To confound the issue, the need for innovative new treatment options is increasing as society struggles to cope with an ageing population and the demands of modern lifestyles. Moreover, the price of new medicines for payers is at an all-time high, with intense debates currently raging between healthcare providers and reimbursement agencies as to whether the high prices for breakthrough drugs such as Sofosbuvir (Sovaldi), Gilead’s Hepatitis C drug which can cost US patients $84,000 for a full 12-week course, or Vertex’s cystic fibrosis drug, Ivacaftor (Kalydeco), which can cost $311,000 per year can be justified as healthcare budgets are subjected to ever-increasing pressures.

The primary reason for the failure of drug candidates in late clinical development is lack of efficacy. Poor target selection, insensitive biomarkers and poor patient stratification methodologies are all major contributing factors for clinical trial failure. The effective selection of molecular targets specifically associated with and relevant to disease is one of the major barriers to successful drug development. If an inappropriate target is selected at the start of the drug development process, it is often only at the end of the process, after spending hundreds of millions of dollars and perhaps a decade of effort that this becomes clear. The diseases where this problem is most apparent are those which place the heaviest burden on our healthcare systems, namely chronic and multifactorial conditions such as cancer, chronic pain, autoimmune conditions, psychiatric conditions and neuro-degeneration.

Historically, drug discovery companies, academia and charities have used their resources to compete with each other rather than prioritising ways to pool their resources to de-risk therapeutic programmes. One of the starkest examples of this is in the area of Alzheimer’s Disease (AD). AD is a particularly challenging area for drug development as the clinical outcomes take years to quantify and the patient heterogeneity is such that large numbers of subjects must be included in clinical trials resulting in a Phase III trial in AD costing in excess of $300 million. Yet this hasn’t prevented pharmaceutical companies from duplicating efforts in an attempt to identify a treatment for the disease. Numerous companies have invested significant proportions of their R&D budgets exploring the potential of monoclonal antibodies that bind to amyloid beta, a target that is undoubtedly associated with Alzheimer’s Disease but whose validity as a drug target is still questionable due to the poor understanding of its
role in the pathology of the disease. This has resulted in numerous costly failures including the recent failure of both bapineuzumab and solanezumab in phase III trials\textsuperscript{6,7}.

The combined forces of market economics and healthcare demands dictate that the model of drug development which encourages these expensive, duplicated failures must change. Over recent years there is evidence to suggest that attitudes and strategies towards the pursuit of new drugs are slowly changing. As an alternative to pursuing single, tractable targets in an industrial environment, a new, more collaborative model is emerging based on partnerships in which the rigour and process of industrial drug discovery is combined with the deep understanding of disease biology from academic research centres and teaching hospitals. This is backed by funding from multiple interested stakeholders (including private, public and charitable organisations) and may provide a potential long-term solution to this problem.

**Target selection and validation**

There are several components to choosing appropriate drug targets: identification of key biological processes and controlling elements that underlie and are relevant to the disease, followed by assessment of the feasibility of developing a drug (or drugs) that will interfere with those processes. The drug target itself could be a single protein (eg enzyme, receptor, ion channel, transcription factor) or could be a combination of two or more proteins, which might require multi-functional drugs or drug combinations.

The use of relevant human disease model systems and disease tissue in these experiments will likely improve the probability of choosing an appropriate drug target. Perhaps most powerful of all is the association of a mutation, deletion or translocation with a particular disease state as revealed by human genetic analysis of individuals with a history of a particular disease. Alternatively, mutational analysis (eg using public source databases such as COSMIC) in patient populations, for example in the case of somatic mutations in cancer, can provide powerful insights into human disease processes. The key to effective target selection is to gain as detailed an understanding as possible about the biological changes that drive disease and the changes in normal control mechanisms caused by the diseased phenotype, using the most relevant human genetic data and models. This will not only inform choice of drug targets, but will also be the basis of defining which patients might benefit from the resulting treatment. Strategies for patient selection are important even at this early stage.

One of the key activities for any drug discovery programme is hit finding to produce probes for further target validation work as well as high quality chemical starting points for medicinal chemistry programmes. This is especially true for new targets which fall outside the traditionally ‘druggable’ target classes (eg inhibition of protein-protein interactions) and is leading to innovative new hit finding approaches. Medicinal chemistry is a particular strength of pharmaceutical companies and allowing academia access to tool compounds through collaboration as well as to the resource and expertise to allow the design of compounds to effectively interact with biological systems enhances the potential for overall success. Industrial-academic partnerships can be much better placed to integrate all of the elements required for a successful drug discovery programme than either academic or industrial groups alone. Large pharmaceutical companies have major strengths in activities that require scale and infrastructure (eg high throughput screening, medicinal chemistry, toxicology, regulatory expertise, Phase III/IV clinical trials and marketing). In academia it is easier to access clinicians, patient biopsies, relations with patient groups, patient databases and clinical infrastructure. Access to
sophisticated clinical networks, patient groups and valuable healthcare infrastructure such as UK National Health Service are all benefits industry enjoys through collaboration. The quid pro quo is that these collaborative projects benefit from the focus and emphasis on effective project management that is characteristic of industry. In academia it is also feasible to pursue high risk, innovative endeavours over protracted periods, whereas in a private setting this is often not feasible. There are now a growing number of examples of industry-academia collaborations, representative examples of which are described below:

Almac and Queens University Belfast (QUB): In the area of oncology a shared focus between Almac Group’s drug discovery and diagnostic business units and the Centre for Cancer Research and Cell Biology at QUB has spawned a collaboration designed to exploit the basic research capabilities and clinical networks of the University together with the industrial process and drug discovery experience at Almac. Supported by a £13 million investment including significant funding from the local government development agency Invest Northern Ireland, the collaboration seeks to push existing Almac Discovery assets through clinical development as well as initiate new programmes based on an enhanced understanding of the biology associated with molecular subtypes of disease which is built upon the biomarker platform.

University of Manchester/GlaxoSmithKline/Cancer Research Technologies (CRT): Also in the area of cancer drug development, the University of Manchester, GSK and CRT have come together to focus their efforts on drug discovery in the specific field of epigenetics. Here GSK will provide starting materials that will allow researchers in the Cancer Research UK funded centre at the University of Manchester to develop molecules targeted towards the post translational modification of key mediators of cancer proliferation. The idea in this instance is that by allowing academic researchers access to materials from industry the process of early drug development can be hastened.

Massachusetts General Hospital (MGH)/The Broad Institute/Amgen: Amgen has looked to its neighbours MGH where biotech researchers will be paired up with researchers at the Whitehead Institute to develop new drugs across a number of areas including immunology, neurology, developmental biology, genetics and genomics. The collaboration will see Amgen contribute $5.25 million over the next three years to facilitate interrogation of the complex biology of diseases with few treatment options.

GSK/University of Uppsala: The pursuit of novel antibiotics is the focus of an ambitious European focused collaboration led by GSK and the University of Uppsala. The $140.6M programme, christened ENABLE (European Gram-Negative Antibacterial Engine), supported by the Innovative Medicines Initiative seeks to establish a significant anti-bacterial drug discovery platform for the progression of research programmes through discovery and phase I clinical trials, with the ultimate goal to complete Phase I clinical trials of at least one novel anti-bacterial for Gram-negative infections by 2019. This collaboration is a very positive example of how a high risk area such as the development of novel antibiotics can be tackled through bringing together the complementary skills of industry and academia.

Pfizer/CTI: Building on the concept of Open Innovation, Pfizer are four years into the establishment of a model for academic-industry collaboration, designed to bridge the gap between early scientific discovery and its translation into new medicines. Pfizer’s Centers for Therapeutic Innovation (CTI) involve placing Pfizer researchers into the labs of academic researchers across the US whose projects benefit from funding for pre-clinical and clinical development programmes and access to antibody libraries and other proprietary technologies. The initiative is reported to be disease agnostic but with an initial focus on biological therapeutics.

Barriers to Collaborative success
Despite clear areas of overlapping interest, the worlds of academia and industry do have different

Massachusetts Institute of Technology (MIT)/Biogen Idec: Also in Boston, Biogen has looked to its neighbours MIT where biotech researchers will be paired up with researchers at the Whitehead Institute to develop new drugs across a number of areas including immunology, neurology, developmental biology, genetics and genomics. The collaboration will see Biogen Idec contribute $5.25 million over the next three years to facilitate interrogation of the complex biology of diseases with few treatment options.
and sometimes competing priorities. The academic researchers’ primary concern, over and above their research interests, is the attainment of grant income, closely followed by the publication of results. Although attitudes are changing, it can be the case that restrictions imposed by grant awarding bodies can discourage project participation by industry. The publication of results is also an area that has to be approached sympathetically by both parties. While premature publication must be avoided to preserve the potential commercial value of drug development projects, the academic researchers’ need for publication must be borne in mind when designing projects and the type of data produced. Appropriate funding models must be developed to encourage and enable collaboration. This could include direct R&D funding from potential payers (eg health authorities and governments) to underpin a consortium-based approach, in return for more cost-effective medicines at the end of the process.

**Open source drug discovery**

Another important trend which builds upon industry-academic collaboration and partnerships is a move towards open source drug discovery. As a prime example of this, the Structural Genomics Consortium (SGC), a public private partnership based at the Universities of Oxford and Toronto, represents a unique open innovation engine. The consortium comprises in excess of two hundred scientists focused on generating high quality novel reagents for pioneer human proteins of therapeutic relevance. These reagents include methodologies for protein production, biochemical and biophysical assays to assess function, novel potent and selective inhibitors to establish protein function in cellular assays and the three dimensional x-ray structures of the protein, protein-protein or protein-ligand complexes to facilitate drug design. All these tools are made freely available to academics, biotechnology and pharmaceutical companies, in order to catalyse target discovery and proprietary projects. The consortium, which is currently celebrating its first decade, is collaborating with more than three hundred academic labs across the world, and is working closely with its nine pharmaceutical funding partners to rapidly produce these outputs. In a recent exciting development, the SGC is now leveraging the proprietary capabilities of biotechnology companies and building relations with patient organisations to rapidly disseminate these tools to all disease experts, and hence catalysing the creation of disease specific drug discovery portfolios. The group are deliberately working on pioneer targets or protein families currently unexplored or deemed chemically intractable.

The impact of this approach has already been very significant. The first inhibitor generated by the consortium (JQ1, a small molecule inhibitor of a subset of bromodomain proteins) in collaboration with GSK and James Bradner (Harvard) has now been distributed to more than 400 labs. The outputs of this endeavour have been remarkable. The group initially demonstrated therapeutic potential in a rare cancer (NUT midline carcinoma), but since then their army of collaborators have shown potential utility in a variety of other cancers, as a male contraceptive or as an agent for reducing cardiac hypertrophy or in treating sepsis. This freely available novel inhibitor has crowd sourced science in an unprecedented manner. It has demonstrated the tractability of this protein family, and resulted in many proprietary programmes, facilitating the progression of at least five proprietary molecules from five organisations into clinical studies. In addition, it has enabled more than two hundred additional publications on this target in less than four years.

Numerous contract research organisations are now using their proprietary resources to advance SGC outputs to more advanced molecules (clinical candidates) for further exploitation in potential partnerships with pharmaceutical companies. This unique public private partnership is creating porous interfaces between all stakeholders in the drug discovery ecosystem, reducing duplication and wastage and catalysing science and drug discovery through the creation of win-win relationships.

In a bold move, SGC scientists are now working with Sage Biotherapeutics, Takeda, the Institute of Cancer Research and the Canadian Institute for Health Research to drive the pre-competitive boundary post ‘Proof of Clinical Mechanism’ (ie Phase IIa studies in small cohorts of patients). The rationale behind this approach is that this is the stage in discovery where most pioneer targets fail, after 5-7 years of proprietary efforts in numerous organisations, often ‘in parallel and in secret’. This represents an immense waste of private (and in some cases public) funds, but more importantly is resulting in the exposure of patients to molecules known by others to be destined for failure. The group have already initiated a programme in cancer, and are in discussions regarding similar efforts in Alzheimer’s Disease, schizophrenia and autism. These types of partnerships may well provide the platform and incentive to radically transform the
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Conclusions
Drug discovery and development is a complex, expensive and high risk endeavour. Yet ultimately, society demands new, innovative drugs to treat diseases which are becoming more prevalent in a modern society. Productivity metrics coupled with an increasing demand from payers for more cost-effective medicines have cast a significant shadow over the traditional model of drug discovery and development. This has led to an increased realisation that by pooling expertise and resources and by sharing the risks, and ultimately the rewards of drug development, a more sustainable collaborative model may emerge in which all stakeholders stand to benefit. This new model must include appropriate collaborative funding models which could include the ultimate payers (such as health authorities and governments), in return for the promise of more cost-effective medicines. The possibility of pooled resources leading to reduced duplication and enhanced probability of success in drug development is surely a prize worth pursuing, as it is patients who will be the ultimate beneficiaries.

Dr Robert Grundy, Director of Commercial Development and Licensing, is responsible for the commercial development of drug discovery and development technologies at Almac. Rob previously held a Marie Currie Research Fellowship at the Schering-Plough Research Institute in Milan and a Principal Scientist position at GlaxoSmithKline before holding the post of Chief Scientific Officer at Cerebricon, a preclinical CRO based in Finland. Iain James joined the Sandoz Pain Unit in 1985 and spent 15 years with Sandoz/Novartis in London. He was then Director of Drug Discovery for Ionix Pharmaceuticals, followed by Senior Director of Biology for BioFocus. He joined Almac in 2007 to help establish Almac Discovery, where he is VP Biology.

Chas Bountra is Professor of Translational Medicine in the Nuffield Department of Clinical Medicine and Associate Member of the Department of Pharmacology at the University of Oxford. He is also a Visiting Professor in Neuroscience and Mental Health at Imperial College, London. Prior to coming back to Oxford six years ago, Chas was Vice-President and Head of Biology at GlaxoSmithKline. He was involved in the identification of more than 40 clinical candidates for many gastro-intestinal, inflammatory and neuro-psychiatric diseases. He was involved in the launch and development of the first treatment for Irritable Bowel Syndrome (Alosetron) and was the first to show that neurokinin NK1 antagonists are antiemetic in preclinical and clinical studies. He has given over 300 invited lectures and in 2012 was voted one of the ‘top innovators in the industry’.

Tim Harrison is the McClay Professor of Medicinal Chemistry at the Centre for Cancer Research and Cell Biology, Queen’s University Belfast, and Vice President, Almac Discovery. Prior to this he was Director, Medicinal Chemistry at Merck Sharp and Dohme’s Neuroscience Research Centre in Harlow, UK.

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