Shaping the future

What areas of science are most important to UK bioindustry?

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UK BioIndustry Association

Life sciences in the UK

The life sciences sector is critical to the health and wealth of the UK and is one of the most important, productive, and globally competitive industries in the UK economy. It generates a combined estimated turnover of £70 billion, employs more than 240,000 people, and comprises 5,600 businesses.[1] The global life sciences sector is expected to reach >$2 trillion in gross value by 2023[2] and its enormous importance to the future growth of the UK economy has been recognised by successive governments.

Through its Industrial Strategy, the government is committed to growing the world's most innovative economy and raising R&D investment to 2.4% of GDP.[3] The life sciences are a key part of the Industrial Strategy, and as a result, industry and government were the first sector to conclude a Sector Deal in December 2017.[4] The success of the life science sector is founded on high quality science and engineering. To ensure this success, it consistently invests more in R&D than any other sector.[5]

The process that discovers, develops, manufactures, and delivers high technology products and services to patients requires creative engagement between business, academia, and government throughout the process. Support at all Technology Readiness Levels (TRLs) is required. This must be underpinned by investment in the relevant foundational science (TRL1-3) to ensure the UK's global competitiveness in the life sciences.

Background

As the trade association for innovative UK bioscience businesses, the BioIndustry Association (BIA) is at the heart of the UK's thriving life sciences ecosystem. The BIA's nine Advisory Committees are vital mechanisms for highlighting the most relevant issues facing bioscience companies. The Committees consist of influential experts from across the sector. Their work informs and guides BIA policy and priorities, ensuring that the needs of the sector are met.

With the formation of UK Research and Innovation (UKRI) in April 2018 and the reorganisation of the UK's science funding system, the BIA's Science and Innovation Advisory Committee (SIAC) led a 'Shaping the future' workstream throughout 2018 to identify those areas of science that are most critical to the ongoing success of our industry.

As part of this workstream, SIAC organised a BIA sponsored workshop in the April 2018 to discuss and refine the workstream's conclusions further. The workshop involved input from several other Advisory Committees, including the Manufacturing Advisory Committee (MAC), the Engineering Biology Advisory Committee (EBAC), the Cell and Gene Therapy Advisory Committee (CGTAC), and the wider BIA

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[1] HM Government (2017). "Strength and Opportunity 2017": https://www.gov.uk/government/publications/bioscience-and-health-technology-database-annual-report-2017
[2] "Life Sciences Industrial Strategy – A report to the Government from the life sciences sector" (2017): https://www.gov.uk/government/publications/life-sciences-industrial-strategy
[3] HM Government (2017). "Industrial Strategy: Building a Britain fit for the future": https://www.gov.uk/government/publications/industrial-strategy-building-a-britain-fit-for-the-future
[4] HM Government (2017). "Life Sciences Sector Deal": https://www.gov.uk/government/publications/life-sciences-sector-deal
[5] Office for National Statistics (2017), "Business enterprise research and development, UK: 2016": https://www.ons.gov.uk/economy/governmentpublicsectorandtaxes/researchanddevelopmentexpenditure/bulletins/businessenterpriseresearchanddevelopment/2016

membership. As deliberations continued, it became clear that recommendations on support for underpinning cross-cutting sciences, the nature of the funding environment, and the review processes operated by funding bodies and the engagement with these by industry, were all relevant to the continued successful development of the sector.

The 'Shaping the future' workstream concentrated on the need for support of scientific research programmes (TRL 1-3) and did not explicitly consider any investment in new scientific infrastructure and institutions. Rather, it recognised that significant investments have been made in initiatives such as the Cell and Gene Therapy Catapult, the Medicines Discovery Catapult, the National Biologics Manufacturing Centre, and the UK Centre for Antimicrobial Resistance.

This paper summarises the conclusions and recommendations reached throughout the workstream. As a member-driven paper, it represents a snapshot of expert views from across the whole sector. As we move into the 2019 Spending Review and the UK's new science funding system takes shape, this will contribute to the BIA's engagement activities with the UKRI and other funding bodies.

Key conclusions and recommendations

An early, clear and important insight that came out of the workstream was that industry needs support for the sciences that underpin the entire process from invention or conception of product, through development to manufacture and transition through supply chains to patient or consumer. This requires improved support for the analytical and bio-processing sciences as well as continuing support for discovery science. Without this, support for discovery alone (or predominantly), is self-limiting and not sufficiently enabling of effective translation and commercial success. This is particularly important for SMEs, which play a vital role in the life sciences ecosystem.

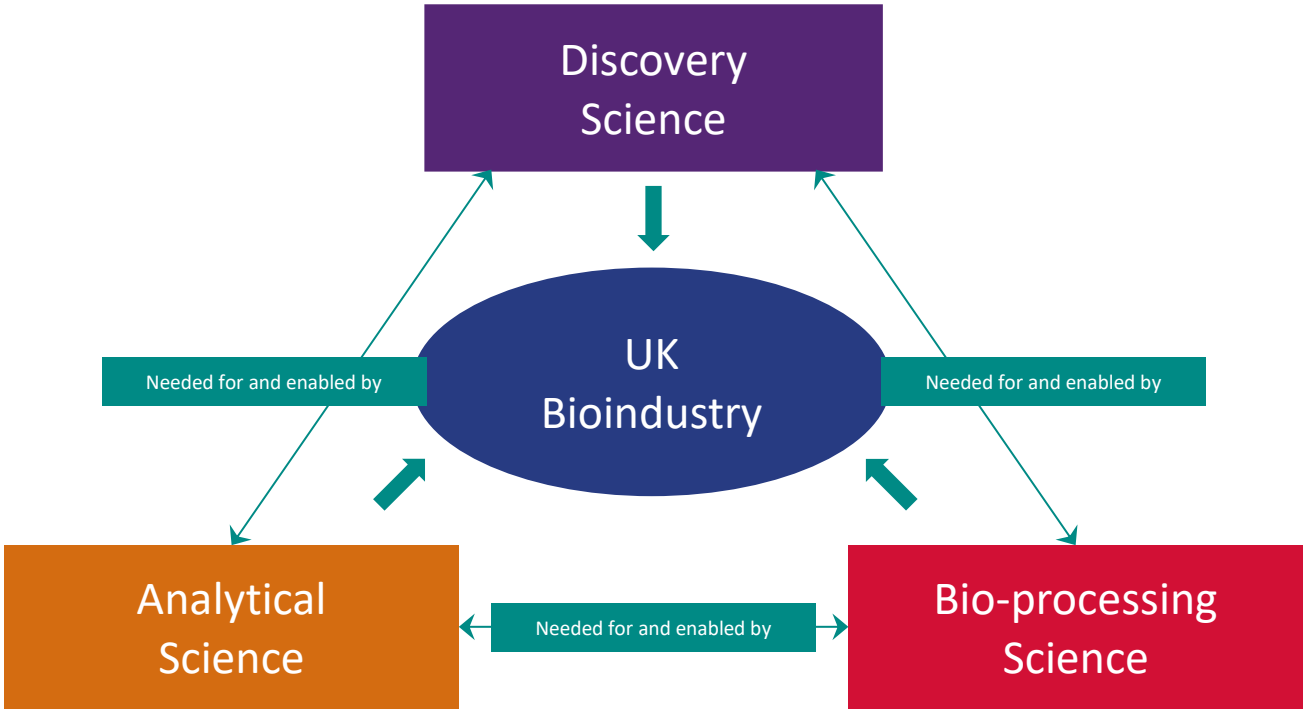
The key conclusions and recommendations are summarised below.

1. A number of areas of science were identified as being critically important to the success of the bio-industry (see summary in figure 2 and detail in table 1).
2. Areas of 'cross-cutting' science were identified as being a vital and underpinning support for the areas listed in 1 (see table 1 and figure 2).
3. The funding of science must continue to support a wide range of discovery science but also must include appropriate support for analytical and bio-processing sciences as all are required to bring products from concept to patients and users.
4. A requirement to support discovery, analytical and bio-processing science should be explicitly built into the remits of the relevant Councils of UKRI.
5. Improved and appropriate peer review processes are needed for discovery, analytical and bio-processing science. These processes could benefit from significant and improved industrial involvement.
6. The consistency of funding broad areas of science is key to the developing health of the bio-industry over the next five to ten years. The sector is not well served by episodic funding initiatives where funding for areas of science appears and then disappears (as exemplified by the disappearance of the Industrial Biotechnology Catalyst and the subsequent lack of support for industrial biotech science in

the following years). The sector can also struggle to respond to episodic initiatives that appear at short notice and with very short response timelines, which can be particularly problematic for SMEs.

7. Funded science programmes should include explicit requirement for broad skills development in post graduates and early career researchers including focus on translational, innovation, and networking skills.

Figure 1. The importance of discovery, analytical and bio-processing sciences for UK bioindustry



Discovery science: The exploration of the new; e.g. pathways, biomes, organisms, enzymes, complex interactions, control and signalling systems, new molecules, information flows etc.

Analytical science: Analytics of data flows, system and molecular properties. To include wet analysis, metrology, novel instrumentation, data (including 'big' data) collection, interpretation and processing methods.

Bio-processing science: Science underpinning the invention and development of processes for the controlled manufacture, assembly and delivery of biological products particularly Complex Biological Products i.e. bio-pharmaceuticals, advanced therapy medicinal products (ATMPs) including cellular and gene therapies, vaccines and whole cell systems.

Figure 2. Summary of science themes identified by the 'Shaping the future' workstream

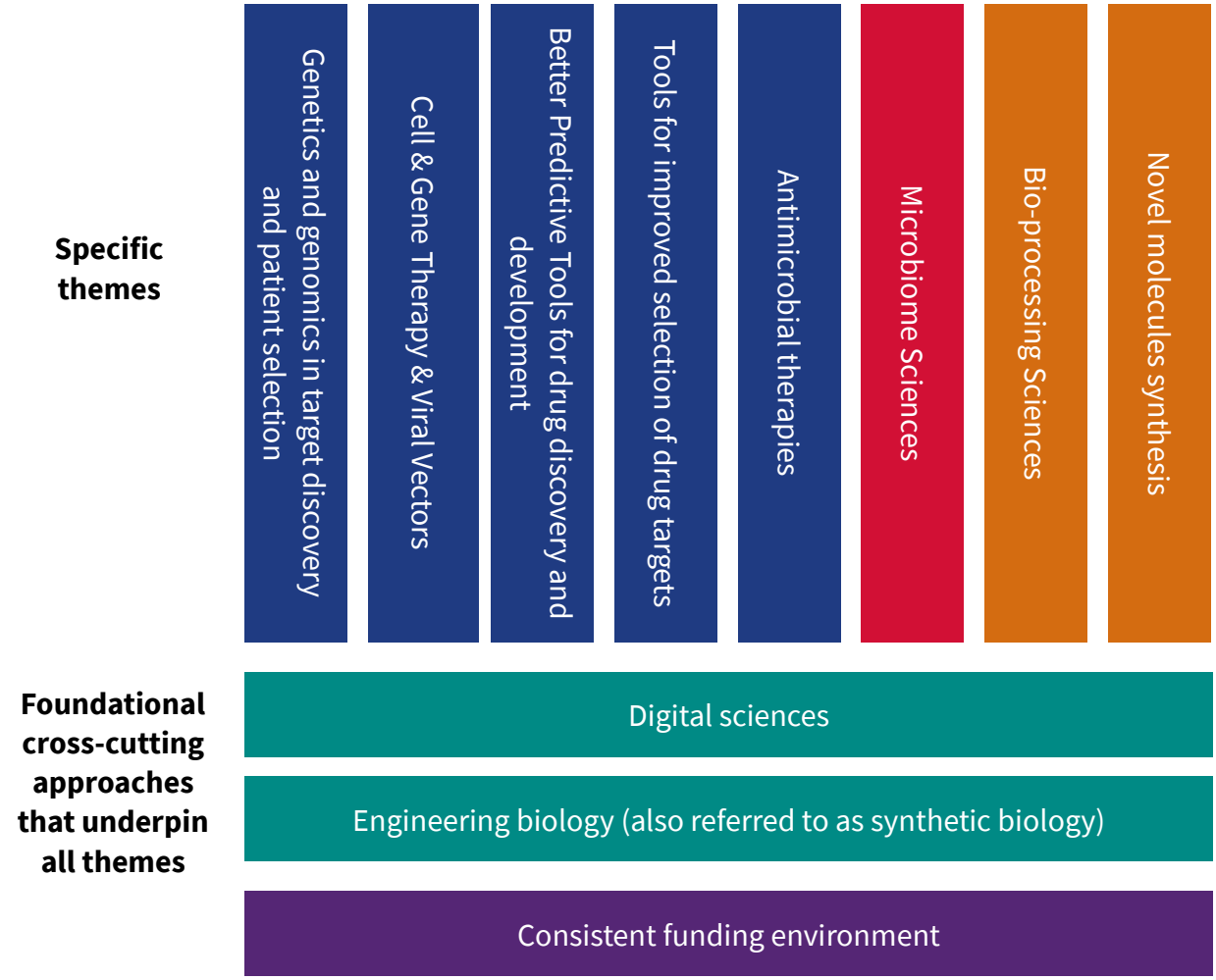


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Table 1. List of topics and themes identified by the 'Shaping the Future' workstream

Scientific Theme/Topic	Rationale
Cell & Gene Therapy and Viral Vectors	**Why is it important?** Development of curative therapies, broader understanding around other diseases from a genetic basis, gene editing approaches to tackle difficult diseases. **What needs to be done?** • Development and implementation of point of care QC analytics, especially for Cell & Gene therapy and Biopharmaceutical medicines. • Investing in improvements to gene editing technology and the delivery of its components to reduce 'off target' modifications and immunogenicity in man and improve in vivo delivery efficiency [Nature Methods 14, 547–548 (2017)]. • Further research improvements, validation and regulatory acceptance for co-culture based organoid systems as toxicology screening packages to replace animal experiments or for use where animal toxicology models are not possible. • Further research and improvements on the design of viral vectors for gene therapy applications e.g. to improve vector tropism, (to enable organ specific delivery) and efficiency of cellular uptake to enable in vivo gene therapy and delivery [*Trends in Biotechnology 33 (12) 777-790, (2015*)]. • Opening up therapeutic intervention in the CNS by improving uptake across the Blood Brain Barrier (BBB), especially for biologicals and cell and gene therapy vectors [*Neuron 89, 70–82 (2016)*] • Support for early stage (Phase I/II) clinical trials for cell and gene therapies, including grant-funded academic material that is currently manufactured overseas • Current capacity is restrictive to perform both early and commercial scale trials from the UK due to constraints in upstream, downstream, fill finish, quality control, supply chain and access to scalable platforms. • Research to understand the long-term impact and curative nature of these therapies. • Research on healthcare economics and funding models in this space. **Examples of ongoing activities/investment:** C&GT Catapult, Stevenage C&GT manufacturing centre, New vaccine centre (£66M ISCF wave 1), NC3Rs/GSK InMutaGene CRACK IT Challenge.
Use of genetics and genomics in target discovery and patient selection	**Why is it important?** Support personalised medicine. Support tool and skills development. • For many years the UK has been a world leader in human genetics and genomics initially by being a key participant in the human genome project and more recently with activities such as Genomics England or the UK Biobank. • Drug discovery is not served well by the issue of high attrition resulting in the cost of a new drug having to bear the cost of all the failed projects. Considerable effort has been made to reduce attrition by a better

	understanding of the quality of candidate drugs through physical chemistry properties, experiments and predictions to ensure appropriate drug at target, target engagement and consequent pharmacology, all leading to increased confidence in likelihood of clinical translation. New science and understanding to go beyond current best practice is still needed to continue to reduce attrition. **What needs to be done?** • In the future the UK should be increasingly involved with the Human Cell Atlas (HCA) providing a unique opportunity for a virtuous scientific cycle touching discovery, translational medicine and clinical medicine putting the UK at the forefront of genomic medicine. Training next generation clinicians to understand this data and feed in to industry? **Examples of ongoing activities/investment**: Genomics England, Industrial Strategy Challenge Fund Wave 2 AI and data economy with £210M available for genetics/genomics under this.
Better tools for more predictive drug (and other actives) discovery and development to enhance the translation of innovative targets to successful medicines.	**Why is it important?** Attrition rates due to lack of translation from preclinical to clinical development stages are high, costing the industry hundreds of millions of pounds annually. This has led to demand for development of new human-based models for efficacy and safety testing based on the technological advances being made in organoids biology, organs on chips, micro-physiological systems, iPS cells, etc. The UK has significant scientific expertise in these areas, but it is disjointed, and we run the risk of losing ground to the USA, Netherlands, Germany (Fraunhofer) etc. if we do not capacity build and increase investment in these areas. There is increasing interest in these technologies from companies across sectors to support better decision making, global regulatory agencies and CROs so the timing is right to support the development and application of these technologies for safer and more efficacious therapies to be brought to market cheaper and more quickly. (A non-animal technologies roadmap for the UK Advancing predictive biology, 2015) **What needs to be done?** • The ability to generate induced pluripotent stem cells (iPSCs) from patients, and an increasingly refined capacity to differentiate these iPSCs into disease-relevant cell types, promises a new paradigm in drug development — one that positions human disease pathophysiology at the core of preclinical drug discovery [*Nature Reviews Drug Discovery* 10, 915-929 (December 2011)]. • Disease models derived from iPSCs that manifest cellular disease phenotypes have been established for several monogenic diseases, but iPSCs can likewise be used for phenotype-based drug screens in complex diseases for which the underlying genetic mechanism is unknown. • Recent advances in the use of iPSC technology for modelling a 'disease in a dish' and for testing compounds against human disease phenotypes *in vitro* are being exploited to illuminate disease pathophysiology, identify novel drug targets and enhance the probability of clinical success of new drugs.

	• Development of human-relevant micro-physiological systems for diseases with histories of poor translation e.g. heart failure, some forms of neoplasia, neurologic disease, pain- with patient variability a component of that effort leveraging iPSC technology. • Development of methodologies for long- and short-term preservation, storage, viability and functionality maintenance together with appropriate predictive diagnostics. • Improved Infrastructure for collection, banking of fresh tissue and human biological and diagnostic samples collected by various agencies of the UK NHS. Also improved data sharing e.g. of genome sequences across groups • Identification of better biomarkers for complex disease states and disease predispositions including the need to develop the tools to support better identification of better biomarkers. • Identification of relevant and suitable Quality indicating Biomarkers for rapid on line and at line analysis of therapeutic cell lines (SC, IPSC, Car-T cells etc). We are only at the very start of this therapeutic revolution and much work is needed in this area to enable effective manufacture and broader use of the technologies. • Understanding of maturity of iPSC; networking/community building, consortia building; engagement with regulators/improved regulatory buy-in; development of next generation analytical tools to support this. **Ongoing activities/investment**: NATs, Medicines Discovery Catapult, NC3Rs(CRACK IT) investment, H2020/IMI funding . Also for biological samples activity through UKCRC TDCC, UK Brain Bank Network, Charity-specific tissue banks, etc, NC3Rs, NHS BT, etc.
Tools for increasing understanding of potential drug targets and their role in disease.	**Why is it important?** Selection of the appropriate drug target to work on remains one of the most difficult and important decisions in the lifetime of a drug discovery project. The following research areas have the potential to be transformative: • New modalities for probing drug target structure at high resolution. • Bioinformatic and gene editing platforms for pathway and interactome analysis. • Development and characterization of high-quality chemical probes for target validation. • Novel biocompatible chemistries for ligation to enable study of the role of potential drug targets in cells and whole organisms.
Better antimicrobial therapies	**Why is it important?** Microbial resistance is highlighted as a global threat and has some intensive funding to develop better drugs (AMR at Alderley park). Part of this government supported strategy identified better diagnostics as a key part of the fight against resistance, but there is currently a dearth of activity in this area. There is potential for low cost commercially-viable models which would require minimal government “pump priming” funding to address “orphan” diagnostic development especially in AMR.

Microbiome sciences	**Why is it important?** Better understanding and development of the global microbiome and human microbiomes as potential and rich sources of new therapeutic vehicles, tools, metabolic pathways, enzymes, complex metabolites (e.g. antibiotics). This will encompass the development of new therapeutic systems, including understanding of efficacy and safety profiles. • It is becoming increasingly recognised that many microbes play a large part in normal human health and disease. In the last five years, the number of scientific papers linking the microbiome to diseases ranging from diabetes and colitis to anxiety and depression has grown exponentially; with a global market value predicted to reach $899 million by 2025 (Markets, 2017). • The gut microbiome is the largest and most diverse of the human microbiome populations in terms of bacterial species (Quigley, 2013), and as such is the most widely studied currently. There is increasing evidence that gut microbiota can play a key role in chemical metabolism (Claus et al., 2016, Wilson and Nicholson, 2017). This is driving pharmaceutical, chemical and consumer product companies to expand their considerations of how the microbiome can affect toxicity and efficacy of their products, and how the microbiome can be manipulated as a potential therapeutic (Cani and Delzenne, 2011, Claus et al., 2016, Enright et al., 2016, Rauch and Lynch, 2012). • Greater than 95% and perhaps as much as 99% of the microbial biome (bacteria, fungi, viruses, protists etc) remains undiscovered and is still poorly explorable particularly beyond the genomic level due to lack of developed tools and analytical methodologies (Locey and Lennon, 2016), (Kowarsy and Quake 2017). This hampers its discovery and exploitation. **What needs to be done?** Field has massive potential as a rich source of tools for to enable new engineering biology activity. Traditionally very strong in UK, but less so now – opportunity to invigorate this and to fund research in this area enabling the development of a new generation of microbial experts and methodologies. **Examples of ongoing activities/investment**: Quadram Institute (Norwich), Innovate UK, BBSRC, Janssen Human Microbiome Institute, small biotech companies in the UK, e.g. Microbiotica.
Bioprocessing science enabling the manufacture of complex biological products	**Why is it important?** Many exciting new products in discovery and development are Complex Biological Products i.e. biopharmaceuticals, advanced therapy medicinal products (ATMPs) including cellular and gene therapies, vaccines and whole cell systems. These are challenging to make, deliver and analyse and fundamental scientific study is needed to develop appropriate product forms, controlled, and predictable manufacturing approaches, supporting

	analytics and delivery systems so that these products can be brought to patients rapidly, cost effectively and safely. **What needs to be done?** • Development of high intensity, high productivity integrated and/or continuous manufacturing systems for production of antibodies and complex biological products. Requires development of manufacturing tools and technologies and appropriate rapid assay methodologies. Many products are on the horizon are still too expensive for broad patient access, something which remains to be address through step changes in manufacturing efficiency. • Development of improved systems for predictable pathway manipulation of production organism genomes for development of improved manufacturing platforms. Still a massive need in this area. • The design of molecules and cellular products with optimised intrinsic properties for manufacture, improved immunogenicity profiles, other features impacting product quality (e.g. PTM) and use e.g. stability. • The molecular design of expression and cellular based production systems optimised for productivity and product quality. This includes understanding which targets to manipulate, how to manipulate them and how to measure relevant system outputs and inputs. • The design and development of cell free synthetic tools and systems. • Computational approaches to predict pathway output and product properties relevant to manufacture and to develop manufacturing control strategies. • Novel computational approaches to complex system modelling • Biochemical engineering studies on scale down, scale up, scale out strategies appropriate to new product types and forms. • The identification and development of appropriate measures and measuring methodologies to characterise and quality assure complex biological products. This will include identification of novel biomarkers indicating product quality for Complex Biological Products including ATMPs. • Automation of large-scale manual processes to achieve consistency, lower cost of goods and ultimately bring the manufacture of therapies near to patients. This will in many cases require fundamental process redesign i.e. more than automating unit operations and bolting them together. (Advanced Therapies Manufacturing Action Plan, 2016). • Development of machine learning approaches to improve product and process design and process automation • Identification and development of long-term preservation conditions for therapeutic cell lines enabling full functionality (10 to 100+ days). • Identification of relevant and suitable Quality indicating biomarkers for rapid on line and at line analysis of therapeutic cell lines (SC, IPSC, Car-T cells etc). We are only at the very start of this therapeutic revolution and much work is needed in this area to enable effective manufacture and broader use of the technologies.

	• Viral vectors. There is a need for new bio-processing tools, technologies, assays and materials to be developed more rapidly. (Advanced Therapies Manufacturing Action Plan, 2016). • Consistent funding of science programmes needed in this area to support pre-existing and planned investment in capacity. **Examples of ongoing activities/investment**: Investment in place – C&GT manufacturing centre, Medicines Manufacturing Innovation Centre, NBMC. Various NIBBS e.g. BioProNET. Relatively little investment in science programmes currently.
Novel chemicals synthesis.	**Why is it important?** Small molecules still have great potential to transform therapy options for patients, but compound synthesis remains a significant bottleneck in the "design – make – test" cycle of drug discovery. Key growth areas which will impact on our ability to make molecules quickly are artificial intelligence (AI), high throughput experimentation (HTE) and continuous flow technology. High value areas for research are: • Robotic systems for rapid chemical reaction screening and high throughput analysis. • Chemical reaction discovery using HTE, for access to novel molecular architectures. • Development of informatics platforms (including AI-based systems) for chemical reaction prediction and synthetic route design.
Engineering biology – cross cutting discipline	**Why is It important?** Engineering biology (also referred to as synthetic biology) is a critical underpinning science for modern biological science. UK has established a leading position in this area of research. It is vital that this is maintained. **What needs to be done:** • Continued expansion of the synthetic biology toolkit including discovery of novel enzyme types and molecular tools (e.g. next generation high impact tools post CRISPR-Cas9). • Exploration and development of growth methodologies for unexplored areas of the microbiome ...rich source of synthetic biology tools. Massively underexplored and unexploited source of molecular tools and novel chemistries. • Development of robust automated control algorithms for rapid synthetic biology assembly • Development and use of using synthetic enzymes to enable more efficient and novel chemistries. • Funding for synthetic biology is continuing under the new UKRI but important that it continues consistently. **Examples of ongoing activities/investment:** Six SBRC (Synthetic Biology Research Centres) and an IKC (Innovation Knowledge Centre) were launched as consequence of the Synthetic Biology Road Map and the identification of synthetic biology as one of the 'eight

	great technologies' by UK Government. Synthetic Biology Centre for Doctoral Training (CDT), a collaboration between the Universities of Bristol, Oxford and Warwick.
Digital sciences – cross cutting and highly diverse theme	**Why is it important?** Establishing leadership in digital sciences is a key enabler for most future developments in biological and biomedical sciences. Artificial Intelligence (AI), big data analysis and the use of in-silico methodologies are becoming increasingly important in various aspects of the biological, chemical and biomedical sciences including biotech and drug discovery and development and personalized medicines. The US and Canada are leaders in this area, but the UK is catching up, albeit slowly – there is a need for continued and expanded investment in the underpinning science and technology and in skills development in these areas. **What needs to be done?** • The management of data, as patient derived materials flow to the factory and 'personalised' therapies flow back, is crucial to ensure that patients receive therapies that work. These systems do not yet fully exist and will need standards and standardised methodologies developing (Advanced Therapies Manufacturing Action Plan, 2016). • Advanced analytical methodologies and strategies are in their infancy both off line and in situ. The way that they talk to automation and data management will be important and require both development and agreed standardisation (Advanced Therapies Manufacturing Action Plan, 2016). • Use of digital wearable sensors in clinical trials**.** In drug development, the clinical trial process is widely known to be complex and painstaking and is often criticized for not being sufficiently patient-centric. It therefore makes sense to innovate this area to ease the challenges, streamline the various activities and create patient engagement. One way to do this is via digital technology and mobile health. Incorporating mobile technology not only streamlines the processes, including the communication between the clinician and a patient, but also reduces the cost of clinical trials. However, in streamlining the process, clinical researchers also ought to consider the usage of a wearable tech in a clinical trial setting ('Made Smarter', Jeurgen Maier, 2017). • Computational approaches to predict pathway output and complex product properties (structure from sequence) including those relevant to manufacture and to manufacturing control strategies. • Extended use of in-silico approaches to evaluate target binding. **Examples of ongoing activities/investment:** The 'AI and data economy' grand challenge under the Industrial Strategy Challenge Fund.
The funding environment	The nature of the funding environment for UK Science is critical to its future health and the economic prosperity that its success brings. Investment is a long-term game and consistency of support rather than support by episodic

	initiative is crucial to the development of the scientific knowledge base and of the talent pool required by academia and industry.