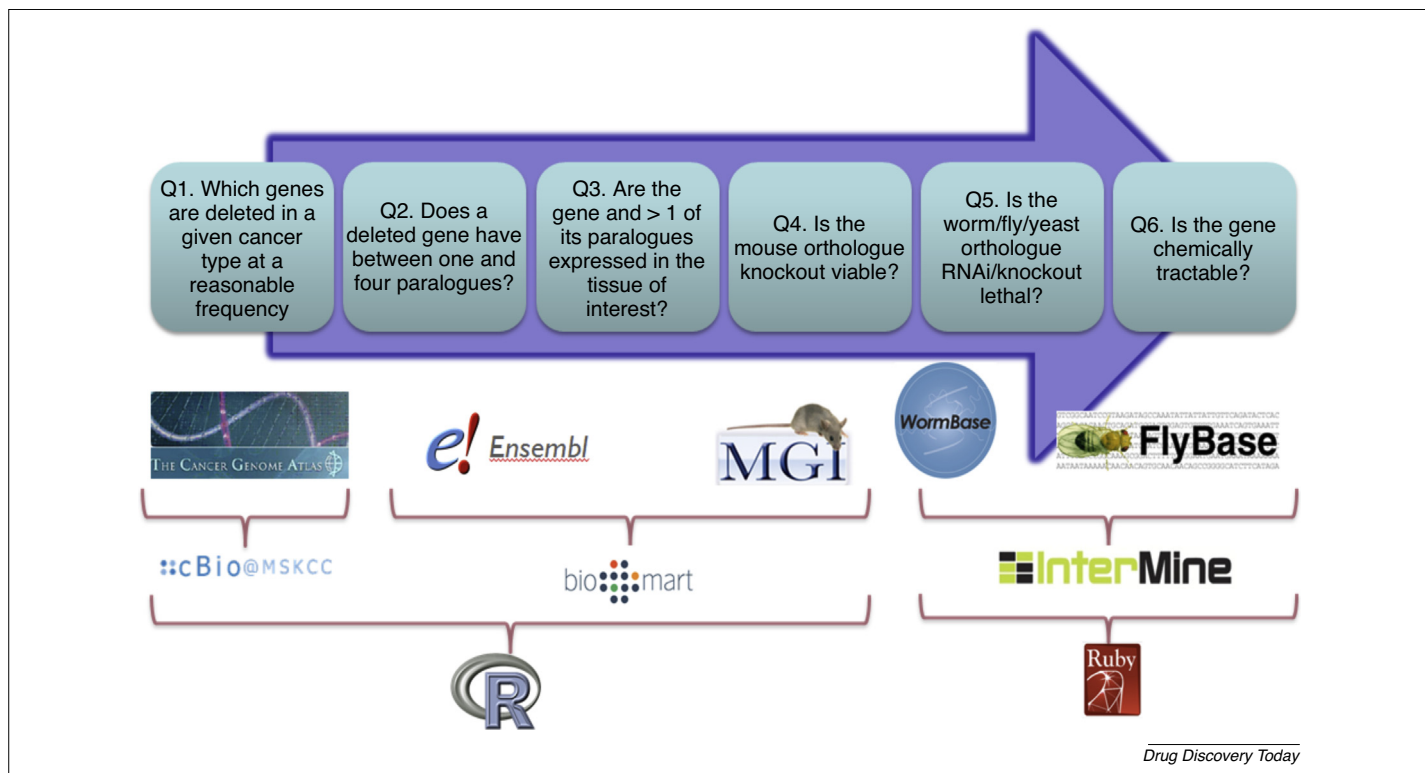


FIGURE 4

Bioinformatics-derived pipeline for identifying and assessing potential collateral vulnerability targets in oncology.

discovery of the putative drug target. We feel that for truly exciting and clinically relevant targets emerging from novel cancer biology, this derisking exercise falls directly within our remit, but we do not have the resources or funding to direct our efforts toward the investigation of every such target that piques our interest. Therefore, we developed a toolkit of approaches that enable us to at least qualitatively assess the relative chemical risk of a target before it enters our full portfolio (Fig. 5). Moreover, this approach also allows us to determine the most cost-effective screening approach to deliver hit matter.

Central to this approach is the biochemical screening of a small yet diverse fragment library, kindly provided to us by our sister group at the Beatson Institute for Cancer Research (<http://www.beatson.gla.ac.uk/drug-discovery/drug-discovery.html>). Rather than using this library purely in a traditional hit-finding approach directly, we use the qualitative output of the screen to derive a hit 'fingerprint' that in some way indicates the relative druggability of a novel target (Fig. 6). Although this approach has some potential drawbacks (such as the potential for spurious hits because of high-concentration biochemical screening and the requirement for a target to have functional and measurable biochemical activity), we have found the output from this tool to correlate well with actual druggability and success in high-throughput screening (HTS) campaigns (Table 1). These results mirror comparative, parallel exercises at AstraZeneca [19].

For known druggable targets such as kinases, it is evident that a higher proportion of fragments display activity at the target and, therefore, the fingerprint is more enriched. For epigenetic targets, such as LSD1 and SMARCA, the picture is less clear, with lower apparent ligandability and, potentially, the requirement for a

more extensive screening collection to deliver tractable hits. For previously undocumented targets, such as the dehydrogenases and DNA repair targets of interest, the observed sparse fingerprint is indicative of lower relative ligandability. Although this does not necessarily preclude their prosecution within the team, it does suggest that access to a considerably larger screening collection may be required to deliver appropriate hit matter at the inception of the project. Whereas this platform forms only part of our target assessment process, it does provide at least some grounds on which to base decisions around chemical tractability and enables assessment of relative chemical risk on emerging targets that might otherwise be dismissed as undruggable, purely on lack of evidence to the contrary. For example, the epigenetic modifier LSD1 is inhibited in an irreversible manner by tranlylcypromine-derived compounds [20], which bind irreversibly to Flavin Adenine Dinucleotide (FAD). However, there remains a paucity of high-quality reversible modulators of this target [21], which displays a large, open, and flexible binding pocket. Our ligandability assessment suggests that such an approach should be technically feasible and work on this area is ongoing [22]. Conversely, recent literature reports have suggested that wild type isocitrate dehydrogenase (IDH) is an oncology target when operating in the reverse direction [23,24] and we have been able to develop an assay platform to quantify this activity. However, our ligandability assessment yielded no fingerprint whatsoever, suggesting this is a difficult target to inhibit chemically. As such, this target was not progressed into hit finding.

Upon completion of this risk assessment exercise, strategies can then be determined to offer greatest chance of success for hit finding. For known accessible targets, such as novel kinases, screening focussed kinase subsets or smaller HTS collections in

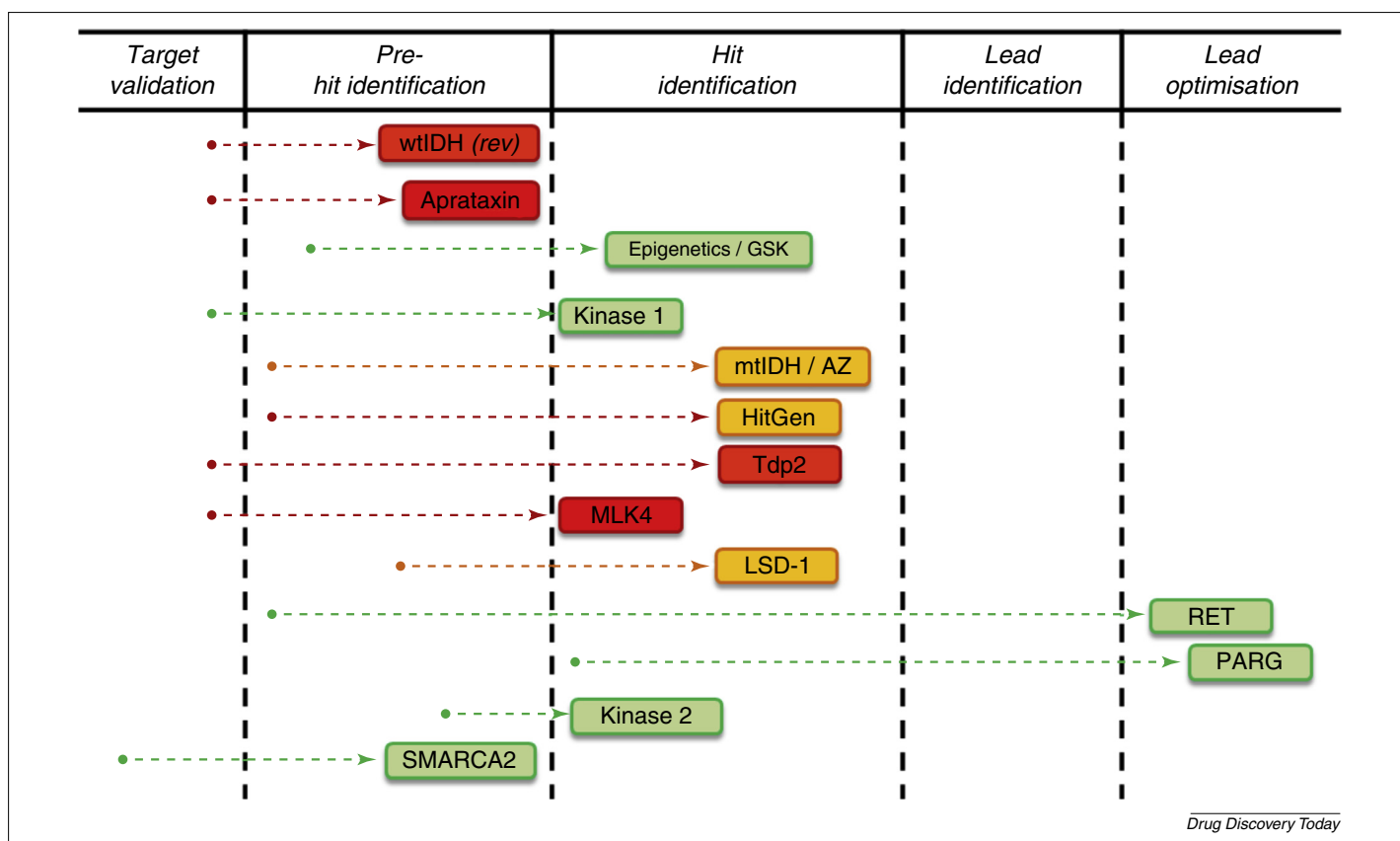


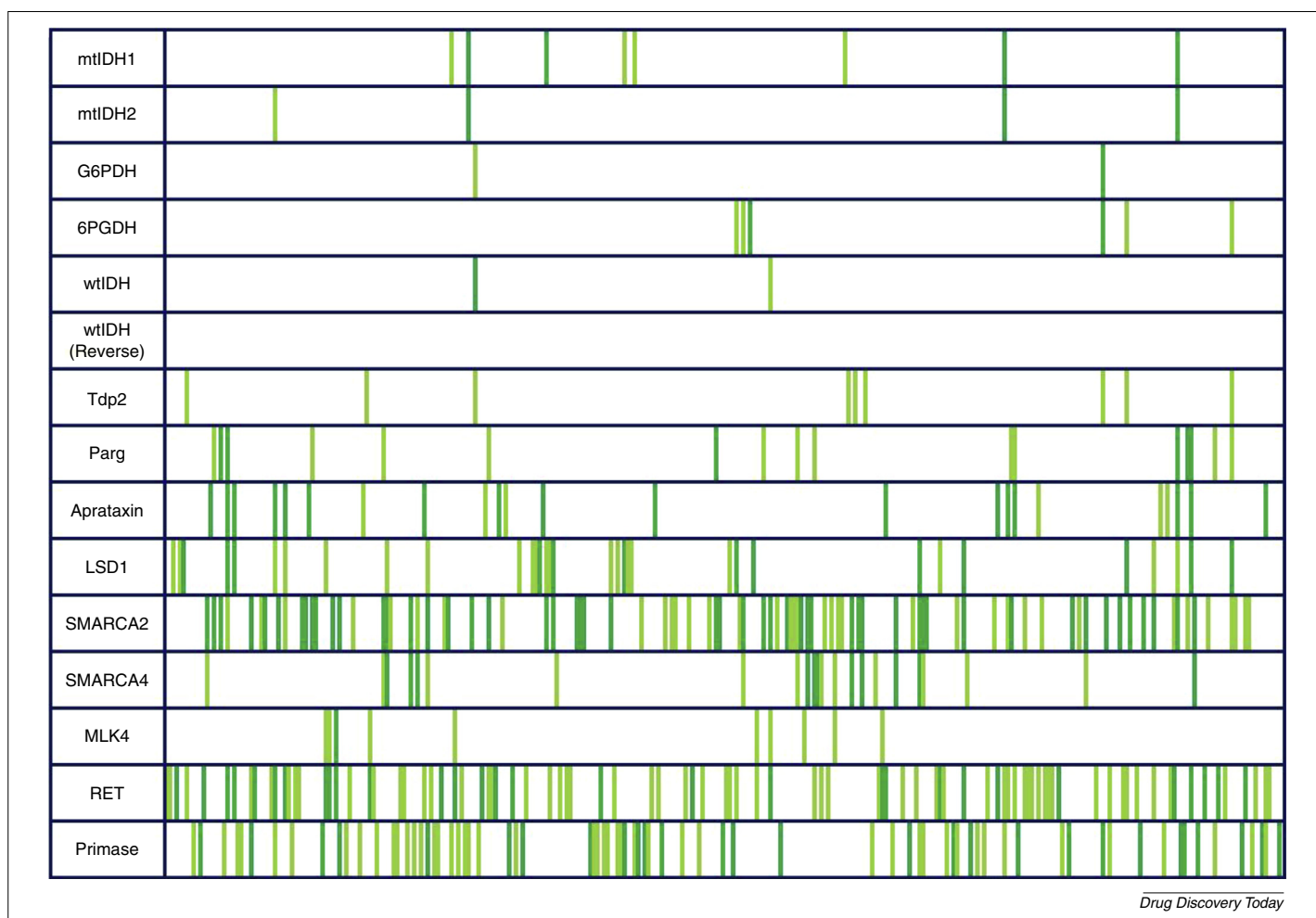
FIGURE 5

The Drug Discovery Unit (DDU) portfolio of targets. Red boxes indicate stopped projects, orange boxes projects that are active with external partners or collaborators, and green boxes those that are being actively progressed internally. Arrows indicate progression from inception of the project.

the 50,000–100,000 compound range might be adequate to deliver robust hit matter for prosecution. However, for more challenging targets, such as the DNA repair targets or dehydrogenases in Table 1, our experience suggests that a more extensive collection will be required to deliver tractable start points with appropriate metrics and likelihood of delivering a suitable small molecule for clinical evaluation.

Naturally, for a small enterprise such as our own, the screening of a compound collection in the order of 1 million compounds or more is unfeasible. Although screening access through consortia initiatives, such as the European Lead Factory (<http://www.imi.europa.eu/content/european-lead-factory>) and EU Openscreen (<http://www.eu-openscreen.eu/>) might offer one option to address this need, some concerns exist around timelines and access to this collection in a manner that is consistent with our own requirements. Particularly, in our mind, unresolved questions still exist around issues such as IP reach through, early and direct involvement in HTS hit triage and structure disclosure, and the overall costs of accessing the screening capabilities. Moreover, with specific regard to the EU Openscreen facility, questions also remain regarding the specific nature of the compound collection and the date at which this infrastructure will be operational. With these questions in mind and an urgent requirement to develop our screening capability, we felt that such initiatives were not appropriate for us as part of an immediate solution. Therefore, we have fostered novel approaches to ameliorate this limitation in our capabilities, primarily through interacting with external partners.

One opportunity that the contraction of early-phase research in pharma has presented to us is the availability of high-quality ‘off-the-shelf’ programmes, residing in industry, but with little or no resource to aid their prosecution. Of these targets, many already have identified hit matter and might also have early structure–activity relations (SAR) and/or supporting structural biology. Assuming that these also fit our critical ‘will it work?’ criteria for clinical alignment, such programmes offer a considerable appeal in propagating our early-stage portfolio. By alleviating the requirement for hit finding, we address our two key issues around target identification and/or validation and identification of tractable hit matter in one fell swoop. Moreover, if we are successful in our endeavours, we are also likely to have a potential future collaborator aligned to pick up the later-stage development and clinical prosecution, in that the originating partner retains a vested interest in future success [25]. One naïve criticism of this model is that it simply offers ‘cheap outsourcing for pharma’. We disagree with this assertion. Rather, such collaborations offer strategic access to technologies simply out of our reach and enable our team to prosecute rapidly a clinically valuable target toward nomination of a preclinical candidate, potentially delivering medicines into clinical evaluation that would have otherwise stagnated in the archives of the pharma sector. The benefits to both parties are clear and the contributions in kind of each party are recognised in the structure of the collaborative agreement. Moreover, although the originating party retains first right of refusal, declination of this option (for reasons such as changing business priorities) grants us



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FIGURE 6

Ligandability fingerprints. Green bars indicate fragment hits for a specific target. Lighter-green bars indicate weaker hits (50–75% inhibition) and darker bars, stronger hits (>75% inhibition). Fragments not hitting any targets are not shown. For definition of abbreviations, please see main text and Table 1.

TABLE 1**Correlation of CRUK-MI DDU HTS campaign output and ligandability assessment**

Target	Predicted ligandability	Observed HTS hit rate
Glucose-6-phosphate dehydrogenase (G6PD)	Low	0%
Tyrosyl-DNA phosphodiesterase 2 (Tdp2)	Low-moderate	0.25%
mtIDH-1	Low-moderate	0.7%
Poly(ADP-ribose) glycohydrolase (PARG)	Moderate	0.9%
LSD1	Moderate-high	0.45%
RET	High	7.5% (kinase subset)

full ownership of the resultant IP and enables us to prosecute clinical development with an alternate partner. This foresight prevents the possibility of a promising late-stage programme stagnating again because of the originating partner being unwilling or unable to conduct clinical development. Such agreements have been effective for us and led to our recent collaboration with AstraZeneca, announced in mid-2013 (<http://www.cancertechnology.com/crt-university-manchester-and-astrazeneca-work-together-seek-new-cancer-drugs>).

An alternate tactic that has arisen from such discussions involves direct access specifically to the compound collections

of the pharma sector, again in a way that offers complementarity and mutual benefit [7]. The contraction of early-phase research in the sector has led to a considerable degree of spare screening capacity and, if a mutually agreeable novel target can be identified, obvious synergies can be exploited to deliver new target opportunities. In this manner, the pharma partner undertakes an HTS campaign and, after joint triage and strategic discussions, our access to this hit matter enables instigation of new internal projects under our direct control, to agreed milestone points. In a similar manner to the model described previously, this delivery triggers a first-right-of-refusal option point with the HTS partner to

commit to later-stage development. Such collaborations are highly 'hands-off' for the partner, alleviating much of the managerial demands of an outsourced programme and enabling our internal teams to exploit our own strengths of nimble and responsive decision-making, free of much of the managerial bureaucracy that we have experienced ourselves within the industry and that often hinders effective and rapid project prosecution. Once again, this approach has been effective for us, instigating collaborative ventures on biologically relevant targets with both AstraZeneca and GSK (<http://www.cancertechnology.com/node/1208>). Indeed, in a unique opportunity, AstraZeneca invited our own staff into their facility and offered access to their entire compound collection and screening capability to prosecute the target in the most efficient manner (<http://www.cancertechnology.com/crt-university-manchester-and-astrazeneca-work-together-look-for-new-cancer-drugs>).

Although these opportunities are valuable in addressing our hit-finding needs and identifying a putative downstream partner that is already strategically aligned with our chosen targets, our ligandability risk assessments suggest that some challenging targets present considerable chemical risk and, thus, require larger screening capabilities than can be accessed through such collaborative efforts. Examples here are represented by mtIDH1/2 in **Table 1**, where strong biological and clinical rationale advocates that this risk is a worthwhile endeavour if an appropriate strategic path can be identified.

For these extreme cases, alternate strategies are required and, to this end, our investigations highlighted the resurgence of interest in DNA-encoded libraries as a method of interrogating considerable chemical diversity against challenging targets. Although this technology has suffered previously from issues such as limited chemical diversity and complexity of deconvolution, the recent and dramatic advances in sequencing technology, allied with a greater cognisance of desirable and tractable chemical space, offer the potential to overcome many of these prior liabilities and this approach is beginning to gain traction in certain pharma segments.

Whereas such capabilities are now available through vendors such as X-Chem (<http://www.x-chemrx.com/index.html>) and NuEvolution (<http://www.nuevolution.com/>), we have chosen to enter into a collaborative venture with HitGen (www.hitgen.com/?p=6486) that enables us to evaluate the applicability of this

technology to our more challenging targets. Our first screens using this technology are now underway and we await with interest the resultant output, to evaluate fully whether such an approach can deliver tractable matter against targets that have failed other hit-finding approaches and enable us to make progress against targets that we would have otherwise found untenable.

Naturally, each target that we consider will offer different challenges and must be considered and progressed according to its own merit and risks. However, we feel that our portfolio of hit-finding collaborations and approaches enables us to prosecute targets more readily from the seemingly readily druggable to the apparently measurable but traditionally undruggable. This diverse strategy offers an opportunity for us to both derisk and prosecute novel targets. As a key part of this prosecution, we are also able to deliver novel, specific, and drug-like chemical tools to key biological partners, which in due course will facilitate the unravelling of hitherto unexplored biology and ultimately deliver more robust target validation.

Concluding remarks

Over the past 5 years, the DDU has encountered many of the problems typically faced by smaller drug discovery enterprises. We have sought to address these challenges in an innovative and flexible manner that we believe increases both the quality and efficiency of our output, delivered through innovative collaborations, logistical pragmatism, and alternate use of technologies.

More importantly, we believe that the approaches we have described are not specific to ourselves, but are more widely applicable to other similar facilities. Given the present expansion of drug discovery activities in the academic, charitable, and non-for-profit sector, we hope that this disclosure will stimulate further discussion around the evolution of drug discovery paradigms and lead to further analysis of (and improvements to) traditional workflows. Although this will ideally result in increased efficiencies and quality of research, we trust that it will also ultimately lead to the delivery of improved therapeutics to patients in a reduced timeframe.

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