CHAPTER 25

The Role of Governments in the Commercial Emergence of Radical Innovation: The Case of the United Kingdom

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INTRODUCTION

Cellular therapy is based on the concept of modulation or repair of function through the administration of cells. Cells have a therapeutic potential that is distinct from small molecules and biologics in that they can sense, respond, and adapt to environmental signals and execute complex responses in a regulated manner. In gene therapy, the goal is to influence the course of various genetic and acquired diseases at the DNA/RNA level. Gene therapy involves viral or nonviral transduction strategies that modify the expression of an individual's genes or repair abnormal genes either in vivo or ex vivo. For many diseases, gene and cell therapy are applied in combination through gene altered cell therapy. Although there has recently been an acceleration in the field, the concept of cell and gene therapies is not new. The first successful haematopoietic stem cell transplantation was recorded in 1968 and is now an accepted treatment for patients whose immune system is defective or has been damaged (Jenq and van den Brink, 2010). The potential for the safe use of gene therapy was first shown in 1989 when tumour-infiltrating lymphocytes were marked by viral gene transfer (Aebersold et al., 1990). The first gene therapy was performed a year later in the United States for the treatment of adenosine deaminase (ADA) deficiency (Blaese et al, 1995). Gene therapy research was stalled for about a decade following some serious adverse events in trials for a gene therapy for X-linked severe combined immunodeficiency (SCID) (Hacein-Bey-Abina et al., 2008) but resumed when safer vectors were delivered. Subsequent clinical research and industry investment has recently led to the approval of the first therapies. Due to better insight into disease biology, cellular mechanisms and rapidly evolving technology, cell and gene therapies are expected to deliver significant medical advances, resulting in step changes in disease treatment, as well as making a significant economic contribution. These medicinal products are based on some of the most advanced therapeutic technologies and supporting science. As with any disruptive technology,

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multiple factors influence the ultimate commercial translation and success. Intrinsically linked with this is the government's role in creating an environment to support the translation and acceleration of world-leading science to commercially viable products that are both safe and effective for patients and address otherwise intractable diseases.

The UK government has, since 2010 (BIS/11/1429, 2011), been developing a comprehensive strategy to ensure that researchers, clinicians, businesses and investors viewed the United Kingdom as the location of choice for life sciences. In addition, appropriate environmental conditions were provided to support the retention and continued growth of a healthy and robust cell and gene therapy industry founded on an outstanding science base. The strategy had identified the need for a fully integrated life sciences ecosystem comprising the UK research and clinical infrastructure joined together with global industries. Several key commitments were made in this original strategy including a consultation on an early access scheme for medicines that were subsequently launched in 2014, significant investment to support the discovery, development and commercialisation of research, an enhanced UK clinical trials gateway, supporting patients in accessing novel treatments and developing a National Institute for Health Research (NIHR) BioResource. In addition, the advances in regenerative medicine were recognised, and building on research investment already made by the UK Research Councils, the government made a substantial commitment to invest in a Cell Therapy Technology and Innovation Centre (TIC) which later became the Cell and Gene Therapy Catapult and through the research councils established a new national research programme in regenerative medicine, the UK Regenerative Medicine Platform (UKRMP) hub (discussed in detail below).

The UK government analysis of the quality and impact of UK regenerative medicine research found that, compared with continental averages, the United Kingdom had more highly cited research on average than the rest of Europe and Asia. North America outperformed the United Kingdom in the number of 'very highly' cited articles, but given that the United Kingdom represents just 0.9% of the global population, these statistics suggests that UK had a strong, world-class, science base in this field (Department For Business, 2011). Historically, the United Kingdom has performed well on measures that capture the outputs of basic science and universities. For example, in 2014 with only 2.7% of research and development (R&D) expenditure, and 4.1% of researchers, the United Kingdom accounted for 9.9% of downloads, 10.7% of citations and 15.2% of the world's most highly cited articles (Department of Business, 2016). When considering the gross domestic spending on R&D, which is defined as the total expenditure (current and capital) on R&D carried out by all resident companies, research institutes, university and government laboratories, the success of United Kingdom is even more significant. The United Kingdom spent just 1.7% of gross domestic profit (GDP) on R&D in 2015, compared with the Organisation of Economic Cooperation and Development (OECD) average of 2.4% of GDP (2.9% of GDP for Germany and Finland, 2.8% of GDP for the United States, 2.2% of GDP for France and 2.0% of GDP for China) (OECD, 2017c).

The United Kingdom has multiple academic centres of excellence in the cell and gene therapy field and many groups are of international standing and produce publications that are both influential and highly cited. Recently, this has started to be reflected in a rapidly developing industrial base (Fig. 25.1; Cell and Gene Therapy Catapult, 2017). In 2017, for example, there were 64 cell and gene therapy companies within the United Kingdom, a growth of +190% since 2012 (Cell and Gene Therapy Catapult, 2017), and UK companies received in excess of £1.3 billion in investment during the period 2013 to March 2017. In addition, a growing number of the cell and gene therapy clinical trials being run in the United Kingdom are sponsored by commercial organisations. This has increased year on year to date, likely reflecting the growing confidence in the UK cell and gene therapy industry, which in turn is attracting private company investment and a significant increase in UK spinouts (Cell and Gene Therapy Catapult, 2017).

Supporting pioneering research and the development and commercial exploitation of new technologies are a central tenant of government policy. These strategies require long-term vision and commitment, over many parliamentary cycles, given the long-time frames of commercial development. The government has both a direct and indirect role in influencing the delivery of this emergent field of medicine, operating a range of policies for science and research, in addition to policies that intervene in innovation markets, including subsidies for research and direct spending on science. In parallel to the university sector, private businesses play a key role in driving sector innovation, and the

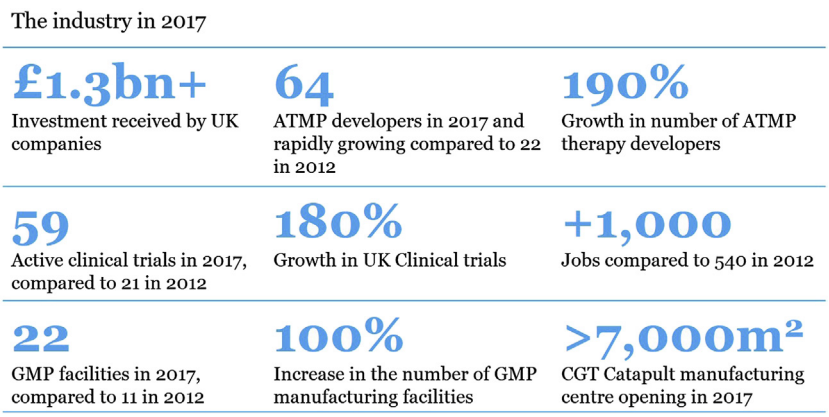
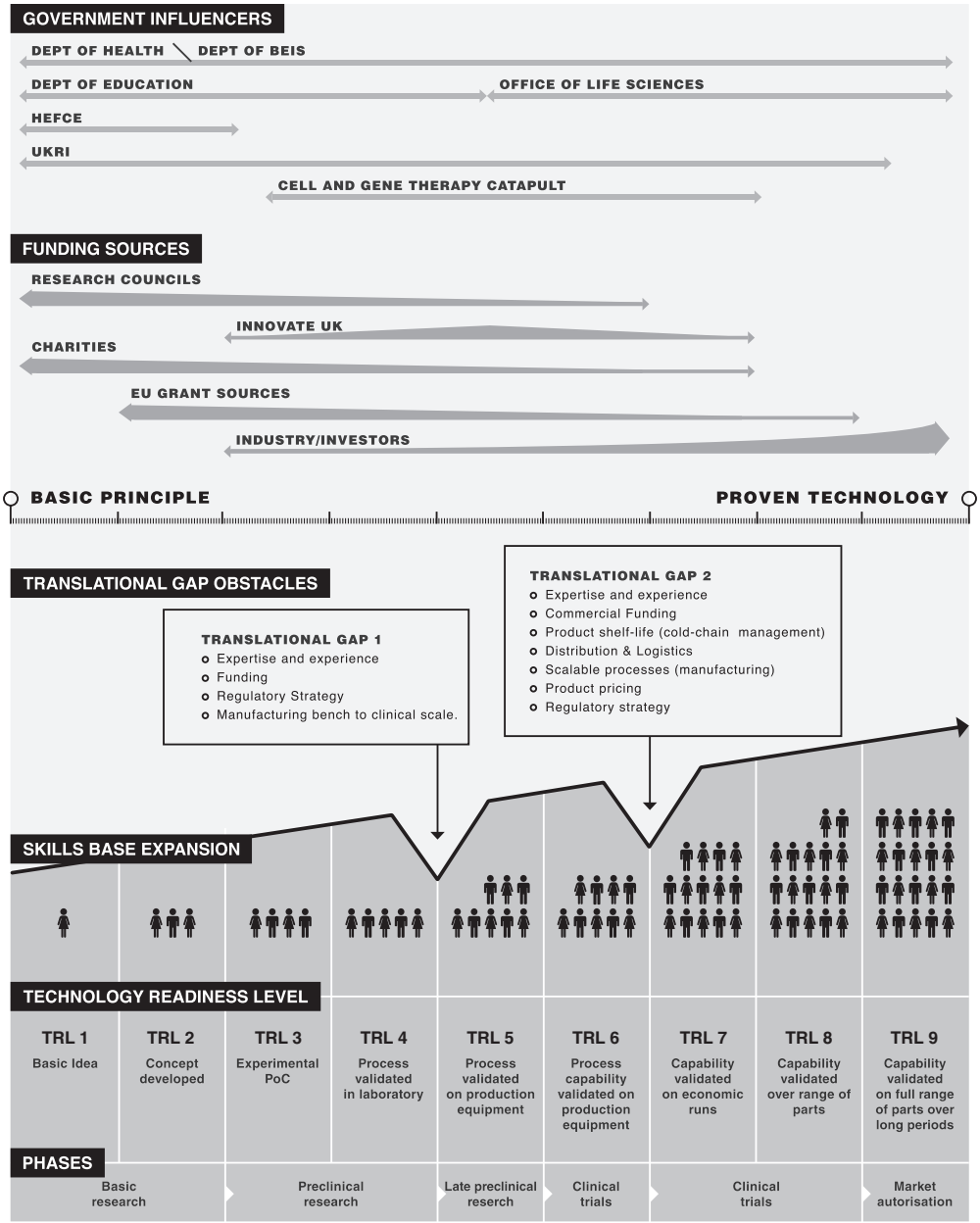


Figure 25.1 ***Growth of the UK cell and gene therapy industry.*** Following 20 years of investment in the research base, the United Kingdom has a critical mass of world-leading research scientists. Following the inception of the Cell and Gene Therapy Catapult, there has been sustained growth in the UK cell and gene therapy industry. This is demonstrated by the growing number of advanced therapy companies, the number of active clinical trials in this arena and the increased inward investment into the industry since 2012. Regulatory pathways that were previously considered complex have now been streamlined, and there is evidence of translatability from the small to the large scale. The supply chain is also evolving; moreover, the new therapies are able to attract investment (Cell and Gene Therapy Catapult, 2017).


GOVERNMENT INFLUENCERS
DEPT OF HEALTH
DEPT OF BEIS
DEPT OF EDUCATION
OFFICE OF LIFE SCIENCES
HEFCE
UKRI
CELL AND GENE THERAPY CATAPULT
FUNDING SOURCES
RESEARCH COUNCILS
INNOVATE UK
CHARITIES
EU GRANT SOURCES
INDUSTRY/INVESTORS
BASIC PRINCIPLE
PROVEN TECHNOLOGY
TRANSLATIONAL GAP OBSTACLES
TRANSLATIONAL GAP 1
Expertise and experience
Funding
Regulatory Strategy
Manufacturing bench to clinical scale.
TRANSLATIONAL GAP 2
Expertise and experience
Commercial Funding
Product shelf-life (cold-chain management)
Distribution & Logistics
Scalable processes (manufacturing)
Product pricing
Regulatory strategy
SKILLS BASE EXPANSION
TECHNOLOGY READINESS LEVEL
TRL 1 Basic Idea
TRL 2 Concept developed
TRL 3 Experimental PoC
TRL 4 Process validated in laboratory
TRL 5 Process validated on production equipment
TRL 6 Process capability validated on production equipment
TRL 7 Capability validated on economic runs
TRL 8 Capability validated over range of parts
TRL 9 Capability validated on full range of parts over long periods
PHASES
Basic research
Preclinical research
Late preclinical reserch
Clinical trials
Clinical trials
Market autorisation

governments' actions directly affect the environment in which they operate. This includes a range of factors such as the stability of the macroeconomy, the regulatory framework, the nature of competition law, the protection of intellectual property (IP), investment in public infrastructure and the development of a conducive fiscal environment. The UK government therefore can and may support innovation in the gene and cell therapy space in many ways from reducing risk, including notably policy risk, to commercially viable levels, ensuring an appropriately skilled labour force and through the establishment of relevant regulatory frameworks and standards. No single set of policies define the perfect innovation environment, and many highly innovative nations operate different systems. The key is to adapt the system to the national culture and the environmental conditions.

BARRIERS TO INNOVATION

Critical to developing the environment that has supported the growth of the cell and gene therapy industry within the United Kingdom has been to understand and define the barriers that can prevent the exploitation of an emergent technology. A failure to address these barriers may have the potential to delay the adoption of cell and gene therapies within healthcare planning, which could lead to promising therapies failing to reach patients. In addition, the risk remains that the commercial development of these novel therapies will be progressed in other jurisdictions decreasing the national economic return as innovation in the cell and gene therapy space occurs within a global market and is fast accelerating.

Development of cell and gene therapies can supposedly be split into nine translation levels (Fig. 25.1). Viewing these, it becomes clear that the major weaknesses in the

Figure 25.2 ***The technology timeline and factors affecting the development of innovative cell and gene therapies.*** The development of new therapeutic products requires the progression of the products through the different developmental phases, from basic research through clinical trials and manufacturing development to final marketing authorisation. This can be categorised as a product passing through the nine technology readiness levels. For this translational pathway to be successful, innovation is a key: this may be expressed in terms of manufacturing strategy or fiscal and regulatory environments to allow the breakthrough of the disruptive change. As well as continuing supportive scientific data, there will also be a need for expansion and development of the skills base, appropriate sources of funding (governmental, international (e.g., H2020) and commercial) and an appropriate government technology environment (reduced policy risk, superior innovation ecosystem). The challenge for any product in development is the translational gaps. Two main gaps have been identified in the translation of innovative therapies to healthcare. The first one arises in the translation of basic research into products for clinical research. The second one relates to the translation initial clinical validation through large scale production and the clinical trials required for product validation. As the complexity of modern biomedical research continues to increase, the major risk is that more potential therapies become derailed by the said translational gaps. The key to success is a complex transdisciplinary and multiorganisational approach; achieving this synergy requires access to a clear innovation infrastructure.

innovation/commercialisation chain and ones that are not unique to cell and gene therapies are the so-called 'innovation chasms' or the 'valleys of death' (Fig. 25.2). There are two important and specific innovation chasms: firstly, the inability to translate promising academic cell and gene therapy research into clinical trials and secondly, to progress promising clinical products into marketed products. There are several contributing factors (Fig. 25.2), some are unique to specific stages of the product development cycle but others can remain a risk in varying forms throughout the process.

Critical to an innovative culture is one where people are willing and able to take risks, balancing these against the expected benefits, without becoming reckless (Annual Report of the Government Chief Scientific Adviser, 2014). Risk is an inherent and necessary force in innovation and should be mitigated through risk management. It is therefore important to provide people with the knowledge and tools to differentiate between risk and recklessness. In addition, an organisation's tolerance to risk will vary. Thus, something with high reward, but high risk, is typically not pursued as the uncertainty is perceived as commercially unacceptable, and progress is stalled. One of the challenges for an emerging field is for investment decision makers to understand what the risks are (both scientific and commercial) and how to manage these. In particular, having processes in place to handle negative outcomes is essential. Early negative data, which is not unusual for an innovative product or technology, can have a significant impact on the progression of a field, unless academic and commercial expectations are managed. Emergent technologies can take some while to achieve commercialisation. The first cell- and gene-therapy products have taken approximately 20 years to reach the market, and many challenges had to be overcome to transform these product concepts into commercial products, and it is important that we learn from this experience and build on the competencies of the different partners (Fig. 25.3).

Emergent therapies and technologies often occur within the academic environment, most likely because of the academic tradition and blue-sky nature of academic research. Such transformational and high-risk research, typically financed by governments through science and technology agencies, can lead to potentially disruptive advances. However, the journey does not end in the initial discovery as the researcher inventor is then faced with multiple challenges of how to progress the technology into the next stage of development in the clinic and ultimately to treat patients, which is an ultimate end goal of the scientific research. Innovation is the foundation of the solution to the problem, but the question arises as to how should a researcher progress inventions through the product development chain (Fig. 25.4). This was the challenge for the early clinical pioneers of cell and gene therapies, the complexity of the products and the control of their actions in a therapeutic setting brought significant scientific, regulatory and economic challenges. Beyond the inherent risk in drug development, these products were faced with the newness of the technology, the absence of benchmarks for regulators concerned with safety and the lack of technologies to manufacture consistently, reliably and cost

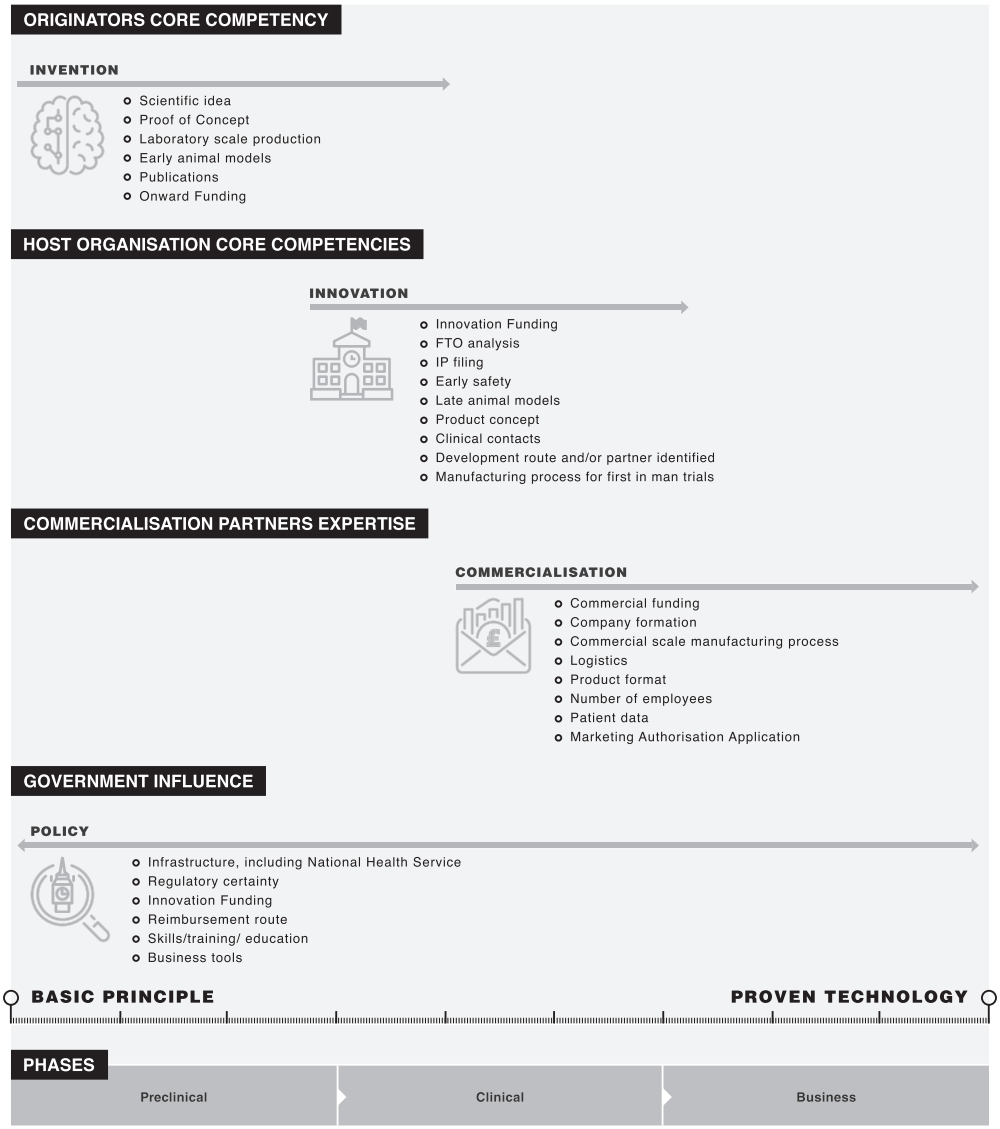


Figure 25.3 ***Organisational competencies.*** To drive innovative breakthroughs requires organisations to have or develop a new set of competencies focused on navigating the corresponding disruptive change. Multiple players will be involved, within an organisation and in different organisations, supporting radical innovation. Specific competencies have been identified as essential to promote innovation. Leading disruptive innovation and change involves creating or doing something radically different that produces a significant leap forward (leap-frogging). Those driving the innovation process must be prepared and have the skill sets to push boundaries, must be able to take decisions based on not only the often-limited data but also from any source, including utilising human connections, leveraging organisational factors and instinct (O'Connor and McDermott, 2004). Leading disruptive innovation also requires managing unsurpassed levels of uncertainty, and there must be an adaptive approach to planning so that as data are generated, assumptions and approaches can be modified accordingly. There is also the need to deal with the unexpected, from alternative technological advances, competitive moves, political and regulatory changes as well as to a myriad of unforeseen events; as a result, an innovative mindset needs to be agile and demonstrate its ability to respond. It is important to recognise and work to the strengths of the different individuals and organisations that will be involved, or influence the innovative breakthrough, but it is also important for a given organisation to understand the areas in which it lacks expertise as this can be one of the fundamental barriers to progress. By working together, radical innovation is more likely to succeed (Kaplan, 2012).

Figure 25.4 ***Factors affecting innovation in cell and gene therapies.*** Product and process innovations are the prime indicators of innovativeness. However, multiple factors affect innovation in the cell and gene therapy field. These can occur at all stages of the product development lifecycle, from the earliest stages (left of the figure) to the more commercial aspects (right of the figure) and likely contribute to the current scarcity of products in clinical practice (Corbett et al., 2017). There are challenges in determining the safety, efficacy and cost-effectiveness of a therapy. A critical success factor is thus the ability to design a cost-effective, robust and scalable process for the product to be manufactured at a commercial level and how the new products will be delivered to patients, comprising not only all the elements of logistics but also all the elements of bed-side patient care. Given the anticipated cost of the new therapies, exemplified by Glybera (alipogene tiparvovec, a treatment for lipoprotein lipase deficiency, which was subsequently withdrawn (Sagonowsky, 2017)), Strimvelis (a gene therapy for Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (Staton, 2016)) or TEMCELL HS Inj (a cell therapy for the treatment of treatment of acute graft vs. host disease (Mesoblast, 2015)), reimbursement strategies are likely to be novel as will the process of clinical access, which may require new treatment infrastructures exemplified by Advanced Therapy Treatment Centres where autologous and allogeneic ATMPs will be administered by a hospital staff well trained in how to use the novel therapeutic modalities. Changes in the regulatory landscape, political and commercial interest can also become hurdles and bring uncertainty. Remarkably, those factors are not independent and issues in one can have knock-on consequences in others. Changes in regulatory frameworks, for example, can lead to unexpected delays in clinical trials with concomitant risks to funding and commercial opportunity.

effectively. The technologies and infrastructure to deliver the therapies to patients also needed to be considered. Therefore, the risk around developing these products was disproportionately high. In addition, funding, which was already challenging and highly competitive in an academic environment, becomes more so as there were no exemplars of costs that were likely to be incurred. Therefore, grant-awarding bodies were faced with the early challenge of whether a proposal for funding was risky or reckless, but given the novelty of the products with limited information to make the decision. At this stage, the researcher can feel isolated with insurmountable barriers to crossing the innovation chasm towards clinical translation. As Professor Adrian Thrasher from Great Ormand Street Hospital and a pioneer in the field of gene therapy recalls 'in the early days the regulatory infrastructure for novel gene and cell therapies did not really exist in a coherent sense. A clear roadmap for investigators was therefore lacking'. Significant delays to progressing exciting innovative therapies are thus at major risk.

There is governmental recognition of the importance of innovation, technology transfer and entrepreneurship for sustained economic performance. One of the key components to successful technology translation is patents; both the application of patents to protect innovative discoveries and an understanding of the freedom to operate in innovative areas where patent 'thickets' have the potential to block innovation progress. The United Kingdom accounts for 2.4% of global patents (BIS/13/1297, 2013) and 3.5% of triadic patents within the OECD (2017a), and in 2016, it was the sixth largest filer of European applications for biotechnology and pharmaceuticals (EPO). Key to the advancement of innovative therapies is that patenting and commercialisation activities by academic staff be recognised in counting towards research activity. In addition, there is a need to recognise that patents require long-term investment which may not always be available within the academic setting where technology transfer funding and resource is limited. An exciting product may subsequently struggle to secure external funding due to limited IP protection.

The product development path also needs to be determined. Funding is clearly crucial and can be limited at both the academic and commercial levels (Fig. 25.2). In the United Kingdom, academic research funding is provided through government-backed research councils (e.g., Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC)) and through substantial support from the charitable sector (e.g., Wellcome Trust, Cancer Research UK, numerous disease-specific charities). Within any given year there is a defined amount of funding available and a robust competition for funds. These funds will typically support the translation of products into initial clinical trials. Should a product have encouraging early clinical data, the developers then need to overcome the second innovation chasm, the path to commercialisation, when costs increase significantly (Fig. 25.2). An academic led project may need to attract external investment, but this requires access to expert resources, motivation, incentives and time;

there is the risk that many promising products remain 'on the bench'. Similarly, within the commercial sector, budgets are established for R&D, and with the uncertainties and perceived risks around innovative technologies, the release of funds may be limited. In addition, innovations tend to cross boundaries and create new categories that will need to be managed within the business environment, determining where the product sits within the portfolio and company priorities, with the concomitant risk of delays and down prioritisation (Schuhmacher et al., 2016). Innovate UK, the United Kingdom's innovation agency, runs funding competitions for businesses looking to develop an innovative product, process or service, as a mechanism to support innovation. From April 2018, the UK research councils and Innovate UK will be brought together under one organisation, UK Research and Innovation, to maximise the value and benefits from the government's investment of over £6 billion per year in research and innovation.

The new ideas that lead to innovation are often intangible, and thus it can be difficult for the original inventors to appropriate all the returns from their efforts, and this can be a barrier to innovation. Some of the benefits from the innovative solution will spill over to third parties in a situation known as a positive externality (Dietzenbacher and Los, 2002). Therefore, market incentives alone may provide too little incentive for research and innovation as there can be a perception of increasing the private (often financial/commercial investors) gain with little inventor reward. Although it could be argued that part of the role of public servants within the research sector is to help to increase the national R&D total productivity factor (TFP), there is still a need for the inventor to feel the benefit of that input. At a basic level, this can be through encouraging researchers to take out patents, as well as being acknowledged for and seeing the medicines they have helped to develop reaching routine clinical use. Another challenge is that firms and individuals may be restricted in the extent to which they can respond to market incentives, due to failures in financial markets, which make it difficult to secure external sources of finance for risky and intangible projects. This can also lead to under provision of research and innovative activities. This can be a significant challenge as the fundamental research that enables emerging medical advances comes from all national jurisdictions; medical research is a competitive international arena. Maximising TFP (e.g., via governmental building infrastructures) and 'free' market prices may be the best answer to providing incentives for inventing and commercialising new products within a given jurisdiction.

One of the largest innovation barriers is decision making (du Plessis, 2007) from within an organisation such as therapy adoption by clinicians to external bodies such as regulatory authorities. While at a national governmental level decision-making may be part of a long-term policy, potentially over many years, industrial organisations will likely be working to much shorter time frames. Although there are differences in timescale between governments and commercial organisations, the general challenges of decision-making remain the same. Key decisions will need to be made to allow the innovative solution to progress. Decision makers may have different agendas (financial, safety or

feasibility) and therefore, decision making becomes more challenging as the number of participants involved increases. There can be a complexity of backgrounds and mindsets, resulting in too many aspects being considered, and this risks derailing momentum. It is not only a key to understand who is a critical decision maker, but it is also important to understand how the decision will be made and ensuring that the right information is available to the right people. Innovation can be complex and many organisations have tools to assess the development or implementation of an innovation, the risk is that these tools can stifle the very thing that they are intended to promote. They are based on measures of success, but for an innovative product or process, these may be very different from industry standards. By identifying the barriers to innovation, the opportunity exists to implement strategies that facilitate the ability of organisations to respond to or address these risks and provide opportunities that may have a significant impact on the commercial exploitation of innovative concepts.

A MODERN GOVERNMENTAL INDUSTRIAL STRATEGY

A challenge for any country is to ensure that innovative solutions can progress to market and thus that a suitable ecosystem and infrastructures exist to nurture its growth.

Investing in Science, Research and Innovation

In 2010, Dr. Hermann Hauser reviewed the UK government innovation policy and the specific challenge of capturing economic benefit from the United Kingdom's excellence in generating knowledge (Innovate UK, 2010). Science and innovation had been recognised as at the heart of the United Kingdom's long-term strategy for economic growth. However, it was acknowledged in the report that there was a critical gap between innovative research findings and their subsequent development into commercial propositions that could attract venture capital investment or be licenced, and that this gap could only be closed by making new technologies investment ready.

To ensure that the United Kingdom delivered on its aims to create a 'knowledge economy', strategies needed to be put in place that promoted investment in and supported research excellence. The Strategy for UK Life Sciences (BIS/11/1429, 2011) was published in 2011 outlining a series of actions to make the United Kingdom a world-leading place for life sciences investment. The strategy set out a vision where academia, the National Health Service (NHS), charities and industry would come together to create an unrivalled ecosystem. The strategy was designed around three main principles: (1) building a life science ecosystem; (2) attracting, developing and rewarding best talent, and (3) overcoming barriers and creating incentives for the promotion of healthcare innovation.

It was also essential that the governmental strategy support those areas of UK industry which had the ability and absorptive capacity to capture a significant share of high-value activity. Critically, it was essential to close the gap between universities and industry

through a 'translational infrastructure' that would provide a business-focused capacity and capability that bridged research and technology commercialisation. The benefits of a government-sponsored translational infrastructure had already been shown in many countries; these included the Fraunhofer-Gesellschaft in Germany, Industrial Technology Research Institute in Taiwan, Electronics and Telecommunications Research Institute in South Korea, Tekniikan edistämiskeskus (TEKES) in Finland and Toegepast Natuurwetenschappelijk Onderzoek (TNO) in the Netherlands. While the United Kingdom had invested in equivalent structures, the report found that the UK approach at that time was by comparison subcritical, lacking a national strategy, and that there was insufficient attention to business requirements and the location of relevant expertise. The conclusions of the Hauser (Innovate UK, 2010) and Strategy for UK Life Sciences (BIS/11/1429, 2011) reports were that the United Kingdom should develop an equivalent capability and that attention should be focused on providing sustained and substantive support for an elite group of TICs that would subsequently become the UK Catapult programme established and funded by Innovate UK. The aim of the Catapults was to bridge the gap between R&D and industry, ensuring that there was a 'translational infrastructure' that would allow the most innovative ideas to be commercialised and drive benefit to the UK economy. The Catapults were tasked with the aim to exploit the most promising new technologies, where there was genuine UK potential to gain competitive advantage and to help deliver new industries of the future, with transformational economic impact. Critical in the development of the Catapult programme has been the hard choices the UK government made in only developing such a capability for platform technologies where the United Kingdom had technical leadership, where there was a defensible technology position, where large global markets existed or had the potential to exist and, importantly, where there was capacity to anchor a significant part of the value chain, from research to manufacturing, within the United Kingdom. Of importance, was the potential to develop industrial clusters. A strong cluster would include a broad base of related businesses located in close geographical proximity allowing the development of pools of specialised worked, suppliers and service providers, as well as potential for the rapid flow of business-related knowledge among related firms, which result in technological spill overs (John and Pouder, 2006; Ketels and Memedovic, 2008). One of the initial Catapults identified was the Cell and Gene Therapy Catapult. The number of UK companies developing advanced therapy medicinal products (ATMPs) had been growing, and the United Kingdom was and remains a world leader in this area with a strong academic science base and a supportive clinical and regulatory environment (Cell and Gene Therapy Catapult, 2017). Over £200 m of public finances had been invested in basic and translational research since 2003, when the then UK government's Technology Strategy Board proposed the launch of its regenerative medicine programme in 2009 (Technology Strategy Board, 2009). What was clear was that the company landscape was dominated by small- and medium-sized enterprises (SMEs) and they faced the

recognised challenges inherent in working with emerging innovative technologies, including technological, regulatory, fiscal and strategic uncertainties. Developing ATMPs required an interdisciplinary approach covering several areas including industrialisation strategy, regulatory and clinical strategy and specialist business development activities such as health economics and market access. In addition, stable financing, particularly for SMEs, was a major hurdle and this uncertainty delayed and even limited innovation. Providing organisations with access to enabling infrastructure, expertise to enable grants to be won and support that addressed their challenges would play a significant role in speeding up research, development and innovation and accelerating routes to market.

The Catapult has therefore provided to the developing UK industry access to the best technical expertise, infrastructure, skills and equipment; resources which companies, particularly spin-out companies, can seldom afford alone; the consequence of which should be to help to increase the national R&D TFP. For innovative technologies, however, the commercialisation challenges do not reside only with small and medium enterprises. For the Catapult to be effective there had to be value to growing the whole industry, and it was critical that there was engagement from a wide cross section of industry including multinationals who were in the process of moving into the field. The Catapult has also had a pivotal role in acting as a connector, sharing expertise to support the translational activities of the UK academic base. By creating an environment for collaborative translational activity between businesses and the research base, the aim has been to create a critical mass of activity which is providing an innovative and entrepreneurial environment, enabling the development of new value chains and facilitating a variety of routes to the commercialisation of new products, processes and services and building an international reputation which will also help to attract inward investment with the ultimate goal of delivering new medicines to patients.

More recently has been the emergence in 2017 of a new comprehensive UK Industrial Strategy covering 10 separate areas, including traditional industrial pillars (investment and trade) and 'enablers' (such as skills or infrastructure), designed to drive growth and productivity across the country (BEIS, 2017). As part of this process, five key industry sectors (low emission vehicles, industrial digitalisation, nuclear, the creative industries and life sciences) are generating sector-specific reports. The first of these to be launched in August 2017 was the Life Sciences Industrial Strategy (Office for Life Sciences, 2017). The Life Sciences sector, including biopharmaceuticals, medical technology, genomics, diagnostics and digital health, are a major component of the current economic base of the United Kingdom, generating £64 billion of turnover and employing more than 233,000 scientists and staff (HM Government, 2016). The key themes of the report include substantially increased funding for research, enhanced incentives for companies to invest in UK manufacturing, action to ameliorate skills shortages and closer collaboration between industry and the NHS. The importance of cell and gene therapies is explicitly recognised as an emerging disruptive technology. In addition, the

report recognises the work of the Advanced Therapies Manufacturing Taskforce (Medicine Manufacturing Industry Partnership, 2016) in developing a clear set of actions to drive up investments in commercial manufacture of cell and gene therapies and recommends that the Advanced Therapies Manufacturing Action Plan should be accepted in full and principles applied to other life-science manufacturing sectors. Overall the strategy looks to capitalise on manufacturing advances and proposes a new collaborative environment where industry and the health system work together.

Innovation Legislation and Policies

Delivery of the Catapult programme alone would not have been sufficient to support the emerging gene and cell therapy industry. Government has a pivotal role to play, specifically in articulating a clear vision and establishing an accompanying stable and coherent policy framework to enable the innovative industry to develop and thrive. Indeed, given the long-time scales in developing innovative solutions, an unstable policy environment could substantially undermine the effectiveness of otherwise favourable policies (OECD, 2013). While changing circumstances and governments may shift policy priorities, within the major UK political parties there has been a general commitment to the delivery of a modern long-term industrial strategy.

The aim behind all innovation policies is to increase productivity and competitiveness (both for the country as well as businesses) and support the development of high-value goods and services. In addition, there are spill over positive effects, such as enhanced capabilities, the generation of general value add and the development of a skilled workforce, as well as social and environmental benefits (Edler and Fagerberg, 2017). Policies that encourage innovation fall into at least four key areas. The first is a commitment by government in investing in science (Office for Life Sciences, 2017). This investment supports both pure and early stage applied research as innovation is often driven from blue-sky research delivered within the university sector. In the United Kingdom, the funding for scientific research and innovation is allocated by independent expert bodies, government funded research councils and Innovate UK (Fig. 25.2). The government has also recognised the important contribution of the charitable sector to innovation, and a legal framework that allowed charities to invest in, stimulate and disseminate research was established (UK Government Charities Act, 2011).

Secondly, there has been a commitment from the government to the infrastructure that supports the science (Office for Life Sciences, 2017). This may take the form, for example, of facilities that can be used across sectors or centres where universities and industry can come together creating an interdisciplinary environment promoting convergent innovation. However, it has also been a key to have policies dedicated to both education and the development of a skilled work force. The innovation policies have also created incentives for business investment. These typically compensate for technology and financial risk for business through grants and fiscal incentives such as the R&D Tax

Credit scheme and Venture Capital incentives. It is also critical to have the policies and infrastructure that promote knowledge transfer as was highlighted in the Whitty report in 2013 (BIS/13/1241, 2013). In the United Kingdom, this is achieved through support for Collaborative R&D, Knowledge Transfer Partnerships and Knowledge Transfer Networks (c£350 m pa). These organisations build links between science and business, by bringing together businesses, entrepreneurs, academics and funders to develop new products, processes and services.

Adoption and access to innovative products is also a key to supporting innovation. Adoption requires at its simplest level a decision to be made and an action to be taken. There must, therefore, be awareness that the innovation exists, interest in the innovation, an evaluation of the innovation, a trial phase to test that the innovation matches expectations and ultimately adoption. Adoption of innovation typically occurs at varying rates (Rogers and Shoemaker, 1971) (Fig. 25.5), and this is true at both an individual, corporate and country level. In the United Kingdom, the accelerated access review (Accelerated access review: final report, 2016) was commissioned in 2015 by the government to make recommendations to speed up access to innovative drugs, devices, diagnostics and digital products to NHS patients, as adoption within the NHS was slower than in healthcare systems in some comparable countries (Department of Health, 2017). The review made a number of recommendations including proposals for more agile adoption of innovation through establishing streamlined mechanisms for prioritising emerging technologies, developing new pathways to accelerate approvals, speeding up adoption, more efficient technology evaluation and aligning national organisations to transform the

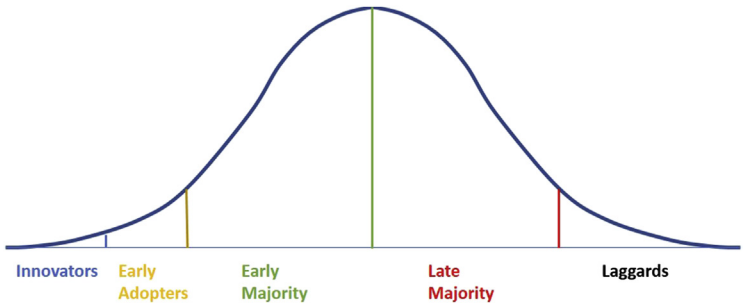


Figure 25.5 ***Technology adoption curve.*** The relative speed of adoption can be plotted as a normal distribution; the Rogers innovation adoption *curve* (Rogers and Shoemaker, 1971). Innovators (~3%) are the risk takers who have the resources and desire to try new things even if they fail. The early adopters (~13%) are selective about the technologies that they start using but will derisk an innovation for the majority of adopters. The early majority (~34%) takes time before adopting an innovation but is willing once the benefits are understood. The late adopters (~34%) adopt innovation in reaction to emerging norms or economic necessity and wait until there is no further debate on validity. The laggards (16%) often make decisions based on past experiences, in many circumstances they are often economically unable to take the risk of new ideas.

NHS's ability to rapidly adopt strategically important medical innovations and those with more incremental benefits (Accelerated access review: final report, 2016). Many other European Union (EU) countries, as well as the European Medicines Agency, have also proposed or introduced schemes to speed up patient access to innovative treatments, especially where there is an unmet medical need, reflecting the general desire for faster, more flexible regulatory systems to keep pace with medical and technological developments. In 2017, the government took the first steps to implement the findings of the accelerated access review with the unveiling of a new package of support to help innovative UK businesses develop medical breakthroughs that are then used across the NHS. In addition, the 2017 Life Sciences Industrial Strategy (Office for Life Sciences, 2017) recommended that the findings of the Accelerated Access Review should be adopted in full.

The fourth key area of innovation policy is delivering enabling legislation and regulation. Without this, there is a risk that regulations and standards can act as brakes on growth and on drivers of innovation. The commercialisation of innovation often requires changes within a nation's legislative structure. Over the last 30 years, the UK government has streamlined roles to improve processes and developed the role of committees that scrutinise the work of the Government. In the British House of Commons, for example, executive oversight and other investigative work are carried out by a set of specialist 'select committees' (Benton and Russell, 2013). Since their creation in 1979, these committees have considerably developed their role in scrutinising government, predominantly through holding enquiries into different aspects of executive policymaking. Although these committees have no legislative power and the government is not required to act on their recommendation, over 50% of recommendations are taken up in some form by government (Benton and Russell, 2013). Although this success rate may appear low, given the number of reports issued, this amounts to a significant number of recommendations acted on per year, and in many cases, these have called for significant policy changes (Benton and Russell, 2013).

The House of Lords also has select committees and these investigate specific public policy, proposed laws and Government activity. In July 2013, for example, the HOUSE OF LORDS Science and Technology Committee, published a report (HOUSE OF LORDS Science and Technology Committee, 2013) into their inquiry into regenerative medicine. This report called for an expert working group to be established to develop a regenerative medicine delivery readiness strategy and action plan for the UK health service. This was accepted by the government, the expert working group convened and by December 2014 its report and action plan was delivered. This report has been influential for the sector, in particular in shaping the regulatory environment. The government enacted through response to this process the development of the Medicines and Healthcare Products Regulatory Agency 1 stop shop, clarifying the roles of the Gene Therapy Advisory Committee and the Health Research Authority (HRA), with all processes resulting in the speeding up of research.

The UK government has a record for developing legislation and policy that enables the UK health and regulatory bodies to become early adopters of disruptive technology as can be seen with the example of the United Kingdom becoming the first country in the world to approve the use of mitochondrial replacement therapies (MRT) (Le Page, 2016). The rapid adoption of the MRT therapies has its history in the emerging challenges of in vitro fertilisation and research with human embryo's in the 1970's and 1980's, with the establishment within the United Kingdom of a Committee of Inquiry into Human Fertilisation and Embryology. The UK legislative framework and the appointment of a regulatory authority in the field (Human Fertilisation and Embryology Authority; HFEA) facilitated the regulation of assisted reproduction. However, the committee and acts were not static but continued to evolve through a number of expert-led consultations resulting in several amendments, the most recent of which allowed the clinical trials for MRT (Castro, 2016). Indeed, the exercise was found to reflect the best regulatory practices used by the most industrialised countries belonging to the OECD (2015), which requires governments to assess the impact of regulatory proposals as early as possible, consult with stakeholders and evaluate the impacts of regulation ex post which is expected to occur in 2019. Regulating assisted reproduction under the umbrella of a single legislative act (the 1990 HFE Act) and a specializsd authority (the HFEA) has been fundamental in allowing the United Kingdom to be pioneering in allowing clinical trials for MRT. The key was having a defined process that allowed recommendations to be made, reviewed and enacted; this key unlocks the research and innovation process.

Cell and gene therapies are often truly personalised and therefore have unique and complex development as well as manufacturing challenges (Haddock et al., 2017). The UK House of Lords Science and Technology Committee report (HOUSE OF LORDS Science and Technology Committee, 2013) into regenerative medicine identified securing reimbursement as a significant hurdle for manufacturers within the field of cell and gene therapy. Particularly, the report questioned the suitability of existing health technology assessment methodologies, suggesting that such methods may unfairly disadvantage highly novel therapies such as cell and gene therapies. In response to the report findings, the National Institute for Health and Care Excellence (NICE) was asked to commission a study to assess whether its current appraisal methods and processes were appropriate to evaluate cell and gene therapies. The appraisal used an exemplar cellular therapy technology (CAR-T cell immunotherapy) and found that although there were risks and uncertainties in the area the 'Technology Appraisals' network used within the United Kingdom, this framework was appropriate for cell and gene therapies (Hettle et al., 2017). The report also identified that where there is a combination of great uncertainty but potentially very substantial patient benefits, innovative payment methodologies need to be developed to manage and share risk, with the ultimate objective to facilitate timely patient access while the technology is immature. By using this exemplar approach, the United Kingdom has not only identified the challenges within its

reimbursement assessment system and set in motion processes to address these but also identified that the system in principle was applicable. Indeed, in October 2017, NICE recommended Strimvelis, an ex vivo gene therapy treatment, as an option for treating ADA–SCID when no suitable human leukocyte antigen–matched related stem cell donor is available (National Institute for Health and Care Excellence, 2017).

Innovation Infrastructure

There have been several important developments in the United Kingdom innovation infrastructure in recent years (Fig. 25.6), not least of which is the emergence of Innovate UK as a significant force. Innovate UK was established in July 2007 (as the Technology Strategy Board) and is the United Kingdom's innovation agency, a nondepartmental public body sponsored by the Department of Business, Energy and Industrial Strategy. It is the prime channel through which the Government incentivises innovation in business. Innovate UK works with people, companies and partner organisations to find and drive the science and technology innovations that will increase productivity and exports and grow the UK economy. Innovate UK is working to accelerate UK economic growth by nurturing small high-growth potential firms in key market sectors, helping them to become high-growth mid-sized companies with strong productivity and export success. Since 2007, Innovate UK has invested over £2.2 billion in innovation and this has been matched with just over £1.5 billion from industry. Innovate UK has helped more than 8000 organisations in projects, and this is estimated to have returned £16 billion to the UK economy and created 70,000 jobs (McKernan, 2017; Innovate UK, 2017). Innovate UK works with the UK Innovation Infrastructure that includes approximately 200 'Research and Innovation Organisations' (RIOs). These are highly heterogenous (Table 25.1) ranging from independent foundations to those linked to universities, and some are private companies; nonetheless, all have in common a significant degree of public support, either in terms of core or programme funding, or research purchasing (Innovation Functions and Policy Issues, 2016). Current UK policy is continuing to develop this system, through new organisations such as the Crick Centre in London and the creation of the Catapult Centres based around advanced industrial knowledge bases. Both the established and new organisations have distinct ownership structures or legal status and continue to play a central role in creating and sustaining innovation-based growth in the United Kingdom.

The RIOs have important direct and indirect impacts on the UK innovation environment through maintaining and developing business knowledge bases in the United Kingdom and in training skilled people to use them and to innovate with them; this is also true with respect to the cell and gene therapy field (Table 25.2). The RIOs through multiple integrated innovation-relevant activities impact innovation in UK cell and gene therapy. These activities may be interdependent, and to some extent indivisible. For example, in the field of cell and gene therapy development, established organisations and

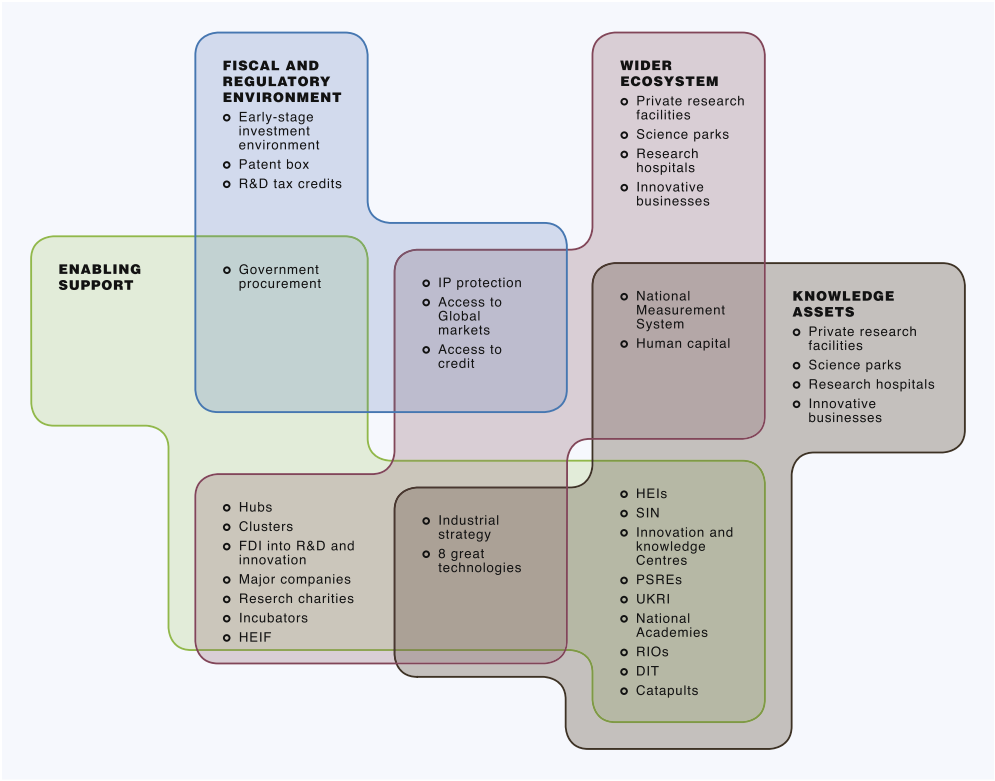


Figure 25.6 ***UK innovation landscape assets.*** There are broad categories of innovation assets (institutions, policies and procedures) which contribute to the United Kingdom's innovation ecosystem. The assets are clustered into four main asset classes: (1) enabling support, (2) fiscal and regulatory environment, (3) knowledge assets and (4) wider ecosystem. The United Kingdom has a world-class research base that provides an excellent source of new ideas and discoveries. The innovation system provides the fundamental support to ensure the United Kingdom has the capability and the capacity to innovate, and notably to innovative in disruptive (i.e., radical, game-changing or transformational) innovation. The Government aims to create an enabling environment and infrastructure, as well as support for essential skills development. The United Kingdom has developed a strong IP rights system, a favourable environment for angel investment in early-stage entrepreneurial companies and R&D and manufacturing bases for many leading international firms. These efforts vastly reduce various business risks including policy risk and operational risk. The United Kingdom has a number of not-for-profit research and innovation organisations that are an integral part of the innovation landscape. More recently, this innovation foundation has been expanded with significant investment in the Catapult Centre Networks, including the Cell and Gene Therapy Catapult, to enable businesses and researchers to collaboratively solve key problems and develop new products and services on a commercial scale. The Catapult centres are also making valuable contributions through providing an infrastructure for sector-based innovation such as the new Cell and Gene Therapy Manufacturing centre. The United Kingdom has a broad range of innovation assets; the governmental challenge is to provide both an overarching vision and a coherent, stable and strategic innovation policy framework to enable these assets to act effectively in concert over the long term (Royal Academy of Engineering, 2015). *(Figure adapted from Royal Academy of Engineering. Investing in Innovation; 2015.)*

Table 25.1 The Research Innovation Organisations System in the United Kingdom Currently Has Four Major Components (Innovation functions and policy issues, 2016).

Organisation Type	Role
Public Sector Research Establishments' (PSREs)	Research and development institutes sponsored directly by government departments or the seven UK Research Councils. These organisations have significant scientific expertise. The Medical Research Council Laboratory for Molecular Biology, Cambridge, for example, has won 14 Nobel prizes, the most recent in October 2009, and many are globally important scientific organisations.
Public Research Organisations' (PROs)	The major standards-setting organisations and research organisations, such as the National Institute of Biological Standards and Control (NIBSC).
Independent Research and Technology Organisations (IRTOs)	These are (mainly) private nonprofit research performers or commercial research enterprises providing R&D services, both to government and business, and many belong to the Association of Independent Research and Technology Organisations (AIRTO).
Catapult Centres	Seek to link business, advanced research and engineering around innovation processes with major business implications.

Table 25.2 Research Innovation Organisations Core Activities Relevant to Cell and Gene Therapies.

Area	Activity
Support to industrial innovation	• Scientific support to industry knowledge bases • Problem solving and advice for commercial firms • Specific product and process development • Creation of spin-out companies • User-initiated innovations
Infrastructure creation and maintenance	• Provision of 'general purpose' technological capabilities • Physical and knowledge infrastructure provision: specialised or large-scale capital goods, instruments and equipment • Personnel training, development and mobility
Public policy development and implementation	• Contributions to policy development • Information for policy implementation • Support to issues of public concern in health

new entities are often moving outside their existing areas of competence. RIOs provide frequent advice, often on an informal basis, that addresses these problems; this is a central collaborative function of RIOs that form an ecosystem supportive of innovation. A problem that is intractable for a particular organisation may be easily solvable with access to wider expertise and collective wisdom. Supporting innovating organisations in practice entails the creation, development, deepening and extension of knowledge related to almost every sector of UK economic activity. Collectively, RIOs are estimated to account

directly for £3.7 bn per annum in gross value add rising to £7.6 bn if indirect and induced impacts are included. These organisations therefore represent an important innovation asset for the United Kingdom, helping to maximise the leverage achieved on direct public investment in innovation (Oxford Economics, 2014).

RIOs are often involved in the provision and maintenance of large-scale and complex infrastructure and equipment. Organisations within a given field often require access to scientific capital goods that go well beyond the capacities that a single organisation can provide. This is the case with the Cell and Gene Therapy Catapult and the provision of a large-scale manufacturing centre in the United Kingdom. Analysis in 2013, by the Cell and Gene Therapy Catapult and others, has shown that the United Kingdom's small-scale academic Good Manufacturing Practice facilities were an excellent source of products for early stage clinical trials. However, analysis indicated that these facilities were expected to be at capacity within 3–6 years as the industry's pipeline matured. A commitment was made by the UK Government to fund the UK Cell Therapy Manufacturing Centre to provide the United Kingdom with the manufacturing facilities needed for later stage clinical studies and commercialisation, with the aim of promoting retention of domestic expertise and jobs, learning lessons from the past when manufacturing capacity shortages impacted the initial deployment of monoclonal antibody therapies. The business model for the Centre is also an innovation in its own right as it facilitates firms establishing manufacturing technologies and systems, whilst at an early stage of company evolution, thus mitigating some of the risk that these innovative companies must take to fully play their role of fuelling the R&D value chain.

Strengthening Strategic Capabilities

A successful governmental innovation strategy requires that academia and industry have the ability to collaborate. As a result, a number of initiatives have been implemented by the UK Government to assist industry and research communities to work together on R&D projects in strategically critical areas of science, engineering and technology. Such collaborative research as well as providing an environment from which new products, processes and services can emerge facilitates the flow of the latest knowledge and thinking from the science, engineering and technology base through to business. The Knowledge Transfer Network, funded by Innovate UK, is one such organisation which specialises in cross-sector collaboration through connecting business, academics and other innovation support providers. Key to the success of these collaborative interactions is the ability to challenge the everyday way of thinking, speeding up innovation, solving problems and finding markets for new ideas. Current government policy has a long-term commitment to knowledge exchange between higher education institutions and external organisations. Driven through Higher Education Innovation Funding, support higher education institutions can utilise their specialist knowledge to help business

organisations of all sizes to become more competitive, innovative and productive. This may be in the form of consultancy, joint R&D projects and collaborations that lead to the formation of new companies and the permeation of intellectual properties in innovation engines where their value will be maximised.

One key area that was critical to solve for collaborative activities between commercial and academic partners was to provide models for the management of IP in collaborative research. A series of models have been developed; these include the Lambert agreement models and the NIHR and the MRC industry collaborative research agreement (Model agreements for collaborative research, 2017; Standard research agreements, 2017). The aim of these model agreements is to maximise innovation while encouraging collaborations. The cornerstone of these model research collaboration agreements is that, at a minimum, a commercial 'partner' (called the collaborator) will have the right to use the results of the project on a nonexclusive basis to promote the use of the results and therefore innovation. In addition, the agreements cover the critical issues of royalty and success payments as well as publication and confidentiality obligations. The framework of these agreements is designed to represent a workable and reasonable compromise for all the parties involved (typically; two) and in total five basic model agreements have been developed to cover different approaches. In addition, a decision tree is provided to help groups seeking to collaborate identify the best agreement model starting point for them. The model agreements are not a substitute for discussion, thinking and pragmatism but provide a workable starting point for discussions. A review of the use of Lambert agreements found that the Lambert toolkit had had a positive influence on some innovative research partnerships between UK universities and businesses (Eggington et al., 2013). The toolkit provided effective support not just where both parties already used it, but especially if one partner had no standard agreements, was new to collaborative research or if the partners had not collaborated before.

As already described, innovation has at its core excellence in research. In 2013, the UKRMP was established. The Platform was a joint initiative between the MRC, EPSRC and BBSRC. The initiative brought together leading multidisciplinary research teams from 20 UK universities and established, in the first instance, five hubs (cell behaviour and differentiation, stem cell niche, safety and efficacy, acellular approaches and immunomodulation hubs) with the critical mass and expertise to address key identified knowledge-gaps in the translation of stem cell and regenerative biology towards clinical application. To support the commercial activity required to bring these emerging therapies to the clinic, the UKRMP works closely with the Cell and Gene Therapy Catapult and has engaged with over 25 companies to date. The Platform has also established international collaborative programmes, engaging world-leading teams in Sweden, France, Germany and the United States. The success of the programme has ensured that in 2017 the three funding partners committed to deliver a further £17 m in investment over 5 years (UKRMP, 2017; New funding boost, 2017).

A key goal in the fields of cell and gene therapies is to progress novel breakthrough therapies to the clinical trial stage. Utilising the power of one of the most integrated healthcare systems in the world, partnerships have been formed, for example, between England's leading NHS organisations and universities resulting in the formation of 20 National Institute of Health Biomedical Research Centres with the goal to conduct translational research to transform scientific breakthroughs into life-saving treatments for patients (Biomedical Research Centres, 2017). These facilities are supported by substantive funding to drive innovation in the prevention, diagnosis and treatment of ill health. Moving forward, the first advanced treatment centres are being formed. The facility at Kings College London in partnership with the National Institute for the Health Research Biomedical Research Centre at Guy's and St Thomas' hospitals, for example, was supported by both Governmental funding through the UK Research Partnership Investment Fund as well as funding from private sector and nonprofit organisations.

Innovate UK has provided long-term support to the area of regenerative medicine and advanced therapies for UK businesses. Since its formation in 2007, Innovate UK has supported work to address translation and commercialisation challenges in the area of advanced therapies and regenerative medicine. In the period 2005 to 2009, Innovate UK (and its predecessor the Technology Programme in the Department of Trade and Industry) committed more than £20 million in cell therapy and regenerative medicine technologies, tissue engineering and cell bioprocessing. This covered a portfolio of approximately 30 projects involving 20 different companies. In 2008, Innovate UK worked closely with the Bioindustry Association Regenerative Medicine Industry Group (now the Cell and Gene Therapy Advisory Committee) and other industry colleagues to build a Regenerative Medicine Programme, which was launched in 2009. This programme allowed Innovate UK to undertake a more strategic approach to supporting this nascent industrial sector. The aims of the programme were to ensure that UK businesses could achieve a commercially competitive edge with global impact. Between 2009 and 2016, through the Regenerative Medicine Programme, the Biomedical Catalyst and a number of other funding streams, Innovate UK has supported a total of 126 advanced therapies and regenerative medicine projects with over £54 million in grants. These project grants have been matched with over £25 million additional funding from industry (Written evidence submitted by Innovate UK, 2016).

Encouraging Investment

Fiscal measures are widely used to incentivise private investment in R&D as a means of stimulating innovation, and the United Kingdom is no exception. One such scheme in the United Kingdom is the Industrial Strategy Challenge Fund (ISCF), which is part of the developing Industrial Strategy. In April 2017, the UK government committed investing £1 billion over a 4-year period to drive progress and innovation in six key areas including in healthcare and medicine (Business secretary announces industrial strategy,

2017). The ISCF aims to bring research and business together to deliver not only social impact but also economic impact. In August 2017 (Sir John B, 2017), details of the £146 million ISCF Medicines Manufacturing Challenge were announced. The challenge aims to accelerate patient access to new medicines through the development of new manufacturing technologies and anchoring high-value, high-skilled jobs in the United Kingdom. The investments include £12 million to double the manufacturing capacity at the Cell and Gene Therapy Manufacturing Centre at Stevenage and £30 million to create a network of three Advanced Therapy Treatment Centres (ATTCs) in the United Kingdom (Sir John B, 2017). The ATTCs will be responsible for developing the systems and infrastructure to support delivery of cell and gene therapies, including final manufacture and supply, clinical trial capability, R&D approval, specialist clinician availability and support services. Once established, the ATTCs should increase at a national-level patient access to cell and gene therapies. In addition, they will aim to establish best practice for the treatments safe and effective delivery, manufacturing and final preparation within a clinical setting, robust connected supply chains, traceability and establish best practice for patient follow up and data capture. The establishment of the ATTCs will set the United Kingdom apart globally for the routine clinical delivery of cell and gene therapies.

The UK treasury department has recently run a consultation to understand the financial challenges faced by some of the United Kingdom's highest potential, most innovative start-ups. In response to the consultation, a plan has been developed that will aim to unlock over £20 billion to finance growth in innovative firms over 10 years. Strategies include establishing a new £2.5 billion Investment Fund incubated in the British Business Bank and significantly expanding the support that innovative knowledge-intensive companies can receive through the Enterprise Investment Scheme (EIS) and Venture Capital Trusts (VCTs) (HM Treasury and The Rt Hon Philip Hammond MP, 2017). The potential impact of this investment is considered not limited to the initial headline figure but potentially, through coinvestment from the private sector lead, to an investment fund nearer £7.5 billion (HM Treasury and The Rt Hon Philip Hammond MP, 2017) for access by innovative firms within the United Kingdom.

Anther fiscal measure is the R&D tax credit scheme where UK tax relief is available when an R&D project seeks to achieve an advance in overall knowledge or capability in a field of science or technology through the resolution of scientific or technological uncertainty. Over 15,000 companies claim around £1.4 billion in R&D tax credits each year (HMRC, 2015). Government analyses have indicated that up to £3 of spending on R&D is stimulated for each £1 of tax forgone. In addition, companies have indicated that these tax credits have contributed to an increase in R&D overall (HMRC, 2010) and increased in size, whether measured by sales revenues or by the number of jobs created (Dechezlepretre et al., 2016). There is also good evidence that R&D tax credits not only encourage businesses to conduct more R&D but also produce good quality patents.

Remarkably, R&D expenditures approximately doubled in the analysed firms and patenting rose by about 60%. Further analyses indicated that firms increased the rates at which they applied for EU-wide patents and United Kingdom only patents, for example (Dechezlepretre et al., 2016). The R&D tax credits are supported by the patent box scheme, which provides an additional incentive for companies in the United Kingdom to retain and commercialise existing patents and to develop new innovative patented products. The patent box is a tax incentive scheme aimed at stimulating R&D in firms by providing favourable tax rates to profits that can be linked to a specific intangible asset, such as a patent.

A substantial body of evidence has shown that public investment in innovation encourages private investment, with a recent report concluding that an extra £1 of public R&D funding gives rise to an increase in private funding of between £1.13 and £1.60 (BIS/15/340, 2015). This is exemplified by the Innovate UK grant scheme. Innovate UK grants are accompanied by coinvestment by the commercial recipient. Firms receiving significant support from government have large and statistically significant results on all measures of innovation activity and output; particularly, receiving a public sector grant doubles a company's spending on innovation (BIS/14/1168, 2014). In addition, public funding can be essential for seeding precompetitive R&D collaborations across sectors in areas where innovation can deliver broadly based benefits (BIS/15/352, 2015). The United Kingdom also attracts high levels of R&D investment from foreign companies. In 2012, 20% of the United Kingdom's R&D investment came from overseas (foreign direct investments (FDIs) in R&D were 53% of GDP) compared with 4% for Germany (FDI in R&D were 24% of GDP) and the United States (FDI in R&D were 24% of GDP) and 1% for China (FDI in R&D were 24% of GDP) (BIS/15/340, 2015; OECD, 2017b). Strategically, with the increasing global awareness of the importance of innovation comes a greater competition for inward investment. As a result, the United Kingdom must continue to develop policies and the appropriate business environment to remain competitive in a global market. As the pharmaceutical sector undergoes deep changes, especially the traditional large pharmaceutical companies that have undergone globally significant organisational restructuring with the concomitant closure of sites and loss of local jobs, through entrepreneurial investment strategies both locally and nationally, the UK Government can seek to maintain skilled jobs and minimise the impact on gross domestic product (Freeman, 2017). Finally, venture capital investment is a key to the growth of innovative industries. In 2016, UK companies (including companies in the cell and gene therapy field) received nearly £700 m in venture capital, more than a third of the total venture capital raised in Europe and more than any other European country (BIA, 2016). Among the European nations, the United Kingdom and Germany are recognised as Europe's most mature venture capital markets (Wijngaarde and Puls, 2017). Within the United Kingdom, London attracts nearly two-thirds of venture capital (Wijngaarde and Puls, 2017). This success in attracting venture

capital is linked to the presence of a significant number of high-growth companies (indeed the highest density of scale-ups anywhere in Europe), a strong business follow on rate, a depth of skilled workers and the United Kingdom being identified as earlier adopter market (Wijngaarde and Puls, 2017).

Other government schemes to support the United Kingdom's investment environment for innovation and entrepreneurship are the EIS and the Seed Enterprise Investment Scheme (SEIS). These schemes are designed to encourage investments in small unquoted companies carrying on a qualifying trade in the United Kingdom and to help small, early-stage companies raise equity finance by offering tax reliefs to individual investors who purchase new shares in those companies, respectively. These schemes have helped to make the United Kingdom one of the most favourable environments for angel investing (Royal Academy of Engineering, 2015). There remain challenges such as access to debt financing; what is more, there is only a limited amount of long-term capital available. These restrictions are especially challenging for SMEs that tend to account for much of the United Kingdom's innovative activity (House of Commons Science and Technology Committee, 2013). Moving forward, the UK government Patient Capital Review will consider all aspects of the financial system affecting the provision of long-term finance to growing innovative firms and will assess what changes in government policy, if any, are needed to support the expansion of long-term capital for growing innovative firms.

PERSPECTIVES

The importance of life sciences within the United Kingdom was recognised in the 2011 'Strategy for UK Life Sciences' (BIS/11/1429, 2011). This report was transformational in the approach implemented by the United Kingdom to access and deploy emerging technologies. Since then, considerable progress has been made in the areas of radical innovation and underlying science funding as well as Innovate UK initiatives, such as the biomedical catalyst and the Catapult programme. Innovation provides the means of developing new tools and approaches to tackle major societal challenges. Innovation is also a crucial contributor to a country's growth and productivity (Rosenberg, 2004; Braunerhjelm and Henrekson, 2016; Grugulis et al., 2017; Minniti and Venturini, 2017). Government has a key role to play in encouraging innovation in priority areas, through direct investment, smarter procurement and creation of an enabling environment. To become a more innovative economy requires the ability to seize new opportunities and adapt to change. But the policies and approaches that are taken will be country specific and in part driven by the national culture (Woodside et al., 2016). In Japan, for example, the Ministry of Economy, Trade and Industry has been instrumental in driving technology innovation and adoption. More recently, however, Japan has been undergoing substantive reform to create a far more vibrant startup ecosystem, a significant transformation in a country where stability and corporate loyalty as opposed to innovation or creativity have long been the

perceived dominant social and business values (Parker, 2016). Europe's modern innovation culture by contrast is complex with no single uniform policy reflecting the differing cultures of the EU member states. Within the EU, there exist some of the leading innovation and technology support agencies, including iUK, the Fraunhofer Institutes, TEKES and TNO. There is also leadership within the European nations in the development and formulation of national innovation strategies. Where Europe has been slower to adapt is in the speed at which capital and labour have been allocated to the most promising innovative concepts in comparison for example to the United States (Ezell and Marxgut, 2015).

The United Kingdom has the advantage of a strong science base, but historically, it has not been as successful at commercialisation and development as nationally it has been at basic research. In addition, the United Kingdom has often been slower than other countries to take up and deploy existing technologies (UK Government Building Our Industrial Strategy Green Paper, 2017). Within the gene and cell therapy space, innovation offers a vital route to developing novel approaches to unmet medical needs and improving quality of life for patients. The research base within the United Kingdom remains strong, particularly in the field of cell and gene therapy development. To support the translation of these therapies into the clinic and the subsequent commercialisation, the UK government has implemented a series of forward-looking policies, strategies and organisations that create the UK business innovation environment (Fig. 25.6). Ensuring a position as a leading innovative nation requires that this landscape is constantly reviewed and adapted to an ever-changing reality. It is also important that a strong and durable entrepreneurship culture is encouraged and nurtured to realise today's potential and to incentivise young talented researchers to further enhance this ecosystem to bring to market tomorrow's radical innovation products. The development of a modern industrialisation strategy within the United Kingdom has been designed, in part to address the long-standing gap between the United Kingdom and competitor nations (UK Government Building Our Industrial Strategy Green Paper, 2017). The modern industrial strategy will seek to address three key areas: Firstly, to build on the strengths within the United Kingdom and extend excellence into the future; secondly, it seeks to close the gap between the United Kingdom's most productive companies, industries, places and people and the rest of the United Kingdom and finally, the goal of the strategy is to make the United Kingdom one of the most competitive places in the world to start or grow a business (UK Government Building Our Industrial Strategy Green Paper, 2017). The United Kingdom must continue to maintain a progressive approach to policy making, fostering interactions between industry, the NHS, academia and research funders to develop an internationally competitive cell and gene therapy industry. The first beneficial effects of the forward-looking policies implemented by various UK administrations since the early 2010s have already brought tangible economic benefits; backed up by sustained efforts, these will bring closer to reality the promises of regenerative medicine, ultimately benefitting not only patients worldwide but also the local and national economy.

REFERENCES

Accelerated access review: final report. Review of innovative medicines and medical technologies. 2016.

Aebersold P, Kasid A, Rosenberg SA. Selection of gene-marked tumor infiltrating lymphocytes from post-treatment biopsies: a case study. Hum Gene Ther 1990;1(4):373–84.

Annual report of the government chief scientific adviser. Innovation: managing risk, not avoiding it evidence and case studies. 2014.

BEIS. Industrial strategy green paper. 2017.

Benton M, Russell M. Assessing the impact of parliamentary oversight committees: the select committees in the British House of commons. Parliam Aff 2013;66(4):772–97.

BIA. Building something great: UK's global bioscience cluster. 2016. p. 2017.

https://www.nihr.ac.uk/about-us/how-we-are-managed/our-structure/infrastructure/biomedical-research-centres.htm, 2017.

BIS/11/1429. Strategy for UK life sciences. 2011.

BIS/13/1241. Encouraging a British invention revolution: Sir Andrew Witty's review of universities and growth: final report and recommendations. 2013.

BIS/13/1297. International comparative performance of the UK research base. 2013.

BIS/14/1168. Innovation: estimating the effect of UK direct public support. 2014.

BIS/15/340. What is the relationship between public and private investment in science, research and innovation. 2015.

BIS/15/352. The Dowling review of business-university research collaborations. 2015.

Blaese RM, et al. T lymphocyte-directed gene therapy for ADA-SCID: initial trial results after 4 years. Science 1995;270(5235):475–80.

Braunerhjelm P, Henrekson M. In: Audretsch DB, Link AN, editors. An innovation policy framework: bridging the gap between industrial dynamics and growth, in essays in public sector entrepreneurship. Cham: Springer International Publishing; 2016. p. 95–130.

https://www.gov.uk/government/news/business-secretary-announces-industrial-strategy-challenge-fund-investments, 2017.

Castro RJ. Mitochondrial replacement therapy: the UK and US regulatory landscapes. J Law Biosci 2016;3(3):726–35.

Cell and gene therapy catapult annual review. 2017. http://fr.zone-secure.net/5521/401487/#page=4.

Corbett MS, et al. Innovative regenerative medicines in the EU: a better future in evidence? BMC Med 2017;15(1):49.

Dechezlepretre A, et al. Do fiscal incentives increase innovation? An RDD for R&D. In: CEP discussion paper 1413. 2016.

Department For Business. Innovation and skills (BIS) and department of health (DH): taking stock of regenerative medicine in the United Kingdom. 2011.

Department of Business. Energy and industrial strategy. International Comparative performance of the UK research base. 2016.

Department of Health, Department for Business, Energy, Industrial Strategy & Office for Life Sciences. Life science sector data. 2017.

Dietzenbacher E, Los B. Externalities of R&D expenditures. Econ Syst Res 2002;14(4):407–25.

du Plessis M. The role of knowledge management in innovation. J Knowl Manag 2007;11(4):20–9.

Edler J, Fagerberg J. Innovation policy: what, why, and how. Oxf Rev Econ Pol 2017;33(1):2–23.

Eggington E, Osborn R, Kaplan C. A report commissioned by the Intellectual Property Office Collaborative research between business and universities: the Lambert toolkit 8 Years on. 2013.

https://www.epo.org/about-us/annual-reports-statistics/statistics.html.

Ezell S, Marxgut P. Comparing American and European innovation cultures. Information Technology and Innovation Foundation; 2015. p. 157–99.

Freeman G; 2017. http://westminster.georgefreeman.co.uk/content/not-end-big-pharma-end-old-pharma.

Grugulis I, Holmes C, Mayhew K. The economic and social benefits of skills. In: The Oxford handbook of skills and training. 2017. p. 372.

Hacein-Bey-Abina S, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 2008;118(9):3132–42.

Haddock R, et al. Manufacturing cell therapies: the paradigm shift in health care of this century. In: NAM perspectives. Discussion paper. Washington, DC: National Academy of Medicine; 2017. https://nam.edu/manufacturing-cell-therapies-the-paradigm-shift-in-healthcare-of-this-century.
Hettle R, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess 2017;21(7):1–204.
HM Government. Strength and Opportunity 2016: the landscape of the medical technology and biopharmaceutical sectors in the UK. 2016.
HM Treasury, The Rt Hon Philip Hammond MP. Financing growth in innovative firms: consultation response. 2017. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/661398/Patient_Capital_Review_Consultation_response_web.pdf.
HMRC. Evaluation of research and development tax credits. 2010.
HMRC. Improving access to R&D tax credits for small business: consultation summary. 2015.
House of Commons Science and Technology Committee. Bridging the valley of death: improving the commercialisation of research. 2013.
HOUSE OF LORDS Science and Technology Committee Regenerative Medicine Report. 2013.
Innovate UK. The current and future role of technology and innovation centres in the UK. 2010.
https://www.gov.uk/government/organisations/innovate-uk/about, 2017.
Bis research paper no. 226 research and innovation organisations in the UK: innovation functions and policy issues. 2016.
Jenq RR, van den Brink MR. Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer. Nat Rev Cancer 2010;10(3):213–21.
John CH, Pouder RW. Technology clusters versus industry clusters: resources, networks, and regional advantages. Growth Change 2006;37:141–71.
Kaplan S. Leading disruptive innovation. Ivey Bus J July/August 2012.
Ketels CHM, Memedovic O. From clusters to cluster-based economic development. Int J Technol Learn Innovat Dev 2008;1(3):375–92.
Le Page M. UK becomes first country to give go ahead to three-parent babies. N Sci 2016. https://www.newscientist.com/article/2116407-uk-becomes-first-country-to-give-go-ahead-to-three-parent-babies/.
McKernan R; 2017. https://innovateuk.blog.gov.uk/2017/04/19/the-uks-future-as-an-innovation-powerhouse/.
Medicine Manufacturing Industry Partnership. Advanced therapies manufacturing action plan: retaining and attracting advanced therapies manufacture in the UK. 2016.
Mesoblast. Mesoblast's Japan licensee receives pricing for TEMCELL® HS Inj. For treatment of acute graft versus host disease. 2015. https://globenewswire.com/news-release/2015/11/27/790909/0/en/Mesoblast-s-Japan-Licensee-Receives-Pricing-for-TEMCELL-HS-Inj-for-Treatment-of-Acute-Graft-Versus-Host-Disease.html.
Minniti A, Venturini F. The long-run growth effects of R&D policy. Res Pol 2017;46(1):316–26.
https://www.gov.uk/guidance/model-agreements-for-collaborative-research, 2017.
National Institute for Health and Care Excellence. Evaluation consultation document: Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. 2017.
O'Connor GC, McDermott CM. The human side of radical innovation. J Eng Technol Manage 2004;21:11–30.
OECD. Supporting investment in knowledge capital. Growth and Innovation; 2013.
OECD. Organization for economic cooperation and development regulatory policy outlook. OECD Publishing; 2015. https://doi.org/10.1787/9789264238770-en.
OECD. Triadic patent families (indicator). 2017. https://doi.org/10.1787/6a8d10f4-en.
OECD. FDI stocks (indicator). 2017. https://doi.org/10.1787/80eca1f9-en.
OECD. Gross domestic spending on R&D (indicator). 2017. https://doi.org/10.1787/d8b068b4-en.
Office for Life Sciences. Life sciences: industrial strategy. 2017. https://www.gov.uk/government/publications/life-sciences-industrial-strategy.
Oxford Economics. The impact of the Innovation, research and technology sector on the UK economy. 2014.

Parker CB. Japan transforming its innovation culture by changing social norms. Stanford News 2016.
Rogers EM, Shoemaker FF. Communication of innovation: a cross cultural approach. New York: The Free Press; 1971. p. 476.
Rosenberg N. Innovation and economic growth. OECD; 2004.
Royal Academy of Engineering. Investing in Innovation. 2015.
Sagonowsky E. With its launch fizzling out. 2017. UniQure gives up on $1M+ gene therapy Glybera https://www.fiercepharma.com/pharma/uniqure-gives-up-1m-gene-therapy-glybera.
Schuhmacher A, Gassmann O, Hinder M. Changing R&D models in research-based pharmaceutical companies. J Transl Med 2016;14(1):105.
https://www.gov.uk/government/news/sir-john-bell-to-unveil-industry-led-proposals-to-build-uks-status-as-world-leader-in-life-sciences, 2017.
https://www.nihr.ac.uk/about-us/CCF/policy-and-standards/standard-research-agreements.htm, 2017.
Staton T. GSK inks money-back guarantee on $665K Strimvelis, blazing a trail for gene-therapy pricing. 2016. https://www.fiercepharma.com/pharma/gsk-inks-money-back-guarantee-665k-strimvelis-blazing-a-trail-for-gene-therapy-pricing.
Technology Strategy Board. Medicines and healthcare strategy 2009–2012. 2009.
UK government building our industrial strategy green paper 2017. 2017. https://beisgovuk.citizenspace.com/strategy/industrial-strategy/supporting_documents/buildingourindustrialstrategygreenpaper.pdf.
UK government charities act. 2011.
https://www.ukrmp.org.uk/2017/03/future-of-regenerative-medicine-looks-bright-with-new-funding-boost/, 2017.
http://www.ukrmp.org.uk/, 2017.
Wijngaarde Y, Puls J. 2016 European venture capital report. 2017. https://blog.dealroom.co/wp-content/uploads/2017/01/2016-European-Venture-Capital-Report.pdf.
Woodside AG, Bernal PM, Coduras A. The general theory of culture, entrepreneurship, innovation, and quality-of-life: comparing nurturing versus thwarting enterprise start-ups in BRIC, Denmark, Germany, and the United States. Ind Market Manag 2016;53:136–59.
Written evidence submitted by innovate UK to the House of commons select committee 2016 regenerative medicine inquiry. 2016. http://data.parliament.uk/WrittenEvidence/CommitteeEvidence.svc/EvidenceDocument/Science%20and%20Technology/Regenerative%20medicine/written/33920.html.