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Into the Valley of Death: Research to Innovation

Authors: John Hudson

Hanan F. Khazragui

John Hudson: Department of Economics, University of Bath, Claverton Down, Bath, BA2
7AY, UK.

Hanan F. Khazragui: Faculty of Medicine and Dentistry, University of Bristol, 39 Whatley
Road, Bristol, BS8 2PS, UK.

Corresponding author: John Hudson, j.r.hudson@bath.ac.uk

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Teaser: The pharma industry and academia are increasingly joining forces to more
successfully cross the Valley of Death, case studies shed light on whether this is working and
who gains most.

Into the Valley of Death: Research to Innovation

Abstract

The pharma industry and academia are increasingly working together, often encouraged by governments, as they seek to bring basic research to the market. This is consistent with newer models of innovation policy which stress interaction between the different agents across the innovation process. We examine this interaction in the UK, the EU and the US in part through several specific examples. They suggest that co-operation is still far from perfect and that academia's return on its research is relatively small. Countries are also beginning to use research as a tool of industrial economic policy.

The phase between research and successful innovation is known as the Valley of Death. The pharma industry and academia are increasingly working together, often encouraged by governments, as they seek to successfully navigate the Valley and bring research to the market. This is consistent with newer models of innovation policy which stress interaction between the different agents across the innovation process. We examine this interaction, in part through several academic research case studies. They suggest that co-operation has been focused on the research stages of innovation and that academia's return on its IPR is relatively small. Countries are also beginning to use research as a tool of industrial economic policy.

The nature of innovation

Until the 1990s the linear model of innovation policy was dominant. This viewed technical change as happening in a linear fashion from invention to innovation to diffusion. The stages of the "Technology Push", version of the original linear model, are: Basic science→Design and engineering→ Manufacturing→ Marketing→ Sales. In this model the role of universities

is often fundamental. However, in the past decade a new understanding of the nature of the innovation process has emerged, which emphasizes its systemic and interactive character [1]. This suggests that innovation should be seen as an evolutionary, non-linear and interactive process, requiring intensive communication and collaboration between firms and organisations such as universities, financial institutions and government agencies. An example of this is the triple helix model which emphasises interaction between university, industry and government [2] and a more system-centred approach to innovation policy [3]. This does not mean that focusing on basic research and on the technological aspects of innovation is the wrong policy, but that it needs to be complemented with the organisational, financial, skill and commercial aspects of innovation.

In tune with this, the OECD [4] argue that much innovation appears to fail because of a lack of co-ordination and a failure to join up all the agents who are part of the innovation process. Finance is often a key constraining factor. Innovation in the pharma industry, where an aspect of the Valley of Death is the translation gap, is particularly fraught with problems. Translation may be defined as the transfer of basic biomedical research into clinical interventions. It correlates with the design and engineering stage of the linear model and the problems are substantial. The time-lag between filing a basic patent on a compound and its commercialization as a drug is long at about 11–12 years and only a small fraction of all synthesized compounds finally enter the market [5]. The average cost of taking a drug from concept to market is estimated to be in excess of \$1 billion and only 20% of approved drugs make more money than their associated R&D cost [6]. Even then, dangerous side effects may emerge for some drugs after several years of sales. This has led to increasingly stringent regulatory approval guidelines, making an already slow system [7] even slower. Further obstacles to translation are discussed in [8]. All of this often makes funding difficult to obtain, particularly for the early stages of translation research.

The changing roles of firms, universities and governments in the pharmaceutical industry

Translation research can be done either by large pharmaceutical firms, specialist SMEs or universities, often via spin-out companies. In recent years the latter have become increasingly common [9]. Moving away from the linear model, there has also been an increasing tendency for industry, encouraged by government as in the triple helix, to finance and engage with academia at an early stage of research, often in the form of research centres [6]. In part universities welcome such engagement because of increased financial pressures. Traditionally the pharmaceutical industry preferred to keep research in-house [9]. But arguably in the face of rising costs and greater difficulties in finding major new drugs, they too welcome greater collaboration with universities [7].

Examples from the UK and the USA

Examples from the Medical Research Council

The UK's Medical Research Council (MRC) in its annual reports and associated documents details the economic impact of research it has part-funded. Superficially it tells a good story. Perhaps the stand out item is the receipt of over \$200m from the drug Humira, an anti-TNF antibody therapy, used to treat arthritis. This uses patented technology derived from research at the MRC Laboratory of Molecular Biology in Cambridge and the Scripps Research Institute in California. By August 2009 it was being used in 80 countries in the treatment of 370,000 patients, and estimated to be the world's top-earning pharmaceutical product with projected sales of \$10billion by 2016 for the US firm Abbott Laboratories. Indeed in April 2012 its sales in the previous year were reported as \$2.3billion. Overall, in the period 2006-

10 the MRC reported that 315 unique patents were granted or published and 99 patents had been licensed. IPR (intellectual property rights) income was £78.9m in 2011/2012 and MRC funding has also contributed to the establishment of 47 start up firms since 2006.

Examples from the Research Excellence Framework impact case studies

These bare bones of the impact of research funding are given more flesh by a series of case studies which can be found on the UK's Higher Education Funding Council for England's website. These were the outcome of a pilot exercise designed to inform the Research Excellence Framework (REF), which is the latest attempt by the UK government to evaluate academic research. A key difference to its predecessors is a greater emphasis on the economic and societal impact of research.

The case studies from Clinical Medicine (details of which can be found on <http://www.ref.ac.uk/media/ref/content/background/impact/ClinicalMedicine.pdf>) include Imperial College's Thiakis, a spin-out company which has been sold twice, ending up with Pfizer. The underlying research pioneered the use of gut hormones as natural appetite regulators. This paved the way for the use of this hormone, related analogues and inhibitors of GLP-1 breakdown in the treatment of diabetes. Several GLP-1 related molecules (e.g. exenatide, liraglutide, vildagliptin) are now either licensed or undergoing clinical trials (e.g. Byetta, NovoNordisk). Further studies demonstrated that i.v. infusion of oxyntomodulin reduces food intake and thus facilitates weight loss. One particular analogue was developed by Thiakis, and was then evaluated by Pfizer as a potential therapy for obesity. However, there are reports that in 2012 Pfizer has ceased to develop this, with its future now uncertain (<http://www.bioworld.com/content/imperial-innovations-regaining-thiakis-obesity-drug-pfizer>). This is representative of the risks to firms of taking on university research, and indeed

vice versa. But it also illustrates the containment of that risk, as part of the payment to Imperial was dependent upon critical milestones being achieved.

The second Imperial College case study involving the treatment for rheumatoid arthritis (RA), does not seem to have directly financially benefitted Imperial from IPR revenues, but amongst the funders of this research are listed GSK and Wyeth, mainly for specific translational research. The case study is linked to the anti-TNF (tumor necrosis factor) drugs of which Humira is one. The research demonstrated that biologic TNF inhibition plus methotrexate markedly inhibits the structural joint damage previously thought to be an irreversible feature of RA and has led to the use of monoclonal antibodies to TNF for other chronic diseases, such as ankylosing spondylitis and Crohn's disease.

Other case studies

The other case studies do not relate to the development of new drugs per se, but there are still benefits to the universities and the UK, and they illustrate the diverse aims behind the public funding of university research. Cardiff's research has facilitated the identification and characterisation of a series of genes for major inherited disorders including autosomal recessive colorectal cancer and Huntington's disease. New genetic tests, developed in Cardiff, which allow earlier and more accurate diagnosis, are now available in the UK and Europe. In North America, Myriad Genetics markets the Colaris AP® testing kit which uses Cardiff's MYH gene technology, generating over £100,000 in royalty income for Cardiff University. However, this is not such a large amount compared to Myriad's revenue from the Colaris AP test, which together with the Colaris test, amounted to \$43.3 million in the fiscal year 2012.

At Exeter and Plymouth, research showed that the most common cause of permanent neonatal diabetes was a mutation(s) residing in a region encoding the pore-forming subunit of

a type of potassium channel which senses and responds to alterations in the ratio of ATP:ADP in the beta-cells. Research at Oxford showed that the early risk of a major stroke in the first few days after more minor 'warning' events, was much higher than had previously been supposed and developed simple clinical risk scores to identify high-risk patients. Finally, at Glasgow a study researched the evidence that smoke-free legislation has a significant impact on heart disease.

The Situation in the USA

For several decades Government policies have been designed to help commercially develop federally supported R&D. These include financial support and encouragement for the establishment of Technology Licensing Organizations and intellectual property centres as well as legislative changes such as the Bayh-Dole Act of 1980. The latest legislative change, the Leahy-Smith America Invents Act (AIA) of 2011, takes effect in 2013. A key aspect is the move from "first-to-invent" to "first-to-file", by which in the event of multiple patent application files, priority will be given to the one filed first. There are several other aspects to this legislation and it has been described as the biggest change to the US patent system since the 1950s. It has in part been designed to reduce legal challenges to patents, but also brings the US system closer to that of other countries. In doing so it may give an inducement for patents to be filed earlier, and this may encourage universities to collaborate with the private sector at an earlier stage.

The NIH in their annual reports seem keen to emphasise that their spending benefits every state and almost every congressional district, rather than the specific impact of spending in generating new products with a stream of license income. They also stress the benefits to health and in general terms that their research has helped keep the US pharma industry in a strong position globally. With respect to individual universities, in the Association of

University Technology Managers (AUTM) survey (see <http://www.autm.net/Home.htm>) of 157 colleges and universities in 2011 licensed income amounted to over \$1.8 billion. For most this was still a small proportion of research expenditures, on average just 2.2%. Northwestern University was the largest earner and their \$192 million was 40% of their total research expenditure. Amongst their outputs is Pfizer's Lyrica, sales of which were \$3.693 billion according to their 2011 Annual Accounts.

An evolving research environment

Ideally the new view of research would suggest that the company marketing the drug will already have been identified and indeed involved in the research right at its outset. However in the traditional university funding model, as illustrated in many of the case studies, this does not happen. To a considerable extent research funders in many countries are operating within the context of a linear innovation model. Requests for funding are received and are evaluated largely on the basis of their 'scientific merit', although economic impact is, superficially at least, beginning to be taken into account. In many cases, only once the research is close to completion does serious thought appear to be given to successfully bringing the innovation to market.

But an alternative scenario, more consistent with newer models of research, is beginning to emerge which sees industry, academia, research funders and even central government, co-operating at the start of a research project. Thus in 2012 Bristol-Myers Squibb announced a collaboration with ten cancer research institutions in Europe and the USA, with the specific aim of facilitating translation research. Whilst GSK and Astra have collaborated with the University of Manchester in translating basic research into new medicines for inflammatory diseases. GSK has several other partnership deals including ones with UCL, Cambridge and Nottingham Universities in the UK and Yale in the USA. In America Harvard joined forces

with Evotec, a German based biotech firm, with a further link to Janssen Pharmaceuticals set up in 2012. This saw an upfront payment of \$8 million split between the two original partners and gives Janssen exclusive access to a portfolio of products designed to trigger the regeneration of insulin-producing cells. There is also specific support for translational research by the EU's Innovative Medicines Initiative (IMI) and the MRC's Developmental Pathway Funding Scheme. Such developments are bringing academics much closer to the private sector in their daily working life. To an extent academia is becoming the *de facto* research arm of the pharma industry.

In Europe too, increasingly there are examples of university centres sponsored by, and identified with, the large multinationals, e.g. the Mitsubishi Genetic Therapies Centre at Imperial College. The French government have funded an initiative to create six world poles of excellence bringing together French firms and publicly funded research centres in a bid to *keep France in the forefront of pharmaceutical innovation and production* [7]. The IMI also supports collaborative research projects and builds networks of industrial and academic experts in Europe. In America, the NIH's Roadmap Initiative also makes some developments in this direction (see <http://commonfund.nih.gov/aboutroadmap.aspx>), with the specific aim of changing the academic culture to foster collaboration.

Concluding remarks

The process of bringing basic research to successful innovation is changing with closer collaboration between industry, academia and government agencies. At the same time in some cases universities are themselves taking new drugs further down the innovation chain through spin-out companies. All these developments should facilitate the more efficient development of new drugs. They may also help with the provision of venture capital and other funding for translational research in general, and early translational research in

particular, which tends to be in short supply. This may then help researchers, universities and government meet their moral, and financial, obligation to translate basic research to clinical validation and benefit.

In addition it is possible that they will lead to universities and industry sharing more equally in the gains from research. The evidence suggests that the income generated from IPR is relatively small compared to the total revenues being generated and the total costs of research. Hence average license income in Europe equals 1.5% of the research expenditures by universities and research institutes and in the US it is 4% (see <http://www.knowledge-transfer-study.eu>). Of course, not all research is intended to directly generate revenue, but the examples we gave earlier suggest that universities and their funders are selling their IPR too cheaply. The work behind some of these case studies has taken over 30 years, mainly funded minimally by research grants and the universities have failed to be effectively compensated when these are successfully commercialised.

However, it is not obviously the case that this integrated approach to university research involving multiple partners will improve the universities' position in this respect. Firstly, even the largest universities do not have the financial and legal expertise to bargain with the pharmaceutical industry (big pharma) on an equal footing, or to efficiently move further down the translational path themselves. This will require a collective pooling of resources and skills. Secondly, a patent is only valuable as a protection of property if the holder is prepared to sue intruders, if not the value of the patent is undermined. Yet universities may be reluctant to do this for a variety of reasons including the direct costs, and the impact on image and job prospects for graduates. Finally, not all collaborations end in success as illustrated in the case studies and the literature survey. The closeness of the relationship between the different partners and the alignment of their diverse goals may well prove important in facilitating such success.

There are also ethical problems involved with this new approach. Firstly it clashes with academia's traditional focus on disseminating knowledge as widely and freely as possible, and risks taking the focus away from high quality research publications [10]. Possibly in an attempt to protect themselves from criticism, some universities are seeking to ensure that products from their IPR are marketed under favorable conditions to the developing world. These include Boston, British Columbia, Brown, Edinburgh, Emory, Oxford, Washington, Yale and UCL. Secondly, it involves, directly or indirectly, public money underwriting the commercial success of some firms and not others.

This use of public money is being done not just to promote research per se, but increasingly as a tool of industrial and economic policy, as in France, with their poles of excellence, Germany and more widely the EU. Even in the US, where there has been a traditionally reliance on market forces, the NIH is beginning to view research as a way of boosting the economy and has long, implicitly sought to strengthen the global position of American companies. However it is also often the case, as in the UK, that the firms benefitting from the research are foreign based multinationals and hence the boost is to other economies. In this context, certainly within the UK, greater domestic support for candidate translation is required to help avoid migration to other countries with greater funding.

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