London as a test bed for innovative models of finance – maximising the economic impact of life sciences research and development

Contents

1. Introduction and Objectives

This paper aims to stimulate debate around the levels of risk undertaken and carried by different parties in funding drug discovery and development. The aim is to position London as a test bed for innovative funding models that will lead to a step change in future investment. Whilst it is critical to place London within the context of its position in the wider cluster of the greater south east of England – and indeed within the UK as a whole – given functional economic linkages, this initial discussion paper focuses on London as a starting point.

Life sciences are a priority area for the Mayor of London, who in April 2014 launched MedCity. The MedCity vision is for London and the Greater South East to be a world leading, interconnected region for life science research, development and commercialisation – delivering health improvements and economic growth. The Mayor is providing £1.125m funding for MedCity over three years.

Advances in genetics and cell biology in the last ten years have opened up opportunities for new drug discovery and development which are unprecedented and reflected in the huge increase in venture investment in the USA. However, Europe has failed to engage fully in this opportunity.

Whilst there has recently been a positive upswing, there remain structural problems in life sciences investment in the UK. There are particular challenges in accessing finance at certain stages of development, including taking promising late-stage research into clinical development, and for Phase 3 trials and beyond.

The need for more long-term, patient capital invested in drug discovery and development in the UK is well documented. More needs to be done to encourage large pools of capital to fund sufficient opportunities in our life sciences sector, to enable some of those opportunities to become successful treatments for patients and to grow successful companies.

Action is required to encourage investment at earlier stages, when a potential product is further from market. At the same time, more patient investment is required. Early investment with a view to a quick exit makes it more difficult to grow companies. It is well known that the UK lacks a tier of mid-sized life sciences companies, in part due to the historically more favourable funding environment in the US, which is attractive for European SMEs.

Increasing access to longer term, more patient finance, and incentivising the development of more innovative business models (including through opening up pre-competitive space and data sharing), could reasonably be expected to deliver economic growth (through the establishment and growth of life science companies) and health benefits (by getting more innovative treatments to market more quickly) for London, and globally.

Drug discovery and development present a high risk for all parties – life sciences companies and investors, as well as policy makers and payers. This risk is due to a number of interlinked factors including the length of time and cost of bringing a new medicine to market, and the high attrition rates for new development stage products. These factors also result in the high cost of new medicines and treatments when they reach the market.

Furthermore, whilst scientific advances increase the potential for health benefits, they also raise uncertainty in terms of product development and regulation. The life sciences sector itself is evolving rapidly, with new approaches to medicine and healthcare necessitating changing business models and increasing uncertainty.

All of these factors are set against the context of a straitened economic and public policy environment with rising pressures on healthcare budgets.

The challenges faced by the life sciences sector have encouraged new approaches such as partnerships, collaborations and alliances, and have led to new R&D funding arrangements being explored. If we are to encourage the provision of sufficient patient capital with a long-term horizon, to support future development of new medicines, mechanisms are required to reduce the risk for all parties. The risk-return dynamic needs to be shifted, primarily for industry and investors, but also for policy makers, payers and regulators.

2. The Challenges

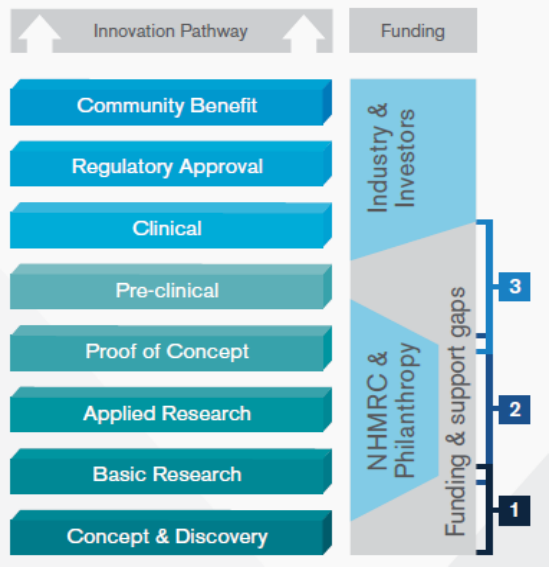
2.1 Insufficient patient capital – structural problems with UK life sciences investment

There are a number of structural issues in terms of access to finance during the drug discovery and development process, including particular challenges for pre-commercialisation activities, in the period of taking promising late-stage research into pre-clinical development and proof of concept clinical trials (Phase 1/2), and for Phase 3 trials and beyond. It is recognised that there will be different barriers at each stage of development.

At the transition phase between promising academic or SME laboratory breakthroughs and the validation of a compound's commercial viability, there is a challenging funding environment. Although many investors may not wish to invest so early in the pipeline, avoiding it leads to a diminished pool of strong future investment opportunities, and, on a larger scale, limits how many compounds will successfully make it to market. For investors who are prepared to invest at an early stage, the high risk associated with testing the feasibility of a product so early in the pipeline naturally places it far from an exit, which is unattractive for short-term capital focused on a quick exit. Trade sales are the most typical exit, but they make it harder to grow companies.

The UK life sciences funding environment has recently improved, with record levels of venture capital (VC) investment in life sciences in 2014,[1] and the return of IPOs (although public markets are not providing growth capital – the cost of Phase 3 trials is too high for venture investors). There is also considerable interest from large pharmaceutical companies in strategic alliances as they seek innovation from bioscience firms. However, more needs to be done to encourage large pools of capital – particularly venture capital but also institutional investors, including pension funds – to invest in this area and from an early stage, with a long-term horizon.

Figure 1 – Funding and support gaps[2]



Key to funding and support gaps:
- 3 – 'valley of death'
- 2 – advancing research and validating directions
- 1 – innovation and discovery

[1] MedCity, 'UK life sciences 'comes of age' with 41% leap in investment http://www.medcitylondon.com/news/uk-life-sciences-comes-age-41-leap-investment/

[2] Figure from National Foundation for Medical Research and Innovation (Australia), 'Impact giving – Advancing medical innovations' http://www.nfmri.org.au/wp-content/uploads/2013/10/NFMRI-Impact-giving.pdf

The life sciences membership organisation Oxford Bioscience Network (OBN) referred to the 'challenges of early commercial translation – the infamous 'valley of death'' in an open letter to the Minister for Life Sciences in March 2015, calling for additional efforts to enhance the investment environment for life sciences SMEs in the UK.[3]

The BioIndustry Association (BIA) has described a 'valley of death' as 'the period between late stage discovery to pre-clinical and Phase 1 clinical development. This includes such steps as candidate selection, optimization, good manufacturing practice (GMP) and toxicology testing.'[4]

In April 2015, the BIA identified particular gaps as being the high pre-clinical GMP costs for biologics (in the region of £2m – around five times more than for simple small molecules) and a 'Phase II funding gap for "true clinical proof of concept"', [5] explaining that:

> 'It is possible to get to about Phase IIa today in the UK using a combination of funding sources and some creativity. However, that is often not enough to convince sceptical industry buyers (especially on novel technologies / unvalidated targets), who often want a randomised, phase IIb trial costing tens of millions before investing.'[5]

Furthermore, United Life Sciences – the partnership of UK life science organisations – has noted that VC investment, which would previously have supported Phase 2 and Phase 3 clinical trials, 'has been reduced since the financial crisis of 2008."[6] The BIA has also stated that "late stage funding is shallow relative to the US.'[5]

However, the majority of UK bioscience companies are pre-revenue SMEs,[6] so accessing finance is critical to their being able to bring new products to market. More could be done to support them.

Data published in March 2015 showed that, whilst life sciences companies in the UK secured $883m of venture financing in 2014, only 12.2 per cent was directed for 'enterprise-size financing rounds' below $5m.[7] OBN argues that 'the relatively small proportion raised for enterprise financing rounds strongly supports the case for continued financing mechanisms to support innovative R&D firms through the equity gap, such as the Biomedical Catalyst.'[7]

Whilst initiatives aimed at addressing funding challenges have been positive, they have not addressed the risk-reward profile of investing in drug discovery and development, or encouraged the provision of sufficient patient capital with a long-term horizon.

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[3] OBN, 'An Open Letter Enhancing the Investment Environment for the UK's Life Sciences SME Sector', 16 March 2015

[4] BIA written evidence to 2012/13 House of Commons Select Committee inquiry 'Bridging the "valley of death": improving the commercialisation of research'. The BIA also noted that that there will be funding and other challenges at various stages of companies' development, which is particular to individual companies, and that the 'valley of death' should be considered a loose definition.

[5] BIA, 'A vision for the UK life sciences sector in 2025', April 2015

[6] United Life Sciences, 'UK Life Sciences Manifesto 2015-20', October 2014

[7] OBN, 'UK Life Sciences Industry Sees Resurgent Financing Year', 16 March 2015. Companies in the Oxford cluster secured $221m venture financing, those in London $147m and companies in the Cambridge cluster $131m. Research by BioTrinity and Peel Hunt.

2.2 Drug discovery and development – a high risk for all parties

The process of drug discovery and development is characterised by uncertainty. It is therefore perceived as high-risk – primarily from the perspective of companies and investors, but also stakeholders such as regulators and healthcare payers. Bringing a new medicine to market is high-cost and time-intensive, and attrition rates for potential new products are high.

Furthermore, medical and technological progress is being made at unprecedented speed, and the life sciences sector is evolving, with business models changing to adapt to new technologies and approaches such as big data, stratified medicine, genomics and digital health. While scientific advances offer increased potential for patient benefit, increased technological and scientific complexity also increases uncertainty in terms of how new treatments are developed and regulated.

The uncertainty of drug discovery and development is set against an economic and public policy backdrop that further heightens the perception of risk, with healthcare budgets under severe pressure. Uncertainty as to whether a new medicine will be reimbursable presents an additional risk for companies and investors.

How can the risk-reward profile be changed for investment in drug discovery and development, to increase appetite for risk and encourage increased investment of long-term patient capital – for both economic and health benefits?

How can pharmaceutical companies be better incentivised to spread their R&D spend by 'transferring' some of the risk and capital need on existing R&D portfolios?

Time, cost and failure – the difficulties of commercialising research

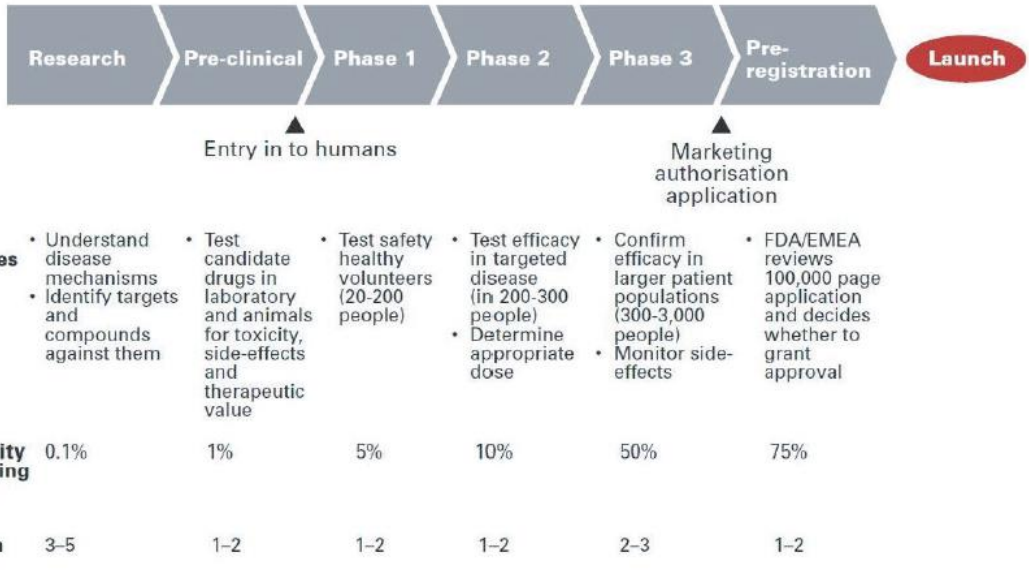
It takes on average 10 to 15 years to develop a new medicine and take it to market.[4] The cost of doing so has been variously estimated from around $1 billion on average[4] to $2.6bn, including the costs of pipeline failures.[8] It has been estimated that for every $5 gained through launching a new drug, $2 are lost through failure.[9] It often costs up to £15m and above to reach Phase 2 clinical trial results, and a further £20m to reach small Phase 3 trial results.[6]

By comparison, the costs of bringing a new product to market are lower in other innovative sectors, such as around £4m in IT and communications technologies.[10]

Furthermore, the attrition rates of new compounds are high. For example, at preclinical stage compounds have a 1 per cent chance of reaching the market, as illustrated in the figure below[11] – although the odds may be better for biologics. It has also been suggested that the likelihood of a new molecule progressing through clinical testing has declined due to higher hurdles, for example to satisfy regulators and demonstrate value.[12] At each stage, investors have to weigh the probability of success against financial cost.

[8] ABPI, 'Reengineering Medicines Development', 2015
[9] Deloitte, 'Measuring the return from pharmaceutical innovation 2014 – Turning a corner?', 2014 (report on a cohort of 12 of the leading life science companies)
[10] Cooksey, 2006, cited in ABPI, 'The many faces of innovation', March 2012
[11] Figure from BIA written evidence to the 2012/13 House of Commons Select Committee inquiry on 'Bridging the "valley of death": improving the commercialisation of research' ('Bioscience 2015' cited)
[12] 'Success rates dropped from 22% in 1983–1994 to 13% in 1997–2007; the decline varies by type of molecule and disease area (Mestre-Ferrandiz, Sussex and Towse, 2012). Some analyses, using different data

Figure 2 – The drug discovery and development timeline[11]



Stage objectives	• Understand disease mechanisms • Identify targets and compounds against them	• Test candidate drugs in laboratory and animals for toxicity, side-effects and therapeutic value	• Test safety healthy volunteers (20-200 people)	• Test efficacy in targeted disease (in 200-300 people) • Determine appropriate dose	• Confirm efficacy in larger patient populations (300-3,000 people) • Monitor side-effects	• FDA/EMEA reviews 100,000 page application and decides whether to grant approval
Probability of reaching launch*	0.1%	1%	5%	10%	50%	75%
Duration (Years)	3–5	1–2	1–2	1–2	2–3	1–2

Drug discovery and development is therefore a riskier prospect for investors than other sectors due to the timeframes, high costs involved and the risk of failure, not to mention the technical uncertainties and regulatory hurdles for newer technologies in particular.

As the Wellcome Trust has explained, 'Transforming a promising research discovery into a viable product may take 10-15 years, with significant and sustained capital investment required over that period. Such opportunities are seldom attractive to venture capital and angel investors, who typically look for a return in five to seven years.'[13]

As a result of the typical investor timeline, investors may not be willing to invest in early stage drug development. At the same time, the high cost of later stages – Phase 3 trials – may not be affordable for VC investors.

Whilst listings by European life sciences companies have taken place on both sides of the Atlantic in 2015 – and several US health/life sciences companies have listed in London recently – it is often observed that venture capitalists in the UK and Europe have a lower appetite for risk than their US counterparts. EY's 2014 biotechnology industry report, 'Beyond Borders', highlighted the under-capitalisation of private European companies compared to their counterparts in the USA, 'as lower appetite for risk meant VCs and public equity committed fewer dollars to these earlier-stage players.'[14] More generally, the Association for Financial Markets in Europe has noted the "greater appetite for risk in US business culture, alongside larger pools of capital".[15]

Other technology sectors that are closer to the market – offering the potential for a quicker return on investment – or are perceived as lower risk, may therefore be seen as more attractive.

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sources and methods, suggest that success rates have continued to erode to as low as 5.5% in 2010 (Evers et al, 2012). Mene Pangalos in Office of Health Economics, 'The Challenges and Economics of Drug discovery and development in 2022', 2013

[13] Wellcome Trust written evidence, in House of Commons Science and Technology Committee, 'Bridging the valley of death: improving the commercialisation of research, Eighth Report of Session 2012–13', March 2013

[14] EY, 'Beyond Borders – Unlocking value', 2014

[15] Association for Financial Markets in Europe (AFME), 'Bridging the growth gap', February 2015

Furthermore, the increasing focus of reimbursement systems on the value of biotechnology products is seeing companies accepting more risk in exchange for market access. In part as a result of pressure from payers, "strategic partners have focused on "derisked" assets and deals that include contingency-based payments."[14]

Increased complexity = increased uncertainty

As the life sciences sector evolves to embrace new, more complex technologies and scientific approaches, the uncertainty of drug discovery and development increases.

The Wellcome Trust has highlighted the example of the European Court of Justice decision that products derived from human embryonic stem cells cannot be patented. Whilst 'in theory there are other mechanisms to protect the associated intellectual property, in practice investors are unlikely to invest in the development of such technologies within Europe unless there is much greater certainty that a successful product will result.'[13]

To take molecular biomarkers for diseases as an example of a scientific advance, whilst there is potential for patient benefit, at the same time developing a host of new potential treatments will require significant time and investment, with a high risk of failure. Such complexity 'presents an enormous number of uncertain prospects that must be triaged by researchers, biopharma business executives, investors, policymakers and regulators.'[16]

A shift has been reported in the industry's research and development focus towards complex therapeutic areas – such as Alzheimer's, rare diseases and cancers with multiple genotypes – with unmet medical need.[17] The complexity of such therapeutic areas means that they have a potentially high return but are also high risk. As summarised by Deloitte:

> 'Big bets in bold new areas are fraught with complexity and uncertainty, while success in mature therapeutic areas is becoming increasingly difficult. As the industry continues to shift toward novel scientific approaches and areas of unmet medical need, the risk profile of R&D investments will continue to increase.'[17]

The BIA has pointed to a funding gap for 'high commercial risk' Phase 2 studies, including tropical diseases and vaccines, but also '"high attrition risk" disease areas like novel drug targets'.[5]

Neuroscience has been highlighted as a complex area where some pharmaceutical companies are decreasing expenditure. The high risk of investment in neurodegenerative research, the particularly high cost of research and longer-than average clinical trials have all been given as reasons.[18,19] Meanwhile, Professor Paul Workman, Chief Executive and President of the Institute of Cancer Research, has signed a World Oncology Forum consensus statement calling for government incentives for pharmaceutical companies to take the risks needed to create innovative new treatments for cancer.[20]

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[16] Fernandez, Stein, Lo, 'Commercializing biomedical research through securitization techniques', Nature Biotechnology, Vol. 30, No. 10, October 2012

[17] Deloitte, 'In the face of uncertainty: a challenging future for biopharmaceutical innovation', 2014

[18] Choi, D et al, 2014, cited in 'Academic drug discovery: a UK alliance of dementia Drug Discovery Institutes', a guest blog by Dr Simon Ridley, Alzheimer's UK, http://blog.bioindustry.org/

[19] Kaitin, Milne, 'Drugs to treat neuropsychiatric disorders have become too risky for Big Pharma', Scientific American, 13 July 2011

[20] Professor Paul Workman, 'Fixing what's broken: why companies must prioritise innovation in drug development', Pharmafile, 9 March 2015

3. The Opportunity

3.1 London's strengths in drug discovery and development

Table 1 below sets out a number of examples of companies originating from London's research base, illustrating the potential market opportunities presented by the Capital's drug discovery and development pipeline. Annex 3 focuses on the opportunities presented by London in just one area – cell therapy.

Table 2 – London drug discovery and development pipeline – examples[21]

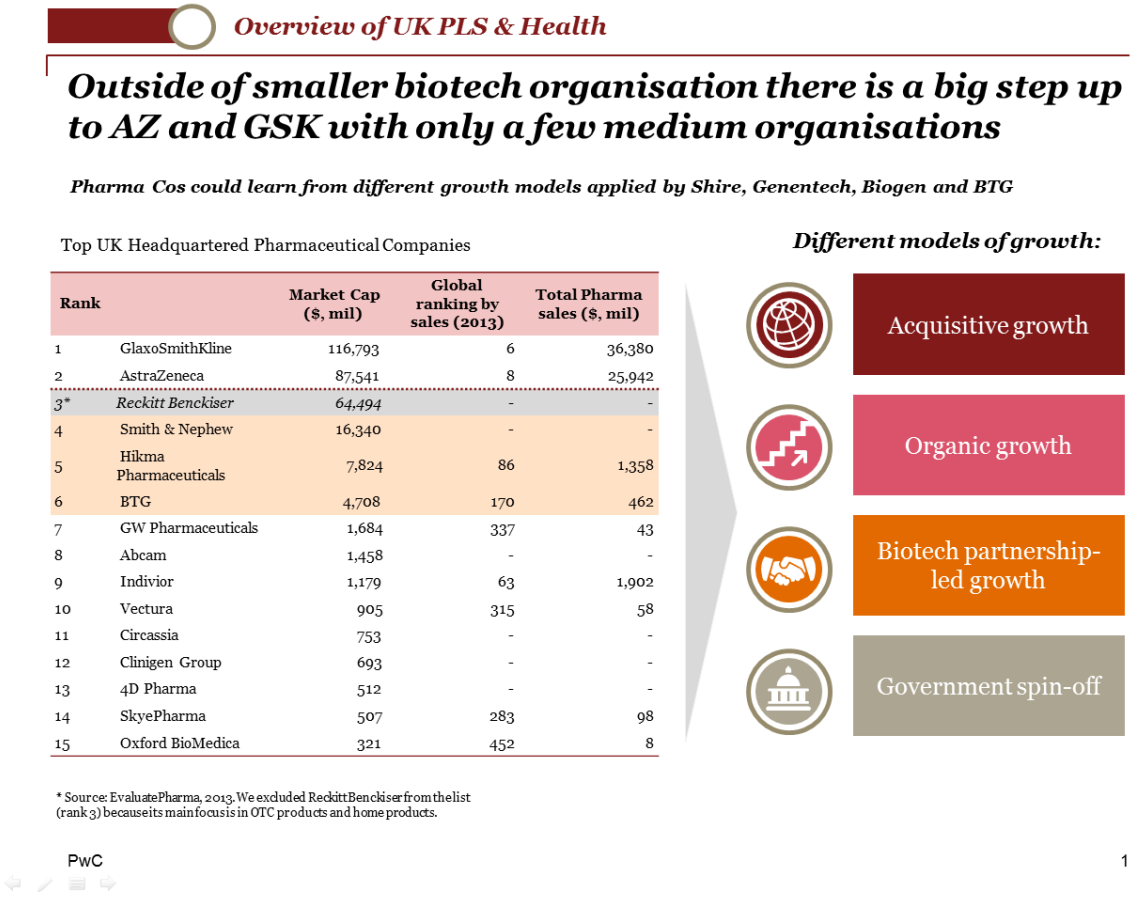
Company	Origin	Description	Data on Progress
Canbex	UCL	Small molecule for treatment of spasticity in MS	Starting Phase 2
Domainex	UCL/ICR/Birkbeck	Contracting Business chemical and protein and own programs	Preclinical
Abzena	School of Pharmacy	Contracting Business antibodies and half-life extension	
Retroscreen	Queen Mary	Clinical trials anti-virals	
Stanmore Implants	UCL	Implant	In use
Respivert	Imperial	Small molecule for COPD - acquired by Johnson and Johnson	Preclinical
Circassia	Imperial	Peptides for allergy treatment	Several in Phase 2 and 3
Spirogen	School of Pharmacy	Antibody-drug conjugates - acquired by AstraZeneca	Preclinical
Arrow	UCL	Small molecule for hepatitis and RSV - acquired by AstraZeneca	Phase 1and 2
Piramed	ICR	Small molecule -oncology - acquired by Roche	Phase 1
Thiakis	Imperial	Peptides for obesity - acquired by Pfizer	Phase 1

Case study: Canbex
The biotechnology company Canbex illustrates the use of alternative capital sources to allow project development. Canbex was funded in London by Bloomsbury BioSeed Fund (BBSF – a university Challenge fund) and Esperante (a small VC), along with the Wellcome Trust. Later funding came from the Fast Forward fund of the US Multiple Sclerosis society and again from UCL Business Plc and the Wellcome Trust. Canbex obtained an Innovate UK grant to support the Phase 1 trial. MS Ventures (the corporate venture arm of Merck KGaA) joined the project as the compound was ready for the clinic. In early 2015 Canbex announced an option deal with Ipsen Pharmaceuticals UK to develop the project post-Phase 2.

[21] Information in table from personal data supplied by Keith Powell, Member of London Enterprise Panel's Digital Creative, Science and Technology Working Group

There is a significant opportunity to enable more projects and SMEs to get started in London from our world-class science base, in order to develop the industry and create career pathways for scientists in the UK. Patient investment is required to grow more companies into global success stories. As the BIA has indicated, partly due to public equity market challenges, the lack of a 'middle tier' of mid-sized companies in the UK makes effective translation harder than elsewhere.[5] Figure 3 below illustrates the opportunity to grow more medium-sized life science companies in the UK.

Figure 3 – Mid-sized life science companies[22]



Overview of UK PLS & Health

Outside of smaller biotech organisation there is a big step up to AZ and GSK with only a few medium organisations

Pharma Cos could learn from different growth models applied by Shire, Genentech, Biogen and BTG

Top UK Headquartered Pharmaceutical Companies

Rank		Market Cap ($, mil)	Global ranking by sales (2013)	Total Pharma sales ($, mil)
1	GlaxoSmithKline	116,793	6	36,380
2	AstraZeneca	87,541	8	25,942
*3**	*Reckitt Benckiser*	*64,494*	-	-
4	Smith & Nephew	16,340	-	-
5	Hikma Pharmaceuticals	7,824	86	1,358
6	BTG	4,708	170	462
7	GW Pharmaceuticals	1,684	337	43
8	Abcam	1,458	-	-
9	Indivior	1,179	63	1,902
10	Vectura	905	315	58
11	Circassia	753	-	-
12	Clinigen Group	693	-	-
13	4D Pharma	512	-	-
14	SkyePharma	507	283	98
15	Oxford BioMedica	321	452	8

* Source: EvaluatePharma, 2013. We excluded Reckitt Benckiser from the list (rank 3) because its main focus is in OTC products and home products.

Different models of growth:

Acquisitive growth

Organic growth

Biotech partnership-led growth

Government spin-off

PwC

1

3.2 London's innovation ecosystem

London is a highly successful world city, with an extremely rich asset base for technology based business formation and growth, well endowed as a place for disruptive and innovative business activity. London offers one of the most competitive business environments globally to start a business, London's global connectivity and its role as a cultural and creative hub, mean bright young people want to live and work here, giving scale and depth to London's labour market. The Mayor of London has launched a long-term infrastructure investment plan for the capital to support future growth, and is investing in regeneration across London. (See Annex 2 for further information on London's innovation ecosystem.)

[22] Slide courtesy of PwC

London may provide an outstanding ecosystem for the formation of science and technology businesses and offer – and generate – substantial clustering and agglomeration benefits. However growing a business is more difficult – particularly one which requires long timescales, and large investment. This is reflected in London's less impressive track record in the commercialisation of research (see figures on bioscience commercialisation indicators in Annex 2).

This paper aims to unlock this growth potential through stimulating new thinking and creating momentum around the need for new approaches to encourage more patient investment in London's science and technology research base, positioning London as a test bed for new models.

London has always been at the forefront of financial innovation, most recently driven by technological innovations that are changing the way the world does business. The proximity of London's world-class financial services infrastructure to London's booming tech industry has driven innovation across mobile payments, retail banking and crowdfunding, for example. What would it take for London to play a more fundamental role in the global order and shake the foundations of traditional drug discovery and development funding models?

4. Innovative Funding Models

The Greater London Authority aims to stimulate new thinking and create momentum around the need for new approaches to encourage the provision of sufficient patient capital, to support future development of new medicines.

A number of funding models are outlined below. How can we learn from existing models in order to fundamentally change the approach to risk in drug discovery and development?

Megafund – Could a 'megafund' – a c. £200m-£10bn investment fund, created using a mix of debt and equity finance – help to finance earlier stage drug discovery and development? A fund of that scale would be able to simultaneously invest in multiple different drugs at different stages of development. By accumulating many varied drug discovery and development projects in a single investment portfolio, the aggregate risk would be reduced, and one or two successful shots on goal would more than compensate for the failure of the remainder.

The megafund idea is based on the principle that the money is available to fund earlier stage drug discovery and development, what does not yet exist is the appropriate vehicle. This vehicle would bring together investors who would not normally invest in biomedical research and drug discovery and development, and in return they would have a percentage of the royalties from successful drugs or licensing revenues that result. The fund would invest in different stages of drug development, including earlier and riskier stages, but spread the risk via compound and stage diversification. Megafunds are designed using techniques found elsewhere in finance – including securitising future revenues, in this case from drug compound licenses, into debts called 'research-backed obligations' (RBOs). Because RBOs are structured as bonds, they can be designed to appeal to fixed income investors (such as pension funds and sovereign wealth funds), who collectively represent a much larger pool of capital than venture capitalists. The main source of cash flow is from the sale of compounds from the portfolio at different stages of their development – profits or losses accrue when the fund purchases a compound in one phase and sells it to another phase. The cash flows from the assets are used to repay the debt and all residual value after the debt is paid goes to the equity holders.

Simulation results

Several simulation studies have been conducted to show how the megafund concept could work. Using a hybrid capital structure, and investing across the full spectrum of drug development, securitised debt can be used to finance the later stage assets and various forms of convertible bonds, and equity to finance earlier stage assets. Fernandez et al (2012) and Fagnan et al (2014) consider an RBO structure consisting of a senior tranche, a mezzanine tranche, and an equity tranche. Because of the complexities of the waterfall and the drug approval process numerical simulations are used to evaluate the financial performance of the RBO securities. Overall results show that a rare disease megafund could achieve average annualised returns for the equity investors from 12-15 per cent depending on the capital structure, with significantly higher IRRs (internal rates of return). Additionally, the provision of a financial guarantee for the debt holders can increase clinical impact per dollar of equity, increase the return on the equity and the fundraising potential for the debt. The potential impact of adding guaranteed debt to an all equity model doubles the returns.

The simulations (conducted on both rare disease and cancer) show how these structures can, in principle, provide attractive returns for debt and equity investors, while at the same time providing a bridge for translational research in the drug approval process. The specific

components of the hybrid structure, however, will depend on the statistical properties of the projects in the portfolio.

It is suggested here that, based on the evidence gathered so far, the megafund model could be piloted in rare diseases where a smaller funding pot (c. £200-300m) may be required - due to the shorter times to market, higher success rates, and accelerated approval times. Nevertheless, an independent feasibility study is required to validate this, assess London's drug discovery and development pipeline, and identify where the fund would have maximum impact.

Further information on the megafund model:
http://www.argentumlux.org/documents/Can_Financial_Engineering_Cure_Cancer.pdf
http://www.argentumlux.org/documents/FAQRBO_final2.pdf

EIB R&D risk-sharing instrument – As part of the InnovFin 'EU Finance for Innovators' programme set up jointly by the European Commission and the European Investment Bank (EIB) Group, "InnovFin Large Projects" is a scheme to improve access to finance for research and innovation projects in the EU. Over the next seven years it is expected that InnovFin products will make available more than €24bn of financing for investment in research and innovation up to 2020.

Within this scheme, in June 2014 the EIB signed an agreement with a biotech firm to provide 'at-risk development funding' of up to €75m for the development of selected compounds in areas such as neurology and immunology. It is anticipated that the EIB will directly invest in the company's R&D expenditures over a specified timeframe. The EIB will receive payments if and when predefined milestone events are successfully achieved, for example regulatory approval.

Woodford Patient Capital Trust – The Woodford Patient Capital Trust raised £800m during its offer period, making it the largest ever investment trust launch in the UK.[23] It has been reported that the fund 'will invest in early-growth companies, typically quoted; and quoted and unquoted early-stage companies, many of which are expected to have a significant exposure to medical science.'[24] Neil Woodford has a track record of investing in life sciences.

MRC Technology Neuro-MAP – Medical Research Council Technology's (MRCT) Neuro-Medicines Acceleration Programme (Neuro-MAP) consists of a consortium of UK and US neuroscience research charities, including the Alzheimer's Society, Alzheimer's Association, Michael .J. Fox Foundation, Parkinsons UK, MDA Association, Alzheimer's Research UK and ALS Association. It seeks to progress industry medicines that have been deprioritised for non-scientific reasons to a point where they become attractive for investment and further development.

As an independent organisation, MRCT brings together the neuroscience charities, academia, and pharmaceutical companies into a process. Charities agree to fund deprioritised assets and the pharma companies agree to share their Intellectual Property (IP) with MRCT. MRCT then invites applications from industrial partners and conducts necessary due diligence, the charities select projects to invest in and private leverage funding is sought, for example from the Wellcome Trust, MRCT subsequently manages the development of the assets until they can be returned to the pharmaceutical company with full rights at a point when it is commercially attractive for them to invest again. The IP owner shares a small proportion of future revenue with the consortium but if it deprioritises the project after the process is completed, the rights

[23] Investors Chronicle, 'Woodford Patient Capital to start trading', 20 April 2014
[24] Investors Chronicle, 'Woodford Patient Capital Trust reveals first investment' 22 April 2015

to licence the asset pass back to the consortium to maximise the potential of new therapies reaching patients. Neuro-MAP is being rolled out during 2015 but is an ongoing process. http://www.medicinesaccelerationprogram.org/

CRT Pioneer Fund – Managed by Sixth Element Capital, the CRT Pioneer Fund is a £50m investment fund established by Cancer Research Technology (CRT) and the European Investment Fund, with the aim of bridging 'the investment gap between cancer drug discovery and early development.' The fund 'will take potential cancer drugs, primarily discovered by Cancer Research UK, from discovery through to entry to Phase II clinical trials before partnering with pharmaceutical and biotechnology companies.'[25]

Syncona Partners - charitable equity model – Syncona Partners is an independent healthcare investment company founded by the Wellcome Trust in 2012 with a £200m initial investment. Syncona operate as an evergreen investor in healthcare products (devices, therapeutics, diagnostics, IT), services and business models.

Operating globally, Syncona Partners makes capital investments usually in the range of £1m to £20m per company, early or late stage, as a majority investor or as part of a syndicate.[26] Sycona takes an active role in identifying, supporting and developing technologies, with the potential to significantly impact the healthcare market of the future,[27] focusing on healthcare companies with defendable technology or transformational business models.[26]

Syncona's approach is to take 'a long-term view towards the creation of sustainable healthcare businesses', and their ultimate aim is 'to hold investments in a small number of significant profitable businesses that have transformed their healthcare markets.'[26]

Further examples of initiatives aimed at bridging funding gaps are outlined in Annex 1.

[25] http://sixthelementcapital.com/funds.php
[26] http://www.synconapartners.com/strategy/
[27] http://www.synconapartners.com/about/

5. Conclusion and Next Steps

This paper has set out some of the barriers innovative companies are facing in commercialising drug discovery, and provided some inspiration from emerging models that are being tried and tested to challenge the traditional risk-reward profile.

There is a need to think creatively beyond London's boundaries. There are natural synergies to be exploited across the Golden Triangle, with links to Cambridge and Oxford and across the Greater South East. Moreover, through leveraging the expertise and lending capacity of the European Investment Bank, London would be perfectly placed to manage a new type of drug discovery and development fund at scale for Europe.

Increasing access to longer term capital would drive a life sciences community that brings innovative therapies to patients, with consequent healthcare and economic benefits – for London, and globally.

Life sciences are a key priority for the Mayor of London. We would like to position London as a test bed for new innovative funding models. The aim of this paper to stimulate discussion in order to bring us closer to that path.

Annex 1 – Funding Initiatives

A number of funding initiatives/sources play a role in bridging the commercialisation funding gap, such as those outlined below (NB this is not an exhaustive list). However, there is room for opportunities offering risk capital that better matches the scale, level and timeline needed for drug development in London/the Greater South East.

- **BioMedical Catalyst** – a funding programme jointly operated by the Medical Research Council and Innovate UK providing support for translational life science opportunities in the UK. UK academics and SMEs can apply for grant to help move their research more quickly from discovery to commercialisation.[28] By June 2014 more than 130 business-led projects had received over £99m funding through the Catalyst, with additional match-funding leveraged.[6]

- **The London Co-Investment Fund** – will invest over £80m from 2014 to 2017 in over 150 science, technology or digital companies based in London and committed to creating jobs in London. £25m has been raised from the Mayor of London's Growing Places Fund to co-invest in seed rounds between £250,000-£1m, led by selected co-investment partners.[29]

- **Pharmaceutical company investment arms** – a number of pharmaceutical companies have created corporate venture investment arms.

- **University innovation funds** – for example, Imperial Innovations is a technology commercialisation company focused on commercialising academic research in sectors including therapeutics and medtech, from Imperial, UCL and the Universities of Oxford and Cambridge. Oxford Sciences Innovation plc was launched in May 2015 – a £300m partnership between the University of Oxford and Isis Innovation, aimed at commercialising ideas and developing companies from the university's scientific research.[30]

- **University of Oxford/Harrington Project** – launched in November 2014, the Harrington Project for Discovery and Development is a $250m US/UK initiative to provide support to physician-scientists for preclinical drug research and early-stage clinical trials. BioMotiv is an accelerator associated with the project, focused on accelerating breakthrough discoveries from research institutions into therapeutics. BioMotiv 'is advancing a portfolio of discoveries into new medicines through an innovative model that efficiently aligns capital and collaborations for the benefit of inventors and investors, and ultimately physicians and patients.'[31]

- **Oxford Invention Fund** – aims to utilise donations to 'fill the gap between current funding support for research and infrastructure in the University and investment from industry and the finance sector, and enable the progression of the most exciting innovations from all departments within the University.' The fund is intended 'to fill the financial gap between basic research and commercialisation of inventions', and the typical investment size is expected to be in the range of £10,000-£250,000.[32]

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[28] http://www.mrc.ac.uk/funding/science-areas/translation/biomedical-catalyst/
[29] www.lcif.co
[30] http://isis-innovation.com/launch-of-300m-partnership-to-boost-development-of-science-and-technology-businesses/
[31] http://www.biomotiv.com/About_Us/Company
[32] http://www.isis-innovation.com/wp-content/uploads/2014/04/OxfordInventionFund.pdf

- **Wellcome Trust Seeding Drug Discovery** – non-dilutive funding for small molecule R&D by institutions and companies in areas of unmet medical need. Early-stage awards provide two years of funding to support the screening of compounds, whilst late-stage awards provide funding for up to four years, to support lead optimisation and preclinical development through to clinical trials.[33]

- **Global AMR fund** – Jim O'Neill's Review on Antimicrobial Resistance has called for a $2bn global antimicrobial resistance (AMR) Innovation Fund to increase investment in early stage research into drugs and diagnostics, and 'jump-start a new innovation cycle in antibiotics'.[34] Currently, there is a limited commercial incentive for companies to develop new products in this area.
  'Prize pots' are also a potential means to distribute funding across multiple projects in areas such as antibiotics where there are pipeline gaps. PwC have developed a potential framework for an insurance approach – whereby payers agree an annual premium to fund an identified insurance solution – which could be used to fund prize pots for different indications that are considered to deliver the most benefit from investment.

- **Other UK government initiatives**
  - SBRI Healthcare – the Small Business Research Initiative for Healthcare is an NHS England programme of competitions for companies to put forward solutions to NHS challenges. Fully funded development contracts are awarded to successful applicants.
  - Collaborative Research & Development – an Innovate UK programme of funding competitions aimed at solving specific technical or societal challenges. Funding of up to 60 per cent of project costs is possible, with award size from £25,000 to £5m or more.

  Whilst the GLA is looking at tax measures, they are not the focus of this report. However, there are a number of tax incentives of relevance to the UK life sciences sector, including:
  - Patent Box – enables companies to apply a lower rate of Corporation Tax (10 per cent) to profits earned after 1 April 2013 from patented inventions
  - R&D tax credits – companies undertaking qualifying R&D activities can claim cash repayments on the qualifying R&D spend
  - Enterprise Investment Scheme (EIS) and Seed Enterprise Investment Scheme (SEIS) – offer a range of tax reliefs to individual investors who purchase new shares in smaller companies

- **Open innovation** – funding of academic-led research based on open innovation. For example, the Structural Genomics Consortium is an open innovation collaboration model focused on novel targets to come up with 'better ideas', which could lead to derisked development projects. Could development then be conducted within an NHS environment? The Consortium pools resources, working with ten large pharma companies who provide private funding and access to their medicinal expertise. High quality reagents are generated through leveraging academic and pharma capabilities, and reagents are made freely available to academia, biotech and pharma to facilitate science and discovery across therapeutic areas.

[33] http://www.wellcome.ac.uk/Funding/Innovations/Awards/Seeding-Drug-Discovery/index.htm
[34] Review on Antimicrobial Resistance, 'Securing New Drugs for Future Generations: The Pipeline of Antibiotics', May 2015

- **Crowdfunding platforms** – for example, Cell Therapy has successfully raised funding via Crowdcube.[35]

- **Overseas initiatives**

    - **Citizens' Innovation Funds (CIFs)** – a model proposed by the BioIndustry Association, based on a similar French scheme, 'Fonds Commun de Placement dans l'Innovation' (FCPI). CIFs would be aimed at mid-net worth individuals, offering an income tax break on up to £15,000 of investment, which would be pooled and used to support innovative, research-intensive companies.[36] The French scheme on which the model is based has raised an average of €500m per year.[37]

    - **Yozma programme, Israel** – the Israeli government's Yozma programme (1993-98) was a Fund of Funds with the objective of creating a competitive VC industry in Israel. $100m of government investment leveraged a further $150m of private sector funds. Each fund had a five-year call option on government shares, at cost plus interest, providing an upside incentive to private investors. The programme is considered to have generated very high VC performance and rates of return.[38] In 2012, the Israeli government provided an anchor investment for a life sciences VC investment fund created managed by OrbiMed. The $222m fund invests in life sciences companies from seed through to growth equity stages.[39]

- **Venture debt**
  Venture debt is also part of the funding 'universe' for life science companies. By some estimates, venture debt accounts for around 10 per cent of life sciences financing to the US industry, and by definition this funding is all for early stage companies.[40] In the UK, the figures are immaterial while in the US this form of financing is going to strong companies backed by well-known, established investors. Management teams, boards and investors seem comfortable with the idea of applying leverage to an R&D business. When used sensibly, this decreases the need for the VC to deploy follow on, thus reserving it for future use. By preventing dilution and avoiding the need to find additional outside investors at financing rounds, management equity is preserved. The additional capital provides companies with a cushion of time and potentially opportunities to open up parallel routes of innovation that help hit value-driving milestones by the next fundraising round. It has been reported that over a period of five years, as much as 40 per cent of the early stage life sciences portfolio of one leading VC firm in the US, Atlas Ventures, has utilised early-stage debt financing.[40]

[35] https://www.crowdcube.com/investment/cell-therapy-limited-17426
[36] BIA, 'Citizens' Innovation Funds: Engaging the public with UK innovation', September 2012
[37] BIA, 'Citizens' Innovation Funds: The case for unlocking the patriotic potential of the public', 2013
[38] Avnimelech, G, 'VC Policy: Yozma Program 15-Years Perspective', 2009
[39] http://www.investinisrael.gov.il/NR/exeres/F6640B8E-4938-4113-B6F0-259CA785B0EA.htm
[40] Life Sci VC blog (Bruce Booth, Atlas Ventures), 'Venture Debt: Under-Appreciated Tool for Building Biotechs', July 2011 http://lifescivc.com/2012/07/venture-debt-under-appreciated-tool-for-building-biotechs/

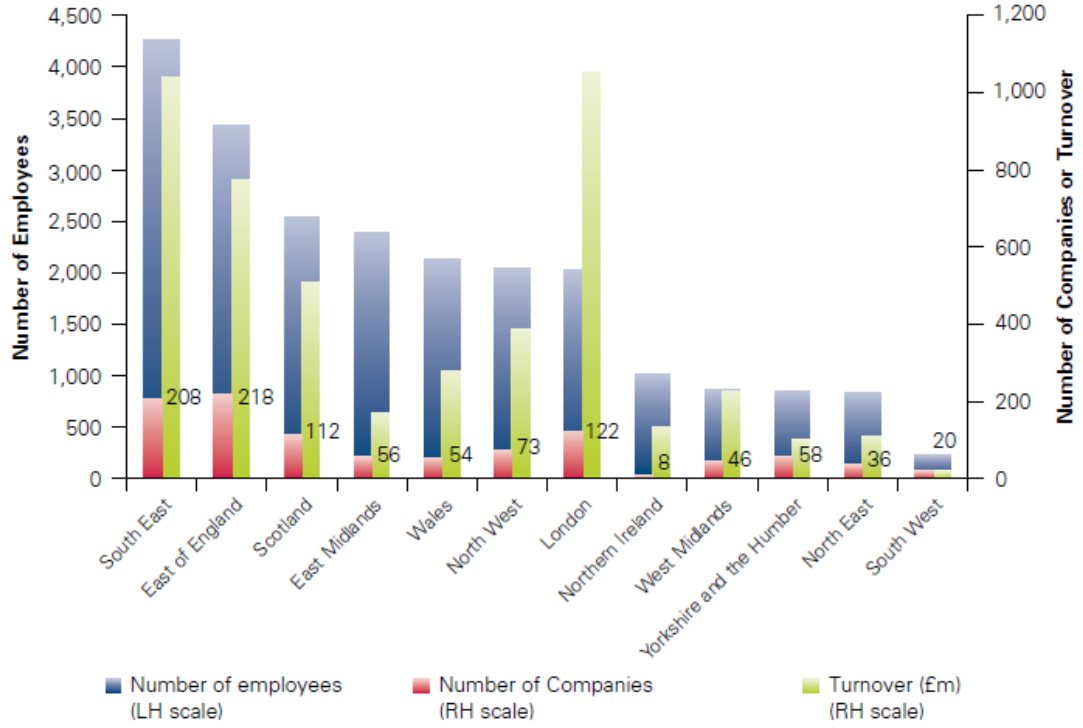
Annex 2 – London's Innovation Ecosystem

Life sciences ecosystem – London offers a 'joined up' ecosystem of research, public and private investment, international companies and skills. Figures 4 and 5 below illustrate the strengths of London and the south east in terms of number of companies, turnover and employment in the medical biotechnology and pharmaceutical sectors respectively. Several pharmaceutical UK headquarters are located in Greater London, including GSK, Gilead and BTG.

£16bn is being invested in London's public sector healthcare, research and teaching annually.[41] London is also home to key institutions – including the Francis Crick Institute (Europe's largest centre for biological research and innovation) and the Institute of Cancer Research – regulators, and a world class research base. Three of the UK's seven Academic Health Science Centres (AHSCs) are in London, and four of London's universities are ranked in the top 100 globally by the Times Higher Education Global University index for 2014-15 for medicine and bioscience:

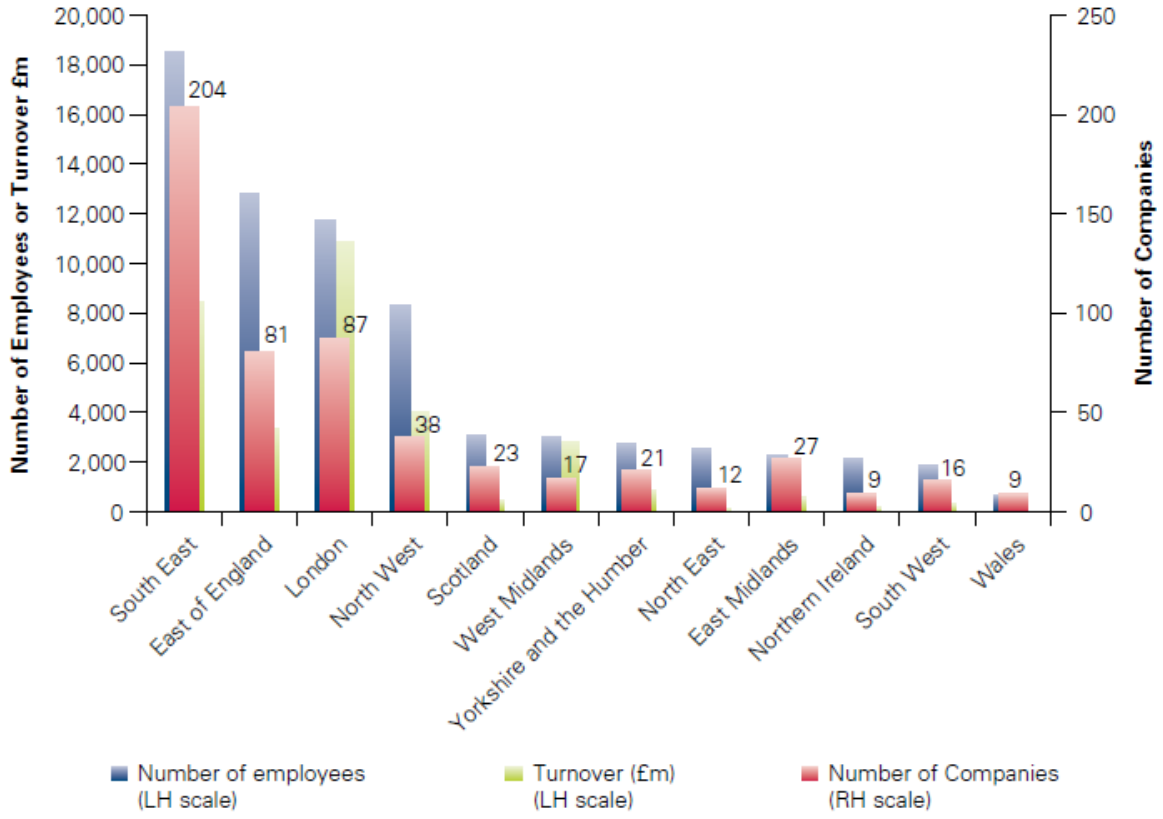
- Imperial is ranked 4th internationally in Clinical, Pre-Clinical and Health, and 10th for Life Sciences
- UCL is ranked 8th internationally in Clinical, Pre-Clinical and Health, and 17th for Life Sciences
- King's College London is ranked 11th internationally in Clinical, Pre-Clinical and Health, and 37th for Life Sciences
- Queen Mary University of London is ranked 49th internationally in Clinical, Pre-Clinical and Health (it is outside the top 100 for Life Sciences).

Figure 4 – The medical biotechnology sector in London and the South East – companies, turnover and employment[42]



[41] London & Partners, 'Why London for life sciences?' http://invest.london/sectors/life-sciences
[42] HM Government, 'Strength and Opportunity 2014', 2015

Figure 5 – The pharmaceutical sector in London and the South East – companies, turnover and employment[42]



The NHS in London – London is home to a highly diverse population supported by a large single healthcare system that maintains extensive patient records. Over eight million patients use the NHS in the capital, over a third of whom were born outside the UK. This concentration of diverse patient groups in a small geography makes it easier and faster to set up complex trials, and identify and recruit the right patient groups working across primary care, general hospital and specialist clinical services.

The city for business – London's role as a global hub of financial and professional services has been a critical factor in the growth of the science and technology sectors. London can claim specialist patent lawyers, venture capitalists and intellectual property experts, which in itself gives London-based science and technology firms distinct locational advantages. At the same time, London's highly specialist financial and professional service providers have been key clients for many of the tech sectors that have blossomed over recent years.

A Global Hub – London attracts and welcomes the best talent from around the world to study and to work; is the first choice location for global businesses, whether from mature or emerging markets and has an unrivalled breadth of global relationships across Europe, the Americas, Asia and Africa.[43]

World leader in financial technology – London is the obvious home for fintech because London is where most of the financial expertise is (in the form of banks, brokers, asset managers, pension funds, hedge funds, private equity firms, insurance). There are 44,000

[43] London First, London Enterprise Panel, 'London 2036: an agenda for jobs and growth', January 2015

employees working in London's fintech sector, more than either New York City or San Francisco-Silicon Valley.[44]

The Creative Engine – London is the best place in the world to be an entrepreneur. The capital has the world's strongest collection of academic institutions and uses them to fuel world-beating innovation. London is the world's capital of culture, reflected in the world's largest creative sector and has the world's largest technology cluster, not counting physical manufacturing.[43]

Infrastructure and regeneration – The Mayor of London has launched the first long-term infrastructure investment plan for the capital: the London Infrastructure Plan 2050. The next steps are now being set out to improve the delivery of London's infrastructure and make sure London receives the investment it needs to support future growth, in areas such as transport and digital connectivity. Through the Mayor's Great Outdoors programme, London's open spaces and high streets are being made more vibrant; new jobs are being created and the local economy is being strengthened. £50m is being invested through the Outer London Fund and £70m through the Mayor's Regeneration Fund in long term sustainable local regeneration projects.

[44] London & Partners, 'Why London for financial technology?' http://invest.london/sectors/fintech

Annex 3 – London's Cell Therapy Pipeline

To illustrate the opportunities offered by London's pipeline in just one therapeutic area, the tables below illustrate the pre-clinical and clinical pipeline of potential cell therapy products.

Preclinical research[45]

Lead institution / company	Collaboration partners	Present stage of development and expected completion date	Next expected stage of development and expected start date	Disease area: indication
UCL Institute of Opthalmology	NIHR	Preclinical Proof of Concept – Jul 2012	Late Preclinical – dependent on funding	Opthalmology: Glaucoma
UCL Institute of Opthalmology	MRC	Preclinical Proof of Concept – Oct 2012	Late Preclinical – dependent on funding	Opthalmology: Glaucoma, retinitis pigmentosa and Age-related macular degeneration
UCL Institute of Opthalmology	TAP Biosystems	Preclinical Proof of Concept		Opthalmology: Corneal replacement
UCL Institute of Opthalmology		Late Preclinical – 2013	Clinical Trial Ph 1/2	Opthalmology: Diabetic Retinopathy (Macular ischemia sub population)
UCL	Qualimed, UCL, University of Eastern Finland, MI, EURAM, QMUL, Yale	Preclinical Proof of Concept – 2016	Clinical Trial Ph 1 - 2016	Cardiovascular: Coronary artery disease
UCL	MRC	Preclinical Proof of Concept – 2013	Clinical Trial Ph 1/2 - 2014	Oncology: lung cancer and pleural mesothelioma
UCL	MRC	Late Preclinical - 2014	Clinical Trial Ph 1 - 2014	Oncology: EBV lymphoma, EBV nasopharyngeal carcinoma
UCL	University of Southampton, Cell Therapy Catapult, MRC	Late Preclinical - 2013	Clinical Trial Ph 1/2 - 2014	Oncology: Multiple myeloma
UCL, Great Ormond Street Hospital, Royal Free Hospital, UCLH	UK Stem Cell Foundation	Late Preclinical - 2016	Clinical Trial Ph 1/2 - 2016	Gastroenterology: Congenital oesophageal abnormalities, oesophageal atresia, oesophageal injury/loss
UCL	Northwick Park Institute for Medical Research, MRC	Preclinical Proof of Concept – 2013	Clinical Trial Ph 1/2 - 2014	Respiratory: Cancer or traumatic injury to larynx

[45] Information in table extracted from Cell Therapy Catapult UK Preclinical Research Database as of April 2014, https://ct.catapult.org.uk/preclinical-database

UCL	Northwick Park Institute for Medical Research, MRC	Late Preclinical – 2014	Clinical Trial Ph 1/2 - 2014	Respiratory: Cancer or traumatic injury to larynx
KCL	MRC	Preclinical Proof of Concept – 2014	Late Preclinical – 2016	Immunology: Autoimmune hepatitis
KCL	MRC	Late Preclinical – Feb 2014	Clinical Trial Ph 1/2 – Apr 2014	Liver: Liver transplantation
UCL	Great Ormond Street Hospital, Biomedical Research Council	Enabling/Platform research – 2014	Clinical Trial Ph 1/2 – 2015	Other: Necrotising enterocolitis

Clinical trials[46]

Sponsor	Lead institution	Clinical trial stage	Year trial started	Disease area: indication
Cell Medica Ltd	Multiple sites, UCLH study chair	Phase 3	2008	Oncology/Blood: CMV reactivation following allogeneic haematopoietic stem cell transplantation (prophylactic)
Cell Medica Ltd	Cell Medica with Birmingham University	Phase 2	2010	Oncology/Blood: CMV reactivation following allogeneic haematopoietic stem cell transplantation (pre-emptive)
Cell Medica Ltd	Cell Medica	Phase 1/2	2012	Oncology/Blood: ADV in paediatric patients following bone marrow transplantation
UCL	UCL	Phase 1/2	2012	Oncology/Blood: Acute myeloid leukaemia; chronic myeloid leukaemia
UCL	CRUK and UCL Cancer Trials Centre	Phase 1/2	2012	Oncology: Acute lymphoblastic leukaemia
Great Ormond Street Hospital NHS Trust / UCL	Great Ormond Street Hospital	Phase 1/2	2011	Blood: X-linked severe combined immunodeficiency
Great Ormond Street Hospital NHS Trust	Great Ormond Street Hospital	Phase 1/2	2012	Blood: Adenosine deaminase deficiency
QMUL	Barts Health NHS Trust / QMUL	Phase 3	2011	Cardiovascular: Acute myocardial infarction
Imperial College London	Imperial College London	Phase 1/2	2011	Cardiovascular: Localised myocardial dysfunction
Imperial College London	Imperial College London	Phase 2	2012	Neurological: Relapsing remitting MS/ secondary progressive MS/ primary progressive MS
Joint UCLH and UCL Biomedical Research Unity (UK)	UCL	Phase 2	2011	Bone and cartilage: Bone regeneration and healing (orthopaedics)

[46] Information in table extracted from Cell Therapy Catapult UK Clinical Trials Database as of April 2014, https://ct.catapult.org.uk/clinical-trials-database

UCL	UCL	Phase 1	2013	Haematological malignancies: CMV seronegative HSCT donors and CMV seropositive HSCT recipients
KCL	Guy's NHS Foundation Trust	Phase 1/2	2013	Genetic skin diseases: Recessive dystrophic epidermolysis bullosa
UCL	CRUK and UCL Cancer Trials Centre	Phase 2	Expected Q1 2014	Acute myeloid leukaemia
KCL	Guy's and St Thomas' NHS Foundation Trust	Phase 1	2014	Head and neck cancer: Locally advanced/recurrent disease for which no suitable alternative therapy is available