State of the Discovery Nation 2018

and the role of the Medicines Discovery Catapult

Joint report by the BioIndustry Association
and the Medicines Discovery Catapult

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AT THE HEART OF DRUG DISCOVERY

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Foreword by Chris Molloy, CEO

What determines the state of a nation? I believe it is a combination of physical presence, active resources and, most importantly, its attitude to the future.

"Biotechnology SMEs are key to UK plc's future and a vital link in the supply chain of new medicines."

Chris Molloy, CEO
Medicines Discovery Catapult

The state of our nation is good, but other countries are increasingly competitive. Twenty-five of the hundred most successful medicines ever made were discovered here.

Our science, technology and national health assets are world class, but often fragmented and poorly signposted even across this small geography. Our finance community is powerful, but often needs persuading to invest in life sciences. Our biotech and related companies are numerous, but do not always possess the skills, equipment and facilities that enable them to grow organically. Instead, they are often acquired by foreign companies. Despite this, our national ambition and attitude remain robust. We are committed to the life sciences industry and its ultimate beneficiary, the patient.

This report is a review of the sector's perceptions. It is not a manifesto. It covers global issues from the perspective of a multinational, and UK issues from the perspective of small and medium sized enterprises (SMEs). Biotechnology SMEs are key to UK plc's future and a vital link in the supply chain of new medicines. Their willingness to take risks and innovate maintains the product portfolios of big pharma.

However, 40% of UK biotech SMEs have less than 5 people[1] with which to manage the drug discovery process – a process that is exceptionally complex. Consequently, the Catapult can be a tremendous help to many of these SMEs. They can benefit from access to scarce expertise, equipment, national assets and know-how.

The report, developed in collaboration with the BioIndustry Association and Innovate UK, identifies improvements in technology and processes these SMEs are asking for: humanised models of drug discovery for better predictability in clinical trials, new computational biology and advanced informatics for more informed R&D, access to the best national knowledge and services – not just the closest – and easier access to consented patient data and samples. We are starting to address these needs.

Whilst these tactical needs are clear and present to today's SMEs, Catapults are also here to help the industry transform. This means going beyond incremental change. It means proving profoundly new techniques that tomorrow's SMEs will adopt: changes in the shape of R&D projects and the patient groups who should drive them; the data they use and generate, and the combination of biomarkers, imaging and drug delivery technologies. We are here to help SMEs work through this transformation. We will do so through 'stepping stone' projects alongside the community, with a vision of the future guided by our board and the sector, and with the ability to take the risks necessary to achieve it.

We are one part of a large UK community of national stakeholders in UK life sciences. This report also indicates where more work must be done – by many interlocking groups – if we are to maintain our heritage position as one of the world's best places for developing new targeted, high value medicines.

Seldom at such a time of massive industrial, regional and political change have the words of novelist EM Forster been more appropriate: "Only connect."[2]

1 *www.gov.uk/government/uploads/system/uploads/attachment_data/file/525102/bis-16-237-strength-and-opportunity-2015-UK-medical-and-biopharmaceutical-landscape.pdf*

2 *Howards End; Penguin Classics; First Printing edition (28 Jun. 2012)*

Executive Summary

Remarkable progress has been made in developing the tools to study human disease. The sector has access to scientific technologies and computational resources beyond the imagination of previous generations, including gene editing and artificial intelligence. However, failure rates at each stage of the "bench to bedside" development pathway are still too high. Around 40% of new drugs fail when they are first tried in a patient.[3] The majority fail at other stages. As a result, the number of drugs launched per $1bn of R&D spend has fallen nearly thirtyfold over the last 40 years, with the established pharmaceutical industry return on capital now at 3.2%, according to Deloitte.[4] If the different sectors of the UK community can work together to reverse this productivity paradox, we can begin a dramatic period of regrowth in our nation's historically world-beating discovery tradition.

The mission of the Medicines Discovery Catapult team is to help make this happen. We have listened to our community and reflect their views in our actions to catalyse change and collaboration. We have reviewed the recent reports on the state of UK commercial drug discovery from the Wellcome Trust, the Biotechnology Industry Association (BIA), the Office for Life Science, the Association of British Pharmaceutical Industry and others. We have run surveys with the top managers of UK companies in this field and conducted interviews with over one hundred of them. This has given us unique insights into the state of the UK drug discovery nation, how we should help, and how any remaining issues or opportunities can be progressed through partnership with charities, research funders, academics, clinicians, investors, and policy-makers.

Industry leaders say that the key issue is the low predictive power of existing pre-clinical models, with academic research supporting this hypothesis. We will address this by bringing more patient-derived approaches into the mainstream. These include advances in patient derived targets and biomarkers, and more complex models, such as organoids, for discovery and pre-clinical research. These technologies need to be woven throughout the discovery process to place the patient at the heart of the research process. Doing so will turn the old one-way "bench-to-bedside" flow into a more complex, iterative learning system as researchers constantly probe and de-risk a candidate and its target. In turn, when that candidate enters the clinic, we can use deep biomarker and clinical datasets to make the preclinical models even more predictive.

The fragmentation and specialisation in our ecosystem creates real challenges for industry, SMEs, contract service providers and academics. No one has all the necessary services in-house. All of us need to find efficient ways to work together, in a sector where intellectual property (IP), regulatory and confidentiality demands make contracting complicated. Success relies on making the ecosystem easily navigable, and in making virtual, collaborative R&D easy and affordable.

Success relies on **making the ecosystem easily navigable**, and in making virtual, collaborative R&D easy and affordable

The explosion in data generation from high-content trials, omics and wearables, combined with increasing data availability from international consortia, makes data analysis a key competitive asset. Data from failed trials and failed pre-clinical projects could be transformative in reducing rework. The UK has a small but excellent core of data and artificial intelligence (AI) scientists developing tools to make this happen, but they rely on effective data sharing.

Our surveys and interviews gave confidence in the UK's strengths in basic science, and the talent that has come out of the pharmaceutical industry, but raised concerns about our ability to combine these in successful translation. We have strengths in some diseases, often supported by research charities, as well as in our history of producing new chemical entities and antibody derived drug platform technologies. The sector cited the potential in small molecules, next-generation antibodies, and IP-savvy re-purposing, as well as advising the Catapult to invest in improved models and focussed informatics.

Some broader issues emerged from our research that require policy coordination. UK academics are half as likely as those in the US to protect their innovation when they make a major breakthrough. They face capability and funding issues at the very earliest stages of translation, known as "concept testing". We also heard from SMEs that there are opportunities to improve many government support structures, and opportunities to make better use of the potential of the NHS. In particular, we need to make stratified trials, research data, and well-annotated human samples easier for innovative companies to access. Skills outside the lab are also vital but often insufficient. We need a deeper pool of general management, project management, and informatics experts. Finally, while early stage funding has improved, for instance with the Biomedical Catalyst, any increase in translation must be pulled through the system by sufficient growth finance if it is to create jobs, as envisioned in the government's response to the Patient Capital Review.

We will support the industry by focusing on those areas where we can be most effective across many diseases (such as improved models of human organs), and highlighting where other parts of the ecosystem are strong or need support. We will coordinate aspects of discovery that impact SMEs the most, along with the major charities, Medical Research Council (MRC), National Institute for Health Research (NIHR), industry groups and the NHS. This understanding has led to five strategic areas:

A) Catalyse 'Disease Syndicates'

to accelerate new discoveries and their translation in the clinic. In partnership with the relevant disease charity, Syndicates will provide a neutral, trusted convener between industry and academia to accelerate the identification and translation of new discoveries into medicines. Through new models of collaborative research, Syndicates will create platforms to plan, develop and coordinate the R&D ecosystem in a disease focussed way, by connecting the real needs of patients and frontline clinicians with research opportunities involving innovative technologies.

B) Develop novel informatics platforms

to unlock currently cryptic data, rapidly identify and qualify new therapeutic targets and characterise early lead compounds. Currently, we have too many vertical stakeholder data silos that stop the flow of knowledge across the horizontal, translational research community. This must change. We need to create interoperability between 'learning systems' that themselves are siloed. We will create a directory of capabilities, molecular assets, their properties, owners, inventors, and link these to experts and organisations - helping UK businesses become more productive. By working with our Disease Syndicates to map "known but unpublished failure" we will sharpen investment focus and reduce the costs of reinventing the wheel.

C) Develop and prove key technologies that humanise discovery

We will work with SMEs and technologists to develop commercially viable tools and techniques that address key barriers holding back the flow of new medicines, especially: new cell testing systems which provide richer information on efficacy and toxicology signaling; complex human-derived model systems recapitulating organs, diseases and systems; advanced sensitive detection and quantitation of biomarker, transcriptomics and lipidomics. This will reduce the failure rate for SMEs and thereby increase their research productivity.

D) Improve sample and data access for all translational scientists

We will overcome a major barrier for SMEs by developing interfaces providing straightforward, well-governed access to real world sample and patient data, working in partnership with the NHS, MRC, national biobanks and data holders, technology transfer offices and Health Data Research UK (HDR UK).

E) Build a national virtual medicines R&D ecosystem

We will catalyse and demonstrate best practice in multiparty drug discovery and early clinical development, across contract research organisations (CROs), academia and industry. This will include a curated network of expertise, as well as project management, informatics and IP services to reduce the transaction times and cost of virtual R&D, ultimately leading to more investable products.

Our plan tackles some, but not all of the issues that the sector faces. SMEs fit into a complicated landscape that includes universities, NHS and government agencies. We can help SMEs navigate this. Issues such as high-quality IP, support structures, stratified trials, funding, and skills require a systemic approach. The MDC will work with others to create long-term solutions to these issues. We have listened to, and are acting on, what our sector needs.

3 *https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf*

4 *https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/measuring-return-from-pharmaceutical-innovation.html*

Context

The Medicines Discovery Catapult's mission is to help support UK SMEs in the area of medicines discovery through to human proof of concept.

We want to see high value medicines from UK discovery science get to patients faster, cheaper and with less risk to both patients and animals. If we do that well, we will build a successful biotech cluster of the scale of San Francisco or Boston. The BioIndustry Association is one of the leading UK industry groups for such companies and shares our ambition. We have collaborated to run joint research into:

- How SMEs perceive the UK environment for medicines discovery and translation
- The specific needs of our sector
- The most impactful interventions the Catapult could make to drive R&D productivity

This research consists of two senior expert online surveys, each reaching over 100 respondents, and about 100 follow-up in-depth interviews. We would like to thank our partners in recruiting those experts including; the Association of British Pharmaceutical Industries, BioNow, the scientific advisors to the Association of Medical Research Charities (AMRC), and the expert translational grant assessors at Innovate UK (IUK) and at the Medical Research Council, amongst others. In particular, we would like to thank the individuals who took time to complete the surveys and talk to us during the interviews.

Chapters 1 and 2 are a snap-shot in perception as to "the state of the nation" in drug discovery in the UK, based on these surveys and interviews. Our scope spans breakthroughs in academic science through to human proof of concept, and so does this research. Our focus is on the economic potential of - and challenges faced by - the sector, and the emerging technologies and new forms of research that could change it for the better. We will conduct this research annually to make sure that we are listening to our community and also to help shape evidenced-based innovation policy for the sector.

We also summarise in chapter 3 our emerging programme of support to the community. The emphasis is on "emerging", as this document is not our comprehensive strategy. Longer term goals include more transformative aspects. It will evolve and adapt given the performance of our programmes, available funding and further dialogue with other stakeholders. However, as our facilities are now open and in use, it is right to make sure the community knows what we can offer to help great UK innovations get to patients.

Chapter 4 identifies five cross-cutting themes where there is a strong need for change to improve the UK ecosystem, not only in our own strategy and programmes, but in the strategy and programmes of other stakeholders. These themes are complex and cross-cutting, and no one stakeholder can solve them alone. They need all of us to "gang up" on the problem. Together we can make the UK a global cluster in medical biotechnology.

We look forward to working with all of you to make this happen.

Chapter 1:
The state of the nation in drug discovery

The economic case for government support for the life sciences is clear, as the sector employs almost 222,000 people in 5,633 companies generating approximately £60.7bn turnover.[5] But UK R&D productivity is lower than the US.

Taking our great science through to the market has been a key focus of policy since the Barlow report in 1946,[6] and research by the BioIndustry Association provides some sense of the prize for patients and the country if we can get to the right solution (Table 1).[7]

Table 1: Size of the opportunity for the UK in biomedical innovation, estimated from benchmarking vs. R&D inputs

Metric (for period 2010 to 2012)	UK relative performance to California or Massachusetts	Absolute gap between UK and California or Massachusetts
Citations per $B research spend	+25% more	
Private follow-on investment	11 times less	~$3B / year
Clinical stage biotech companies	3.5 times fewer	~150 companies
Sector wage pool	2.5 times lower	$8B / year

We and the Cell & Gene Therapy Catapult are an important part of a portfolio of UK government initiatives to change this, complementing broader reforms by UK Research and Innovation (UKRI) and UK government policy as a whole (e.g. fiscal incentives for knowledge-intensive sectors and disease-centred long-term R&D). This report, based on over 100 expert interviews and e-surveys of another 250 experts, aims to present an overview of **perceptions** of the UK's medicines discovery sector today. Perceptions matter when companies choose where to invest.

Perceptions matter when companies **choose where to invest**

1.1 Global R&D productivity is in crisis

There is a global need for better and more affordable medicines, with the burden of disease rising faster than GDP due to an aging population and the rise in chronic diseases. However, we also live in the era of high potential science, thanks to massive increases in biotechnological productivity. Drug research technologies have improved radically over the last 30 years. For instance, genomics has seen a ten billion-fold reduction in cost per base pair since the 1960s. Over the same time, X-ray crystallography has seen a ten thousand-fold improvement in the number of structures published per year by teams such as the Structural Genomics Consortium and others. The speed and throughput of drug screening programmes has likewise been transformed. Many of these productivity improvements are the basis for India and China's genomic and drug discovery contract research organisations (CROs).

5 *www.gov.uk/government/uploads/system/uploads/attachment_data/file/525102/bis-16-237-strength-and-opportunity-2015-UK-medical-and-biopharmaceutical-landscape.pdf*

6 *http://www.foundation.org.uk/Events/pdf/20171018_Summary.pdf*

7 *Source: A vision for the UK life sciences sector in 2025, based on detailed economic benchmarking against R&D inputs 2010-2012. Note this is before the devaluation of the pound versus the dollar since the Brexit referendum – the gap will now be larger*

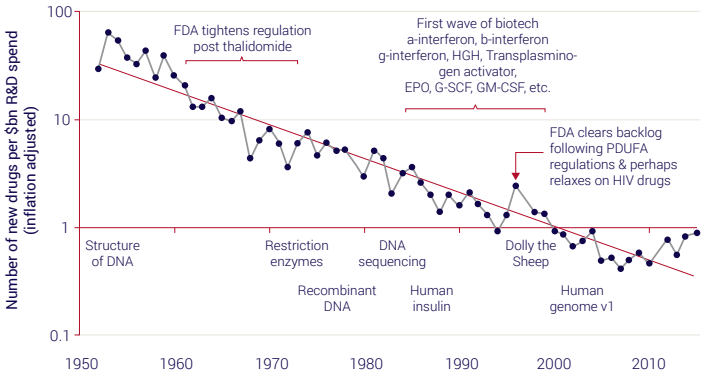
Unfortunately, this has not translated into more new drugs per dollar spent on R&D. Costs per new drug have increased to $1.8B each, from hundreds of millions 20 years ago. Pharma R&D returns have fallen below their cost of capital, leading them to outsource to smaller companies. Deloitte's annual surveys of pharma R&D productivity have seen returns on investment fall to 3.2%. Recent research extrapolating this shows that if this trend continues, established pharma returns on R&D capital will fall to 0% in 2020.[8]

Nothing is proven in medicines discovery until we have proof from human trials. On average, 63% of drugs pass Phase I safety, but only 31% pass Phase II human proof of concept and only 50% pass on through Phase III to FDA approval.[9] When looking at drugs in new classes, or for new targets, or in complex diseases like Alzheimer's, the success rates are much lower. The most expensive trials are at Phase III, so the more we can do in earlier phases to eliminate weak drugs faster, the better for the health of patients and volunteers in trial, and for the economic health of industry.

1.2 The R&D model must be retooled

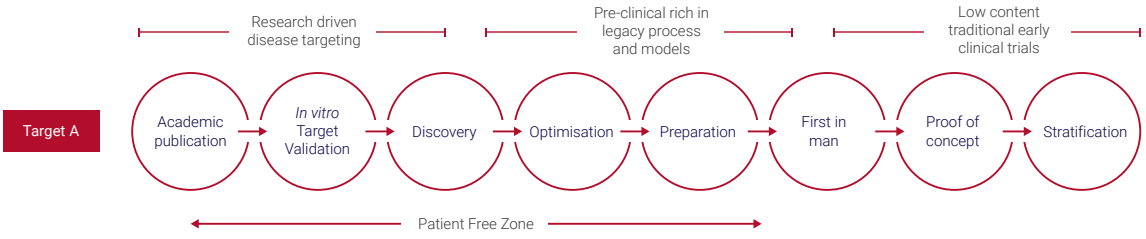
Through our sector engagement, we have heard that the problems lie in the traditional "bench to bedside" R&D process. Historically, scientists would discover a new cause of disease, and proceed to try and make drugs against that cause, eventually taking new chemical entities into clinical trials and then the market, as laid out in Figure 2. Within each step are many complex, scientifically demanding industrial processes, all aiming to identify and prove that a non-toxic chemical or biological drug is likely to beneficially influence the disease.

Figure 1: Long term productivity of drug discovery is in decline (courtesy Jack Scannell, UBS)



This meant that the preclinical research process was patient free, and relied on animal models of disease and toxicology that were a poor approximation of humans. Small improvements in the predictive value of these models could improve global R&D productivity more effectively than improvements in large scale "screen more, screen faster" methods, with quantitative modelling suggesting that an improvement in the correlation between preclinical models and clinical performance of 0.1 is worth 100x improvement in brute force efficiency.[10]

Figure 2: a schematic of the traditional bench to bedside drug discovery model



8 https://endpts.com/pharmas-broken-business-model-an-industry-on-the-brink-of-terminal-decline/

9 Clinical Development Success Rates 2006-2015, BIO-Amplion

10 Scannell JW, Bosley J (2016) When Quality Beats Quantity: Decision Theory, Drug Discovery, and the Reproducibility Crisis. PLoS ONE 11(2): e0147215. doi:10.1371/journal.pone.0147215

1.3 The UK must focus on high value products and services

This creates an amazing opportunity for the UK to make drug discovery smarter. China and India have competitive pre-clinical research industries with significantly lower unit labour costs than the UK. If we try to compete in this area of drug discovery, we will fail. Instead, we should compete in the **higher value** areas where our expertise can differentiate to the level of our relative costs. In particular, we can compete by developing technologies to humanise drug discovery. This includes not only human genetics, but also the complex interplay between human organs, such as the liver and immune system, and disease or drugs.

An improvement in the correlation between preclinical models and clinical performance of 0.1 is worth **100x improvement in brute force efficiency**

1.4 The UK must humanise drug discovery - starting with the patient

Our interviews and surveys identified many emerging technologies that can "humanise" the drug discovery process. These technologies make the early stages of research more predictive of how a drug will work in real life. They can generate a wealth of humanised *in-vitro* data, resulting in better drug candidates entering human trials. The benefit is lower attrition and therefore improved research productivity for industry. We need to do this by:

We should **compete in the higher value areas** where our expertise can differentiate

1. Starting with patient-derived targets and biomarkers, which create candidate drugs that are highly selective for proven human disease targets in well-defined patient sub-groups, not animal targets.

2. Humanising discovery and preclinical models to ensure drug candidates have been screened in complex predictive models for toxicity and efficacy, especially:

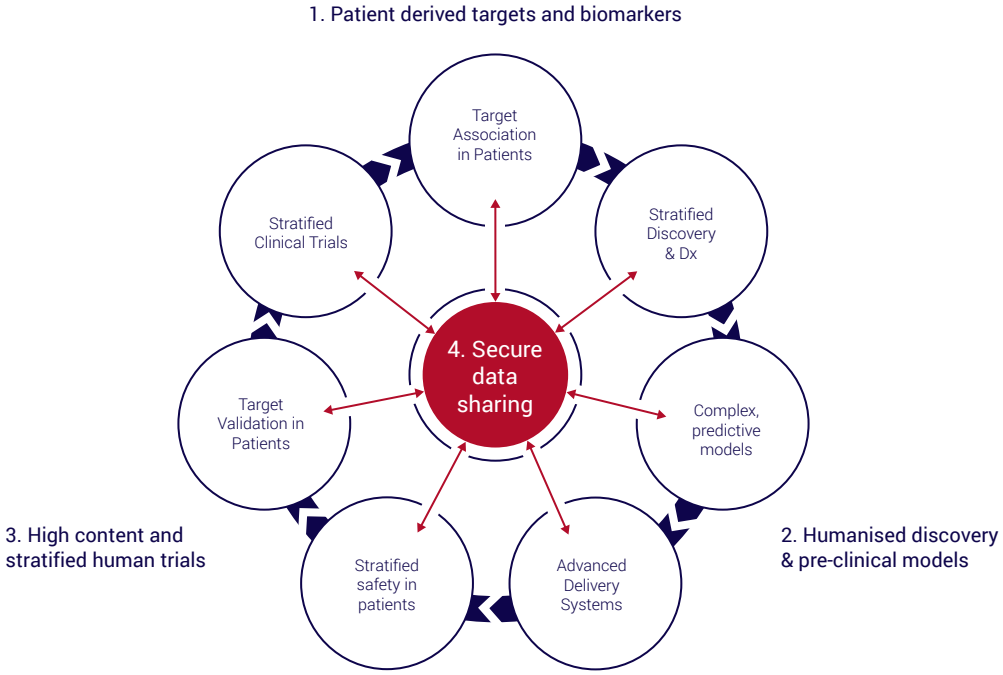
   a) For a broad range of possible off-target effects in many human tissue types, genetic subgroups, and complex organ-to-organ interactions, using the emerging complex toxicology models

   b) For humanised *in vitro* evidence for disease-modifying target engagement in advanced disease models

3. Clearly defining the sub-populations of patients likely to have a high benefit for any risk (given either the disease pathophysiology, the implicit mechanism of drug action or human pharmacogenomics). With regulatory approval, we could get early evidence of potential efficacy in Phase I, by performing Phase I in patients rather than unrealistic healthy volunteers, using technologies such as omics, imaging and wearables, and confirming drug metabolism and toxicology in a broad range of human genetics.

4. Reusing and mining the wealth of information we will generate, through appropriate data sharing. This needs to cover the whole of human health research, not just clinical trial transparency.

Figure 3: The humanised drug discovery process



Patient-derived targets and biomarker technologies are great examples of the bedside-to-bench research at which the UK excels. This is exemplified by the study of disease using large scale, deeply profiled cohorts such as those developed by the MRC's Psoriasis Stratification to Optimise Relevant Therapy discovery and innovation consortium[11] and by the NIHR's BioResource.[12] These can provide strong association of new targets with a given disease, and occasionally its cause. Causation can be found from the rare natural experiment that can, with appropriate follow-up, provide proof. Examples include the natural PCSK9 knock-outs found in the Dallas Heart study[13] and the Cambridge patient with an auto-antibody to thrombin that prevented blood clotting except at epithelial tears.[14] Both have gone on to become major new drug classes, led by alirocumab and ichorcumab respectively.

There are many emerging technologies that can make pre-clinical drug development more humanised. Most are derived from human stem cells and the resultant technologies that allow us to create and sustain human tissue in the laboratory. Just 20 years ago, keeping such tissue alive in the lab was a challenge. Now, thanks to pluripotent stem cells, advanced culture methods, microfluidics and precision gene editing we can manipulate the way such tissue grows and differentiates, even down to the substructures of cells and the stratum of the disease which the model reflects. When linked to large human cohorts, we can develop libraries of disease models that reflect the molecular spectrum of human disease, just as the Sanger Centre has done with their library of cancer cell lines. These complex predictive models, when used appropriately, have the potential to be much more discriminating in their ability to weed out the false positives in drug discovery i.e. those compounds that are too toxic, or insufficiently disease modifying.

The most frequently used approach to improve the patient response rate in clinical trials is stratification: the identification of patient groups who are more likely to respond, generally through molecular tests. It is well known that this improves trial success rates. There is a range of technologies that can be used

11 *http://www.psort.org.uk*

12 *https://bioresource.nihr.ac.uk/*

13 *Hall, S, 2013, Genetics: a gene of rare effect, Nature V496 p152*

14 *https://www.fiercebiotecbh.com/r-d/ichorcumab-blood-of-gods*

to measure this. For example, positron emission tomography (PET) imaging can show that a compound is reaching diseased tissue, at the right concentration and even with target engagement. These three indicators are the main causes of clinical failure found by Pfizer in the evaluation of their pipeline.[15] Other examples include advanced wearables, blood metabolomics, and adaptamer technologies.

We must use information from a wide range of sources and experiments to improve the validity of the target mechanism and the candidate for both disease modifying and toxicology potential. Given science does not stand still, a watching brief needs to be kept across all the relevant domains of knowledge, as shown in figure 3, to make drug discovery truly collaborative, multi-disciplinary research.

1.5 The UK must join up its skills and assets in new forms of collaboration

Our interviews suggested that making collaborative R&D the norm, not the exception, requires systemic change in the UK. We will explore some of the practical challenges to this in the second half of chapter 2. But first, let us review why this is a strategic imperative for the nation.

The UK ecosystem today is a large, but highly fragmented galaxy of high quality teams. There are hundreds of small biotechs, thousands of academics in basic and clinical research and a growing number in academic drug discovery centres. There are hundreds of preclinical and clinical CROs, a range of NIHR Biomedical Research Centres and Clinical Research Facilities[16] and a handful of major pharma R&D centres. Our interviews highlight the importance of collaboration across this infrastructure to improve productivity. This is ***'virtual R&D' on a national scale***. This will involve management of projects through a network of expert providers, including early translation taking place inside academia through initiatives such as iTAc, an emerging public private consortium supported by the Catapult and targeting the diseases of ageing. This virtual R&D approach was also highlighted by a call for a centrally managed, nationally delivered Translational Fund in the 2017 Life Sciences Strategy delivered through an association with the Catapult, MRC and NIHR.

Collaboration will be needed as no single organisation can ever hope to have all the skills needed to manage the discovery system end-to-end. There is so much innovation that there will inevitably be a number of specialists in each niche, innovating as much around service as around knowledge and IP. The best drug developers will choreograph these specialist skills to make their research as fast-to-fail and capital efficient as possible.

There have been some national collaborations in clinical research, notably the Translational Research Collaborations established by the NIHR's Office for Clinical Research Infrastructure.[17] The 17 MRC Stratified Medicine Consortia and 6 MRC/EPSRC Molecular Pathology Nodes have created discovery and innovation platforms, identifying new markers of stratified treatment response, risk, and progression across a broad range of high-burden diseases. Cancer Research UK's Centre for Drug Development and network of Drug Discovery Units are an example of a charity taking strategic leadership in one disease.[18] The UK needs to develop and evolve more collaborative approaches for discovery research.

No single organisation can ever hope to have all the skills needed to **manage the discovery system end-to-end**

15 *Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. Morgan P et al. 2012, Drug Discov Today, 17(9-10):419-24*

16 *www.nocri.nihr.ac.uk*

17 *www.nihr.ac.uk/life-sciences-industry/access-to-expertise-and-collaborations/collaborations-for-early-phase-translational-research/*

18 *http://www.cancerresearchuk.org/funding-for-researchers/drug-discovery-and-development*

1.6 The UK must treat medicines R&D as a data science

These new discovery technologies have led to an explosion of data. This may be data from the clinic, high dimensional screening processes and models, or -omic platforms and cohorts. Harnessing the explosion of data requires great data science and advanced analytics. Data interoperability will be essential, and we will need to blend public and private data in new ways. Augmented and artificial intelligence will be needed to lift the few possibly interesting interactions to human observation, and this is an area of strength for UK SMEs.

However, our data science relies on the availability of correct and comprehensive data. Academic incentives to publish quickly and a lack of funding for critical experiment reproducibility means that the false positive rate for concepts in the academic literature is estimated by Pfizer at 50%. As one of our drug development CEOs put it "*I understand why it happens, but what a waste! We now always repeat the key academic experiments.*" In addition to this lack of reproducibility, there is an issue with not sharing negative results. It is well known that in both academia and industry failed clinical trials rarely get published, let alone failed pre-clinical experiments. Yet it is essential that we find ways to learn effectively from such failure, if nothing more than to avoid repeating the same experiments. We also need to extend this to preclinical research and make earlier identification and publication of negative results the norm, not the exception. There is much to do across academia and industry to improve reproducibility and incentivise sharing negative results, although we have come a long way.

Underlying technologies like genomics or wearables turn the analogue of nature into digital. Their increased use, driven by falling costs, is also turning clinical development into a data science. Some cancer and cardiovascular trials now generate petabytes of data per patient, thanks to deep omic profiling. Companies are increasingly using UK expertise to manage and mine those data. From a drug discovery perspective, the more we can re-use data, the more effectively we can hunt for cures. Reproducibility and publication bias create structural deficits in that data ecosystem that reduce our ability to screen out false positives via informatics.

As a community, we must work together in the best traditions of science towards the common good, and the common truth. If we organise around what is best for patients, we can find solutions to culturally complex problems – be they clinical trial transparency, the reproducibility crisis, or how to validate and improve these emerging research tools. To do this effectively will require great data science, and making #datasaveslives a daily reality.

"I understand why it happens, but what a waste! We now always repeat the key academic experiments."

Drug Development CEO

The more we can re-use data, the more effectively we can hunt for cures... as a community, we must work together in the best traditions of science towards the common good

Chapter 2:
The strengths and opportunities for the UK

We believe that the UK will achieve more if it plays to its strengths, rather than trying to do everything. If we are to be successful for UK plc, then we should listen particularly to the needs of commercial innovators in UK SMEs. We must also be mindful of the key role of academia in supplying ideas, creativity and intellectual property to that sector.

We have used phone interviews and online surveys with leaders from SMEs, and experts recommended from the BioIndustry Association, the Association of British Pharmaceutical Industry, BioNow, the Association of Medical Research Charities and the translational grant assessor communities at both Innovate UK and the MRC. The BioIndustry Association also kindly shared research it had commissioned on the ecosystem earlier this year.

2.1 Basic science is seen to be the UK's primary strength

The BioIndustry Association asked 128 of its senior members to rate the ecosystem from bench-to-bedside as part of its submission to the government's life science strategy (Table 2). The results show that the UK is positioned strongly in the international arena in terms of basic science impact and reputation. This is to be expected in a country with 11 of the world's top 100 universities and 26 Nobel laureates in medicine or physiology. The UK also has a track record of innovation that changes the lives of patients, from antibiotics to the first antiretroviral drugs for HIV and the first antibody based drugs. This intrinsic creativity is a critical strength.

Perceptions are good for basic science, and show room for improvement in large-scale trials, accessibility of real world data and NHS uptake. However our research also suggests that perceptions lag behind the reality of recent progress in clinical trials by organisations such as the NIHR and Health Research Authority (HRA).

Table 2: Industry perception of the UK ecosystem from bench to bedside, Q1 2017

How would your rate the UK biomedical innovation ecosystem in the following areas for translation to patient impact?	Overall UK Capability	Overall UK Funding	
1. Basic discovery science	3.8	2.6	
2. Initial IP filing, exemplification and concept testing*	3.0	2.3	
3. Pre-clinical development (Lead optimise to IND)	3.0	2.2	
4. Early clinical development (eg PI / II)	2.9	2.2	
5. Large scale pivotal studies (eg PIII)	2.3	2.4 (Flip to exit)	0.6 (Build & IPO)
6. Industry accessible real world health data	2.1	1.8	
7. Care system uptake of innovation	1.2	1.1	

Score:
- World class (4)
- Ok but could be improved (3)
- Problematic (2)
- Significant issues (1)

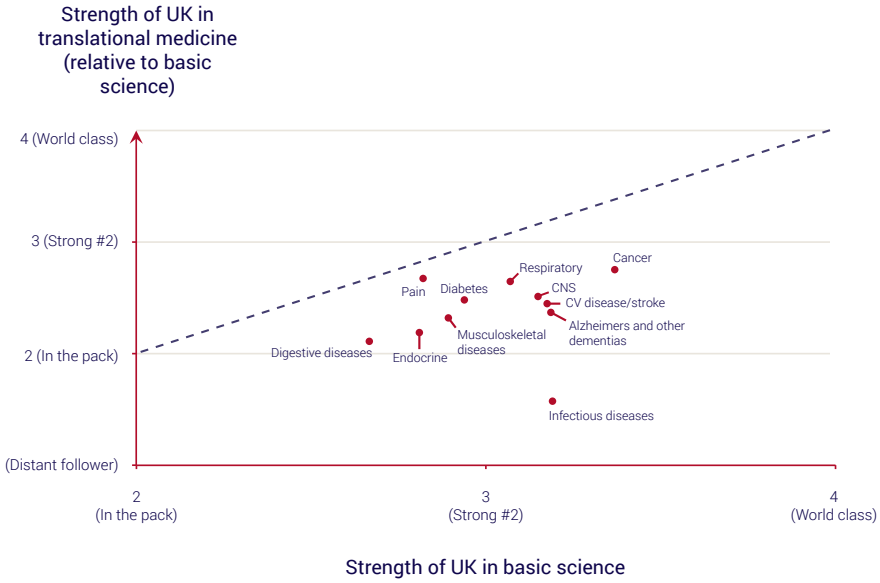
** Initial IP filing, exemplification and concept testing was rated as problematic by academics who we interviewed*

We will examine some of the issues that make the system work less well later in this chapter, but first we review the research results on our national strengths.

2.2 Disease science and research charities are critical system enablers

Understanding the biology of disease enables translation, as it connects unmet clinical need to basic science. We asked over 100 experts to rate the diseases in which they were most knowledgeable. They were asked about the UK's strength in both basic science and translational medicine for the top 12 disease areas by disease burden.

Figure 4: Expert perceptions on the relative strengths of the UK by major disease, Q3 2017



Ranked on 1 to 5 scale of: 1 = Distant follower 2 = In the pack 3 = Strong #2 4 = World class 5 = Best in world

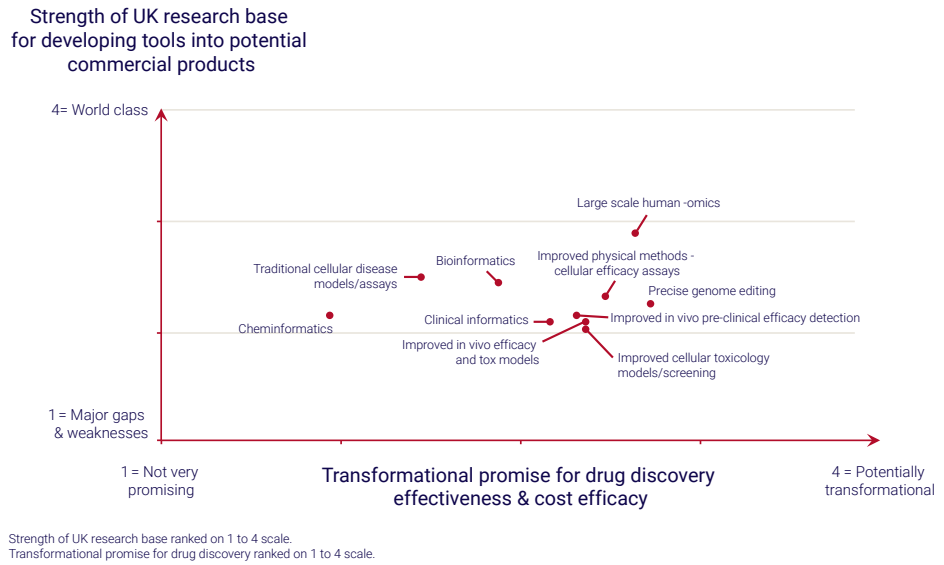
The results in Figure 4 suggest the UK's perceived strengths are in cancer, respiratory, central nervous system and cardiovascular science. In each case, however, the perception was that it is weaker in translational medicine than in basic science. The other broad implication, suggested in Figure 4, is that **the UK has better translation where it has larger charities**. These include, for example, Cancer Research UK, British Heart Foundation, British Lung Foundation, Diabetes UK, Arthritis Research UK and Alzheimer's charities. We did not ask specifically about rare diseases. However they were frequently cited as an area of strength thanks to the Wellcome Trust and many well organised patient groups. UK disease charities are strong relative to other European countries. They create natural focal points around which to unlock complex research collaboration, shown by programmes such as MindMaps.[19] They have strong expert networks across their science advisors and grant-holders who provide the "soft power" to get things done. They also represent the voice of the patient in research.

2.3 The UK is strong in many enabling technologies and should invest in models and informatics

A) Enabling technologies are those research tools that wrap around drug discovery to make it more effective, no matter what its underlying platform technology. Our research on enabling tools revealed perceived UK strengths in large-scale human omics, followed by novel methods to probe cellular assays (such as high resolution mass spectroscopy) and precise genome editing (Figure 5). Sector interviews particularly noted the UK's strengths in gene editing and advanced human cell models. The latter includes stem cell, organoid and organ-on-a-chip technologies that can work across disease, as well as the wealth of stem high resolution and CRISPR-Cas9 edited human *in vitro* models at the edge of academia.

19 *https://mitochondrialdiseasenews.com/2017/04/05/imanova-mrc-funding-mind-maps-study/*

Figure 5: Expert perceptions on the potential of various enabling tools, and the strength of the UK in them



Strength of UK research base ranked on 1 to 4 scale.
Transformational promise for drug discovery ranked on 1 to 4 scale.

B) Experts also noted the UK's rich legacy of disease cohorts as a major differentiator globally. Taking these to the next level as a source of well validated drug targets is a major priority for the government's Industrial Strategy. Our interviewees were particularly interested in using next generation omics and target profiling technologies from single cell sequencing such as the Human Cell Atlas programme, through to cellular mass spectrometry methods to profile these cohorts.

C) Finally, the UK has strengths in informatics and systems biology. Sustained investment has nourished a unique set of skills, be it in bioinformatics with Sanger / European Bioinformatics Institute, or the Farr's clinical informatics network. However interviewees stressed the need for more data scientists (which the Life Science Industrial Strategy also highlighted). In addition, we need to make these data sciences more integrated.

The government has taken steps to support informatics. For example, Health Data Research UK (HDR UK) has been established through a £50m partnership investment led by the MRC, together with the health research departments of England, Scotland and Wales, the Economic and Social Research Council and the Engineering and Physical Sciences Research Council, Wellcome Trust, and British Heart Foundation. The recent Life Sciences Sector Deal describes how apprenticeships can take an increasing role in addressing skills gaps in data science, and that the government will work with the Institute for Apprenticeships to prioritise development of standards brought forward by employers in the life sciences sector, starting with bioinformatics, medical informatics and cheminformatics.[20]

Experts noted the UK's rich legacy of disease cohorts as **a major differentiator globally**

20 171206_Industrial_Strategy_Life_Sciences_SD_Accessible_PDF_DPS.pdf

2.3.1 Where the Catapult should invest

When asked where we should support enabling technologies the results were clear: humanising drug discovery. Forty three percent of votes were in better models, with 56 of 90 votes across the three variants of human models (Table 3). As a result, the priorities seem clear; humanise and validate the many emerging *in vitro* models and invest in informatics and new methods to query them.

Table 3: Expert votes for various enabling technologies where the MDC could enhance drug discovery

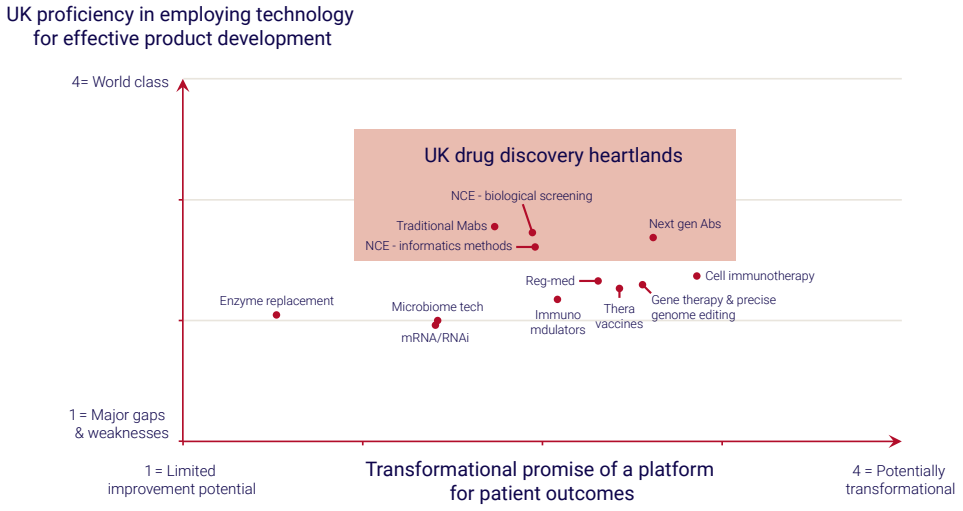
Number of expert votes for various technologies	Deep profiling of human cohorts	Improved animal efficacy and toxicology models	Models from precise genome editing	Improved cellular toxicology models and screening	Traditional cellular disease models / assays	Improved in vivo pre-clinical efficacy detection	Improved physical methods for cellular efficacy assays	Clinical informatics	Bioinformatics	Cheminformatics	Total	%
Target association	24										24	11%
Improved underlying disease models		34	26	18	12						90	43%
Improved technologies to query those models						26	23				49	23%
Improved informatics								25	20	3	48	23%

2.4 The UK is strong in new chemical entities and antibody-derived drug platform technologies

We asked experts for their perceptions of UK strengths across major drug platforms. The "heartlands" for UK drug development (and so potentially for us) was seen to be in three major areas (Figure 6):

1) Novel chemical entities (NCEs) discovered from biological screening and structural biology / informatics
2) Traditional humanised antibody technology
3) The next generation of such technologies such as bi-specifics and antibody drug conjugates

Figure 6: Expert perceptions on the potential of various drug platforms, and the strength of the UK in them



Transformational promise for patient outcomes ranked on 1 to 4 scale.
Proficiency in employing tech for effective product development ranked on 1 to 4 scale.

In contrast, our sector experts consistently rated the UK as less strong in enzyme replacement and microbiome-derived medicines. Various cell and gene therapies also featured, with particular strengths and interest in cell immunotherapies, in cancer and other diseases. This is where the Cell and Gene Therapy Catapult continues to demonstrate strong sector impact. This overall picture is perhaps not surprising, given our historic strengths arising from MRC Laboratory of Molecular Biology / the Winter patents in monoclonals and successes of the UK's structure-based design companies like Astex and Heptares.

The Cell and Gene Therapy Catapult **continues to demonstrate strong sector impact**

2.5 The Catapult could support small molecules, next-gen antibodies and re-purposing

When asked where we should invest to support the UK, the results prioritised novel small molecules and emerging biologic technologies. Traditional monoclonals (Table 4) were a lower priority. There likely remains much therapeutic mileage in monoclonals (with experts rating their potential similarly to NCE). As a mature technology, however, there is less need for our support (less than 3% of votes). Reassuringly, 40% of votes went to areas already being prioritised by the Cell and Gene Therapy Catapult.

Table 4: Expert votes for various drug platform technologies that the MDC could invest in

Number of expert votes for various drug platform technologies	NCE from biological screening	NCE from informatics / structural methods	Immuno-modulators	Therapeutic vaccinces	Next gen Abs	Enzyme replacement	Traditional Mabs	Gene therapy & precise genome editing	Immunotherapy	mRNA/RNAi	Total	%
New chemical entities	24	23									47	23%
Protein based biologies					33	6	2				41	20%
Immunmodulation & therapeutic vaccines			23	9							32	16%
Gene and cell therapies								39	26	16	81	40%

Commercial repurposing was not presented as an option in this research, but came up repeatedly in interviews as a potential opportunity for the UK (especially in genetic disease or other areas with better *in vitro* models). Commercial repurposing gives a new lease of life to an existing compound with additional IP to extend its use. An example is the PDE5 inhibitor sildenafil, which Pfizer repurposed and marketed as Viagra for erectile dysfunction[21] and then subsequently repurposed for pulmonary arterial hypertension as Revatio.[22] We welcome the AMRC's recent report on repurposing and rescuing medicines in this context.[23]

21 *(Kling J (1998). "From hypertension to angina to Viagra". Mod. Drug Discov. 1: 31–38)*
22 *(Ted T. Ashburn & Karl B. Thor, Nature Reviews Drug Discovery 3, 673–683 (2004)*
23 *https://www.amrc.org.uk/publications/repurposing-and-rescuing-of-medicines*

2.6 We need to support the creation of investable IP in academia

The Life Science Industrial Strategy noted that *"between 2011-2016 the UK published 80 papers per patent, compared to just 7 papers in Germany and 11 in the US"*. This comparative lack of IP helps neither patients nor the UK economy. However, purely increasing the number of patents may not be the solution: patents that are filed too soon, with incomplete data or commercial gaps, can hinder future development.

Our research found two underlying causes, the first due to the incentives against "patenting before you publish" in UK academia (relative to the US), and the second due to the limited capabilities and skills to do the very early stages of translation (known as concept testing) to industry standards.

The Wellcome Trust commissioned research in 2014 as to the willingness of UK academia to patent and so initiate translation, measuring those behaviours relative to the US, and the underlying causes.[24] They found that:

> "In the UK, the principal metric for academic success is paper citations. This pressure to publish can disincentivise UK researchers from filing patents. [Our survey of 1700 authors] showed that UK academics were about half as likely to patent as their counterparts in a top US cluster, with nearly a third of UK respondents saying that their decision was based on the need for publications "to drive grants or my career".

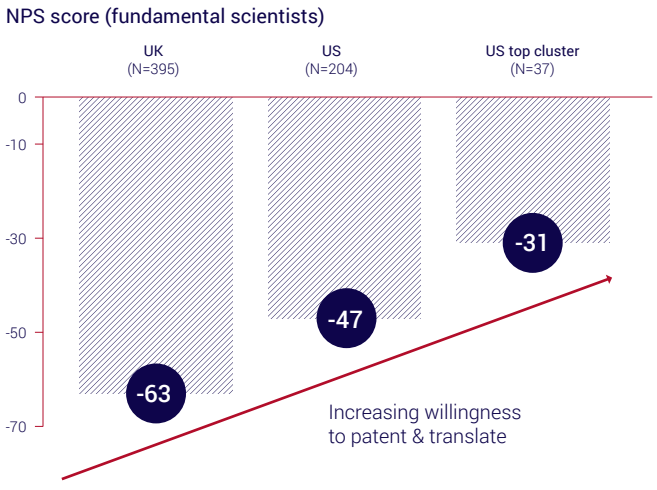
In the second area of concern, concept testing, smaller companies in Table 2 rated their own ability to do the first steps of translation well. However, the interviewees perceived that academic concept testing needs improvement in the following areas:

- Concept testing to industry standard, with appropriate controls and to GLP standards
- Patent writing
- The critical importance of *in-vitro* efficacy relative to standard of care data, in order for *in-vitro* efficacy vs. placebo data to be commercially useful

In the UK, the principal metric for academic success is paper citations. **This pressure to publish can disincentivise UK researchers from filing patents**

Figure 7: Relative willingness of academics to patent

How likely would you be to recommend patenting to an academic friend or colleague with a major research breakthrough?



24 https://wellcome.ac.uk/sites/default/files/wtp057817_1.pdf

These concerns echo the research commissioned by the Wellcome Trust:

> "Concept testing enables researchers to carry out a few critical experiments to demonstrate that an innovative or high-risk idea has commercial potential. It is relatively inexpensive, between £50,000 to £250,000 per proposal.
>
> The review highlighted that there is a significant funding gap for concept testing. As well as exploring ways to increase funding, it will be important to ensure that this can be accessed with minimal bureaucracy, as securing a small amount of seed investment can often be more difficult than applying for a large-scale grant.
>
> In addition to this lack of funding, the review identified a capability gap. Academics often lack the knowledge that enables them to design a set of experiments that give investors the confidence to back an idea."

These issues in the capabilities, funding streams and incentives to drive the supply of high quality IP from academia are critical and will require coordinated intervention. We can help by facilitating access to the industry skills and capabilities to tackle appropriate concept testing, working in partnership with other stakeholders such as IUK and the MRC and their Biomedical Catalyst, Development Pathway Funding Scheme, Confidence in Concept and Proximity to Discovery initiatives. We will pick up on these issues in chapters 3 and 4.

2.7 Joint efforts are required to validate the humanised *in vitro* models developed in academia

Experts said that too little effort goes into validating and disseminating best practice in disease and toxicology models. In particular, interviewees pointed out that many potentially powerful human *in vitro* models remain in academia. There they have no obvious commercialisation path in the UK, given they often lack IP and so are hard to spin-out.

We also heard that it is hard to validate and compare these models, given the need to test them against a shared set of successful and failed drugs. Public private partnerships could be appropriate for such validation.

This is a chronic issue. As one interviewee put it, *"The good models yield cures, and so become academically and commercially interesting for a while until those cures are mature. As a result, we are left with the poor models that don't yield cures."*

We know from interviews that there are many interesting models in academia, mostly from stem cells. However, as the same interviewee pointed out: *"Disease models are hard to commercialise for academics that develop them, as they better fit service business models like CROs rather than spin-outs. And the return profiles are relatively unattractive compared to drug development – one model does not make a company."*

Finally, a number of experts pointed out that such validation is not a good fit for conventional grant funding.

> Many potentially powerful human *in vitro* models **remain in academia**

"The challenge is that these [advanced models] are businesses that are high skill and low IP, and hard to spin-out. They can be valuable businesses precisely because of the trade secret aspect and difficulty of scaling these skills. We also need competitive validation of the emerging models, i.e. which model or combination of models is best. We need something like an innovation prize to drive this, as the 2 years of a typical academic grant is just too short."

Industry Academic Alliance leader

We know other stakeholders are acutely aware of this. For instance, the MRC has "strategic awards for research on the evaluation and validation of human and animal models" and Experimental Medicine Challenge Grants to help address the issue, and it is an area of focus for NC3RS.[25]

2.8 Support structures are not highly rated by SMEs

The BioIndustry Association (BIA) asked its members to rate the service from the various government funded support structures across the ecosystem. The methodology used was Net Promoter Score, a widely-used industry metric of customer satisfaction.[26] The structures covered:

- Department for Business, Energy and Industrial Strategy funded, via Higher Education Funding Council for England (HEFCE), for instance the Technology Transfer Offices (IP licensing) and university grant contracting departments (collaboration set-up)
- Innovate UK structures such as the Knowledge Transfer Network, Innovate grants and the Catapults
- NHS support structures: Academic Health Science Centres, Academic Health Science Networks, and NIHR Office for Clinical Research Infrastructure
- National Institute for Health and Care Excellence and Medicines and Healthcare products Regulatory Agency

The challenge is that these [advanced models] are businesses that are **high skill and low IP**, and hard to spin-out

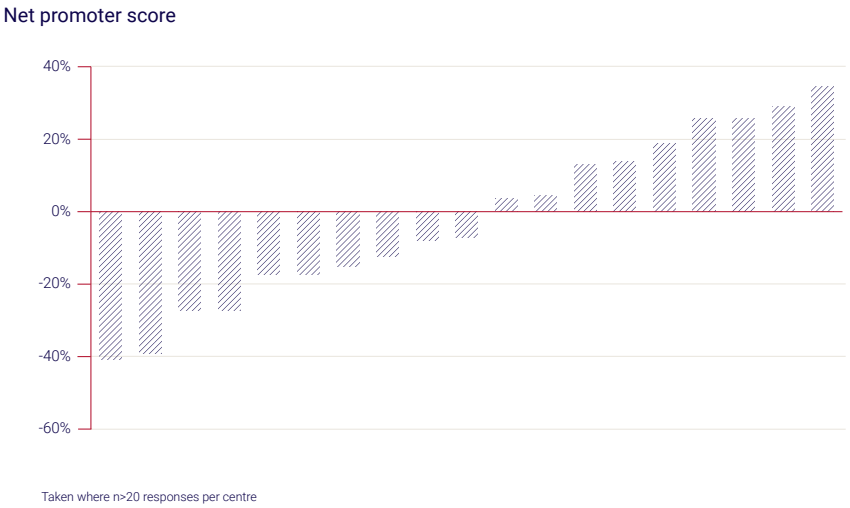
The MHRA and Innovate UK grants were the only support structures rated positively. Table 5 show the range of NPS scores from the ecosystem, raising concerns about SMEs satisfaction with the services that they are being offered.

Table 5: Range of Net Promoter Scores (NPS) for 12 government support structures

Lowest	25 percentile	Median	75 percentile	Highest
-65%	-55%	-48%	-34%	29%

25 https://www.nc3rs.org.uk/
26 https://en.wikipedia.org/wiki/Net_Promoter

Figure 8: Industry views on the ease of pre-clinical collaboration with various NHS Trust-University pairs



We also asked about at the challenges in creating pre-clinical industry/academia research collaborations, and how this varies across the UK. We started with the main NHS University clusters, as identified by RAND in their recent bibliometric survey for NIHR.[27] The anonymised data is provided in Figure 8.

This data shows how variable an experience SMEs have had (or expect to have) in collaborating with different academic-NHS institutions. This does not mean that overall industry collaboration is in decline; for example, the Biomedical Research Centres received £130 million of industry funding in 2014-15; an increase of more than 30 per cent on the previous year.[28] However, it suggests that the SME experience is dramatically different across the country, with room for improvement in at least half of the centres.

This data shows how variable an experience SMEs have had (or expect to have) in **collaborating with different academic-NHS institutions**

Interviews suggest that the root cause of dissatisfaction are twofold. Firstly, in IP negotiations some technology transfer offices have unrealistic valuations on their relatively raw IP. Secondly, contracting in some universities is very slow and inefficient. These issues are referred to in the Dowling Review *"Technology transfer offices need to prioritise knowledge exchange over short term income generation, and further work is required to improve approaches to contracts and IP agreements"*.[29] We welcome the government's response to this, and the work at the Intellectual Property Office to update the Lambert toolkits.[30]

27 *Bibliometric analysis of highly cited publications of biomedical and health research in England, 2004–2013 accessed at https://www.rand.org/pubs/research_reports/RR1363.html*
28 *www.TimesHigherEducation.com/blog/global-desire-uk-science-know-how*
29 *https://www.raeng.org.uk/publications/reports/the-dowling-review-of-business-university-research*
30 *https://www.gov.uk/government/publications/business-university-research-collaborations-dowling-review-government-response*

2.9 The fragmentation of the ecosystem makes translation hard

Interviewees reported that three key enablers of more efficient drug development are missing:

A) a vibrant, high quality and complete fee-for-service ecosystem of specialist providers of emerging drug discovery solutions set up for academics and small companies to use
B) the right signposting and support for users to get advice on appropriate research options in what is a very fragmented and complex ecosystem where quality of service matters hugely to the science[31]
C) contracting norms between various parts of the ecosystem, for instance SMEs and universities, to allow efficient and timely progression of the science[32]

As one senior academic put it: *"A drug discovery project requires immense effort, tenacity, and luck to effectively create a bespoke virtual CRO."*

The NHS, with its cradle to grave records on an entire population, could be **highly differentiating for biomedical research**. SMEs perceive the NHS as potentially a great asset but not easy to work with

There is a silver lining to this fragmentation. Downsizing of big pharma has released industry talent into the ecosystem. Much of that talent has gone on to form specialist small CROs and drug discovery consultancy firms. This could be highly complementary to the basic science strength we have, but there is work to do to break down the silos and join the dots.

2.10 SMEs find it hard to access NHS assets

The NHS, with its cradle to grave records on an entire population, could be highly differentiating for biomedical research. However, with current operational pressures and funding constraints, there is very little time for translation for busy frontline clinicians. In this context, the NIHR's role in supporting clinicians and other healthcare professionals to do research is vital.

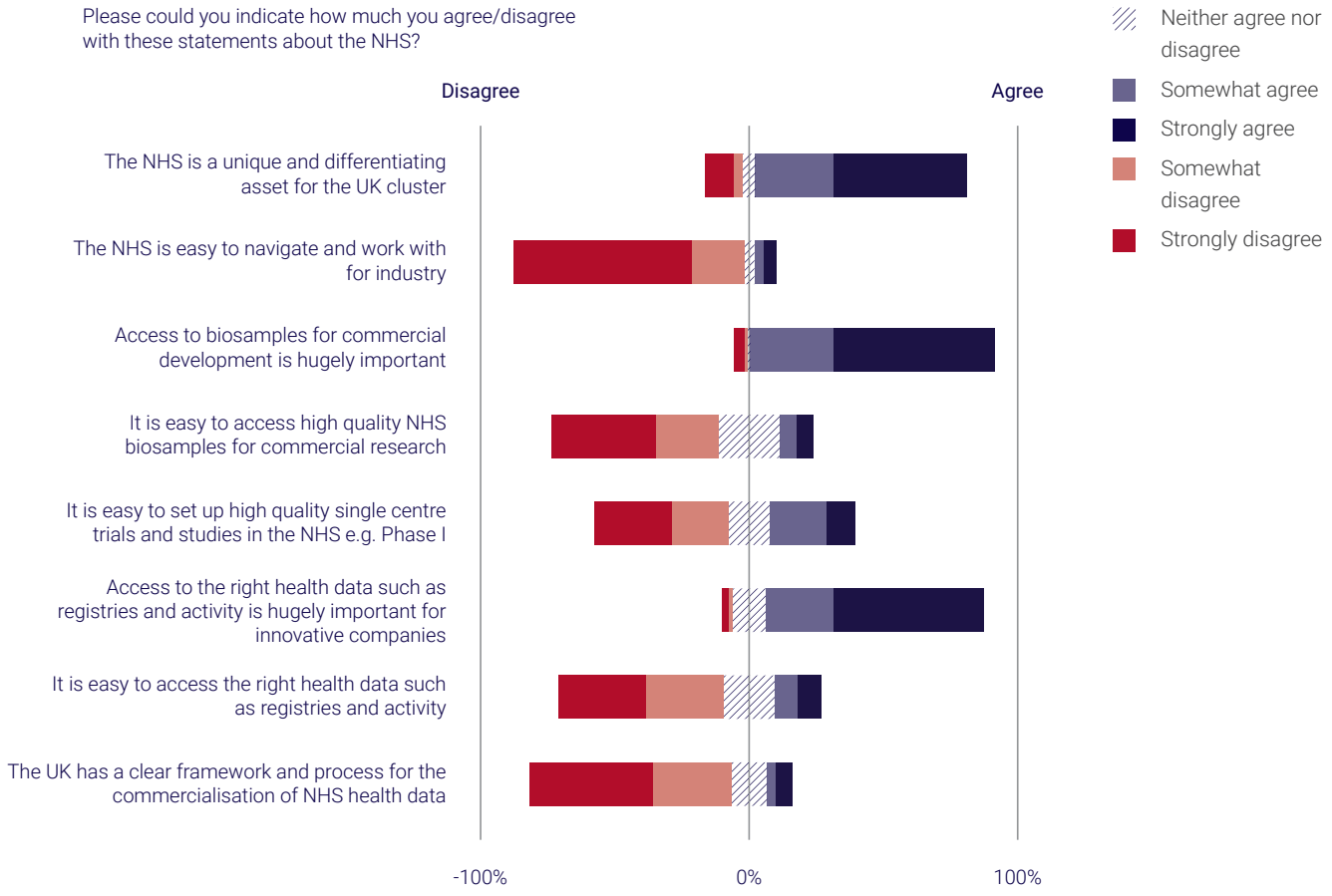
Experts also said that UK regulations and local processes make access to critical experimental medicine enablers challenging. A Medicines Discovery Catapult follow up survey underlined that well annotated human samples are hard to access by diagnostics SMEs:

80% of SMEs found accessing UK samples unexpectedly difficult with the result that 75% imported samples from abroad.

Figure 9 shows that SMEs perceive the NHS as potentially a great asset but not easy to work with. In particular, access to samples and health data, and to a lesser extent single centre trial set-up, were seen as challenges. Similarly to collaboration, this doesn't mean overall commercial research is shrinking, as the Clinical Research Network Portfolio delivered 15% more studies in 2016-2017 than the year before.[33] However, there is clearly an issue with SMEs, who find it difficult to realise the potential of the NHS.

31 *For clinical research in England, the NIHR provides sign-posting via its Office for Clinical Research Infrastructure.*
32 *For clinical research, the MRC, NIHR and ABPI designed the model Industry Collaborative Research Agreement (mICRA) for collaborations involving the pharmaceutical and biotechnology industries, academia and NHS organisations in the UK.*
33 *www.nihr.ac.uk/about-us/how-we-are-managed/managing-centres/crn/key-statistics.htm*

Figure 9: SME views on the importance of the NHS and the challenges in accessing it



As an example, some countries have developed a competitive advantage when it comes to precision medicine. In France, the Institut National du Cancer implements national molecular testing ahead of proven clinical utility to allow industrial trial recruitment. They do this for patient equality of access, as well as to make commercial research easier. In stratified oncology, many pharma now routinely recruit the bulk of European Phase III patients in France.[34]

As well as the challenges in negotiating site costs individually with extremely resource constrained NHS trusts, the survey also highlighted practical challenges in trial set-up and execution such as: accurate site feasibility information, robust methods to identify suitable patients, pragmatic staffing and data capture solutions. NHS England, the HRA and NIHR are currently consulting on how they can work together to further improve commercial clinical research set-up and reporting.[35]

UK regulations and local processes **make access to critical experimental medicine enablers challenging**

34 *Interview with Prof. Fabien Calvo, former Director INCa, and analysis of INCa's Etudes Cliniques database, November 2017 from http://www.e-cancer.frProfessionnels-de-sante/Le-registre-des-essais-cliniques/Le-registre-des-essais-cliniques*

35 *www.hra.nhs.uk/about-us/news-updates/consultation-simplifying-arrangements-research-nhs/*

A gap identified was inappropriate regulatory processes for N-of-1 research, often on very sick patients who need experimental access in hours, not months. Participants with US experience pointed to the FDA Physician Investigational New Drug (IND) and expanded access processes as best practice in this area.[36] UK companies such as GW Pharma have taken large numbers of patients into trial via this programme. It may be that the UK Clinical Research Facility Network could play a valuable role in helping to deliver research involving this type of experimental medicine.[37] We also heard that observational research, and the informed consenting process for it, were often seen as being just as burdensome as interventional research, despite carrying a significantly lower risk of harm to patients.

2.11 There are skills gaps in commercial leadership, project management and data science

There are critical skills shortages in generalist commercial management, project management and data science. The BIA estimates the UK is short of 150 senior management teams (i.e. credible, generalist series B investable talent). In addition, most industry experts we contacted said that the UK suffers from a dearth of data science and informatics skills. As a result, they were having to source those skills from the US and continental Europe. We also heard that there are critical skills shortages in certain types of science.

The following quote gives a flavour of the shortage of senior management:

> "The critical talent is investable C-suite management. And by running on virtual for decades we've not renewed that talent pool. When you look around it is always the same faces"
>
> **Non-executive Director, multiple biotechs**

There are **critical skills shortages in generalist commercial management, project management and data science**. The BIA estimates the UK is short of 150 senior management teams

As well as a scarcity of senior managers, interviewees highlighted a lack of project managers:

> "Good project management is critical and in short supply. They are the expert generalists that can choreograph the various pieces of translational science"
>
> **Science director, early stage discovery CRO**

While this is a common sentiment, we also heard experts saying that such talent is currently available from recent downsizing by pharmaceutical companies. But making a career as a project manager outside of a large company is hard as opportunities for career development are limited and small biotechs offer little job security. In addition, respondents noted that project management is undervalued in academia and often does not fit university pay-grades well. As a result, we risk losing such talent.

36 *https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm*
37 *http://ukcrfnetwork.co.uk/*

2.12 Growth equity is critical to pulling the IP through the system, and in short supply

While there are increasing venture funds available to small companies, the UK today lacks the late stage money to pull assets through the system and build local wealth. The Patient Capital Review made recent recommendations on this, and the Life Sciences Sector Deal has announced plans to release £20bn of incremental capital over the next 10 years. It is essential we succeed in delivering significant change in growth equity, or UK small companies and IP will always be sold prematurely to the US where they will create jobs and wealth, and not here in the UK. In the words of our experts:

> "At the moment companies are lauded for selling their early technologies or products to big pharma. But in reality, this means that end products are not developed in the UK and not controlled by the UK and jobs are not created in the UK, so we have just given our early investment to someone else. Industry funding is given and received without consideration for the long-term benefit of the UK.
>
> What is a successful exit strategy for a VC is not a good result for the country. Innovation disappears with little benefit to the English or Scottish economies. We are a feeder for a larger US market. Government needs to encourage innovation that originates in the UK to be developed in the UK, and we need the funding solutions to make that possible"
>
> **CEO drug development biotech**

Chapter 3 will cover our emerging plan where it intends to lead change on these issues. Chapter 4 covers the issues that require broader ecosystem coordination.

It is essential we succeed in delivering significant change in growth equity… **Government needs to encourage innovation that originates in the UK to be developed in the UK**, and we need the funding solutions to make that possible

Chapter 3:
Catalysing change – the emerging role for the Medicines Discovery Catapult

Left:
Medicines Discovery Catapult's headquarters within Alderley Park, the Bio and Life Sciences Campus in Cheshire

In response to these challenges and opportunities, the Medicines Discovery Catapult has a clear plan for a new national facility for collaborative sector-led R&D. Our scope covers new approaches to the discovery and clinical proof of targeted medicines, diagnostics and biomarkers. Our approach to reconfigure medicines discovery, engage patients and define clinical needs is built around collaborative disease-based groups, known as 'Disease Syndicates'. We will complement these new groups with expertise and capabilities in discovery technology and data science, based in our cutting-edge lab at Alderley Park and collaborating nationally. We will also undertake ambitious support programmes to enable access to consented patient samples and data, as well as providing a virtual R&D platform to link up the UK discovery services community.

Our stakeholders are the hundreds of small companies working in and around medical discovery across the country - **42% of biopharma companies have less than 5 employees**

A more detailed overview of our emerging programme is below.

3.1 Catalysing disease Syndicates

Our approach to reconfiguring drug-discovery R&D is to establish disease-based 'Syndicates'. Anchored by the relevant medical charities to provide the long-term vision and focus, Syndicates will bring together patients, industry and other relevant organisations to conduct high-impact research, leading to the development of new treatments. We will underpin Syndicates with effective coordination and management, members' engagement and the provision of an appropriate collaboration framework.

Syndicates will identify failures and opportunities in disease-specific technology and process. They will tackle these through their members' combined capabilities and expertise. Syndicates will help join-up a research ecosystem that is currently very fragmented, and will improve research productivity.

Syndicates will help join-up a research ecosystem that is currently very fragmented, and will improve research productivity

3.2 Develop innovative data science approaches

High value medicines discovery relies on excellent data science applied to the right data to drive better decision making. We will build data science capabilities and expertise, including machine learning and artificial intelligence. In addition, we will develop world-class 'collaborative intelligence' platforms built on deep expertise in bioinformatics, chemoinformatics and drug discovery. Combined with the UK's excellence in structural and systems biology excellence, we will develop new software and data for collaborative R&D or commercial benefit to the UK. Target prioritisation and validation algorithms allow objective unbiased evaluation of therapeutic opportunities; they are also responsive to technology and data breakthroughs (CRISPR-Cas9, BioBanks, etc.). Finally, we can act as an honest broker, enabling sharing of vital private datasets securely, when organisations would hesitate to grant full data access for commercial or consent reasons.

High value medicines discovery relies on **excellent data science**

3.3 Drive key discovery technology development

We will apply the latest medical discovery technologies and techniques and help them move from our lab to SMEs. We are already investing in capital assets that are too expensive for a small company to own, require specialist embedded expertise and/or are not sufficiently established to be commercialised yet. These already include solid state nuclear magnetic resonance and high-resolution mass spectrometry. Having listened to our sector, we will focus our lab work on models that will humanise toxicology and efficacy more effectively across various organs. Examples include 3D cell culture (also known as 'organoids') and induced pluripotent stem cells. Whilst toxicology is the main driver of small molecule attrition, the ability to also simultaneously measure efficacy as well as toxicity-related pathways enables a broader analysis of target responsiveness and pathway activation. Establishing human

organ models, pathway and omics mapping (and associated analytical tools) will also provide the basis for the humanisation of medicines R&D. This multi-year programme of work will pull promising technology out of academia and into commercial use.

We are enabling precision medicine by providing easier access for SMEs to complex and high cost biomarker identification and validation platforms, along with sophisticated informatics. These make it easier for SMEs to progress a drug candidate alongside a clinically-relevant biomarker.

Other emerging target discovery and validation technologies, such as single cell sequencing, are under review.

3.4 Improve patient sample and data access

As well as the equipment and expertise for delivering collaborative research programmes, we will also invest in enabling access to the raw materials of discovery science: consented patient data and samples. The UK has millions of samples and billions of datapoints collected from UK patients. Yet we know that small companies struggle to access them. Working with others, such as the UK Clinical Research Collaboration Tissue Directory and Coordination Centre and HDR UK, we will support and develop directories of consented tissue and data, as well as research services for SMEs procuring access to these assets. We will also ensure that SME requirements are known to data owners, and support these owners in building brokerage services around their datasets to ensure that smaller companies can use the data on reasonable terms.

The UK has **millions of samples and billions of datapoints collected from UK patients**. Yet we know that small companies struggle to access them

3.5 Build a virtual R&D network

Our stakeholders are the hundreds of small companies working in and around medical discovery across the country - 42% of biopharma companies have less than 5 employees. We will help them to work with each other by building and nurturing a national network of personal expertise and service providers that companies can call on affordably. These will incorporate standardised contracts for the typical work packages that most medicines R&D goes through. By establishing close relationships with best-in-class academic and commercial service providers, we can guide and support SMEs and academics to obtain critical project data in a more timely manner, making their assets industry consumable and financeable.

We have begun to develop ‘pop-up advisory panels’ to allow companies to **identify the most efficient approach to validating medicines** in multiple diseases at various stages

Services such as project management will also be available for companies and academics who need them. We will also work to define contract norms to make it easier for academics and SMEs to sub-contract aspects of their research where appropriate. We have begun to develop ‘pop-up advisory panels’ to allow companies to identify the most efficient approach to validating medicines in multiple diseases at various stages. Our virtual R&D team will also monitor the overall market for emerging gaps in UK capabilities that MDC could address in future. Finally, drug discovery is global. We may therefore be able to help smaller UK CROs develop skills and services for global export markets.

Chapter 4:
Shared issues and opportunities

Our strategic themes are designed to support UK SMEs in the key areas of need where the Catapult model and leadership can be most helpful. However, there are cross-cutting issues raised by the sector where other organisations are better placed to lead. Here, we can play a supporting role to ensure that the voice of the SMEs is heard, as well as monitoring progress. Table 6 shows three areas where we will monitor the situation for potential future action: new chemical entities (NCE) from screening, protein based biologics, immunomodulation and therapeutic vaccines. This leaves five cross-cutting themes that will require complex multi-stakeholder solutions:

- Maximising the supply of investable IP from academia
- SME support structures
- Stratified human trials
- Skills gaps
- Funding gaps

Table 6: Issues and opportunities raised by the sector, and MDC's strategy to respond

Issues & opportunities	MDC Strategy	Comments
NCEs from computer aided design	Lead	MDC Informatics theme
Target association	Lead	MDC Science & Tech and Informatics themes
Improved models	Lead	MDC Science & Tech theme
Tech. to query models	Lead	MDC Science & Tech theme
Data science	Lead	MDC Informatics theme
Fragmented system	Lead	MDC Syndicate and Virtual R&D themes
Leveraging system assets	Lead	MDC Sample & Data theme working with Industrial Strategy, HDR UK & NHS initiatives
Cell & Gene therapies	N/A	Led by Cell and Gene Therapy Catapult
NCEs from screening	Monitor	Supported by UK CROs – MDC to monitor
Protein based biologics, Immunomodulation, and Therapeutic vaccines	Monitor	Potential for future MDC capital investment – MDC to monitor
High quality IP supply	Collaborate	Cross-cutting theme
Stratified human trials	Collaborate	Cross-cutting theme
Skill gaps	Collaborate	MDC mentoring/Cross-cutting theme
Funding gaps	Collaborate	Cross-cutting theme

4.1 Areas to monitor

The sector survey highlighted the development of new chemical entities from screening as a strength for the UK. Since there already exist a number of commercial suppliers for screening, we need to be sure that we are not competing with them. As a result, we will monitor this area closely during 2018 to understand where/if there are gaps. Platform technologies around protein based biologics and immunomodulation and therapeutic vaccines are opportunities too. We will monitor them as potential areas for future capital investment, but have initially focussed our capital on areas identified as higher priority (target association, improved models and data science).

4.2 Cross-cutting theme: high quality IP supply

The creation of UK Research and Innovation represents a great opportunity to address some of the issues identified around the supply of investable intellectual property. Also, we welcome the Wellcome Trust, Royal Academy of Engineering, Royal Society and Academy of Medical Science's commitments to "Transforming UK Translation"[38] in this area, as well as the scrutiny and recommendations of the House of Commons Science and Technology committee in 2017. Given the increasing specialisation of medical discovery technologies, we welcome proposals that would allow technology transfer offices to specialise and innovators to access this specialist support nationally. We also welcome HEFCE's announcement of an additional £100m in funding for the technology transfer offices[39] to incentivise universities to work together across England, supporting collaborations in technology transfer and in engaging with business. The funding should enable universities to pool expertise sustainably, respond flexibly to industrial and regional priorities, and make it easier for businesses to access opportunities to work with them.

The creation of UK Research and Innovation represents **a great opportunity to address some of the issues identified around the supply of investable intellectual property**

Interviewees from SMEs raised concerns around a lack of funding for creating high quality IP. However, the MRC invests over £40m each year on Confidence in Concept and the Developmental Funding Pathway Scheme.[40] We will therefore work with the MRC and others to better understand this concern. Creating high quality investable IP is difficult and requires expert, well-resourced teams. Working with other major stakeholders such as UKR&I, the Wellcome Trust and the disease charities, we will catalyse high quality IP supply improvements.

4.3 Cross-cutting theme: SME support structures

While the aim of our research was to understand how we could best support the sector, we also heard that many SMEs would not recommend working with the support structures that are designed to help innovation. This feedback was variable by geography and organisation, but it shows that there is a need to better understand the issues and potential solutions. We are ready to help any organisation that wants to tackle this issue, at both the national and local level. The Samples and Data Theme will work on specific access issues for SMEs in those areas. We will repeat and expand these service level surveys and publish them annually to monitor and drive continuous improvement.

38 *https://wellcome.ac.uk/sites/default/files/transforming-uk-translation-20170725.pdf*
39 *http://www.hefce.ac.uk/news/newsarchive/2016/Name,112630,en.html*
40 *https://www.mrc.ac.uk/about/our-structure/research-boards-panels/developmental-pathway-funding-scheme/*

4.4 Cross-cutting theme: stratified and high content human trials

Humanising drug R&D relies on target validation and association in patients, which in turn relies on the ability to deliver stratified patient trials using molecular typing of human samples. The UK's strong clinical academic workforce and experimental research infrastructure enables stratification. However, operational and funding pressures on the NHS make it difficult to put the necessary testing and recruitment processes into practice across a large patient population. Initiatives such as Genomics England and TracerX show that this is possible, but have been based on a level of institutional support and funding that the SME sector doesn't have. The precision medicine funding stream of Innovate UK and, if successful, the Industrial Strategy Challenge Fund in this area, will form a vital source of collaborative funding for smaller companies. We also welcome the work of the NIHR Office for Clinical Research Infrastructure[41] and Cancer Research UK[42] in supporting this area and we will work with them and others to ensure that smaller companies can also access this vital capability. We note that the NHS has committed to a national molecular pathology service that is digitised, and that HDR UK aims to transform the depth of data collected during trials. There will, however, remain much work to do in this area to coordinate these various elements to benefit the health and wealth of the nation.

4.5 Cross-cutting theme: skills gaps

The medicines discovery sector has been historically led by staff from pharmaceutical companies. They have benefitted from intensive training and experience in how to integrate different skills, teams, and priorities. As these pharmaceutical companies are employing less people, this traditional talent pool is shrinking and aging. We need to find ways of developing UK talent faster and more effectively.

We will work with the various stakeholders to contribute to this. For example, we may develop a mentoring framework (in concert with other national stakeholders, including national and regional trade organisations) that will leverage our networks and understanding of the SME community. We also support the concept of Digital Fellowships alongside Health Data Research UK. Through such a scheme, clinical data research experts can be exposed to SMEs, bringing expertise to those who need it and valuable industry exposure to those whose skills have been generated in the public sector.

4.6 Cross-cutting theme: funding gaps

Our interviewees emphasised a specific issue in funding high-growth companies. The establishment of long-term funders such as Syncona is welcome, and we look forward to the recommendations of the Patient Capital Review[43] to broaden this support. The new £2.5 billion Investment Fund incubated in the British Business Bank could have a significant impact in our sector, providing sufficient funds are put into life sciences, further ensuring that value is returned to UK plc.[44] Additionally, we see opportunities for the Syndicates to attract funding to previously neglected therapeutic areas (e.g. ethical or 'mission' investors, as the Dementia Fund has shown).

4.7 Coda

Thank you for reading this State of the Discovery Nation 2018. Thanks also to the hundreds of people across the UK SME community for their contributions to it. The state of the nation is good and shows great opportunities. We will conduct research annually to ensure that we continue listening to our sector and shaping our strategy in response to evidence. Our ambition is to go beyond incremental change to transform the industry, and we look forward to working with you to achieve it.

41 *https://www.nihr.ac.uk/life-sciences-industry/documents/Brochures%20and%20flyers/NIHR_Stratified_Medicine_Capabilities_brochure.pdf*
42 *http://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/our-research-partnerships/stratified-medicine-programme*
43 *https://www.gov.uk/government/publications/patient-capital-review*
44 *https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/661398/Patient_Capital_Review_Consultation_response_web.pdf*

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