consider whether it is really appropriate to have the same approach to impact for research applications in synthetic biology as they do to those in pure mathematics.

Everyone agreed that a lot of scientific activity is routine and procedural, rather than the stuff of Nobel prizes and profound changes in theory. However, even routine science only works because of scientific culture and values. If they are undermined, then even routine science will also suffer. For example, progress is often made by data gathering, fastidious checking, and care and attention to detail, all of which most of the time don't produce any impact, but which are vital to the integrity of the process of science, and occasionally throw up something new.

The research council representatives were at pains to emphasise their continuing support for pure science, and it is agreed by all that they are not intending to undermine blue skies research in any way. However, it is often the case that institutions and individuals over-respond to incentives and that schemes such as pathways to impact have unintended consequences.

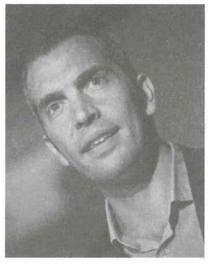
Many of those present expressed concern about doctoral training centres and the overall reduction in postgraduate grants and the removal of postgraduate funding from responsive mode grants.

Many voices objected to increased research council micro-management of science.

See article by Professor Ladyman in Science in Parliament Summer Issue 2011 (Vol 68 No3)

IS SCIENTIFIC FREEDOM THE ELIXIR OF CIVILISATION?

IS NURTURING THE RESEARCH ENVIRONMENT AN ALTERNATIVE PERSPECTIVE?



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This analysis of research environment is unashamedly set in the context of science that it might help to enable. We are at a cusp in the development of the UK that will be defined by the opportunities we identify. We have long been scientifically creative and we are well-placed as a nation to embrace science as a possible industry even more heavily. Based on these strengths, we stand at a good point from which to evaluate various potential models for ways forward.

An illustrative burgeoning area stems from a 50-year-old revelation of Biology at the molecular level. Francis Crick powerfully and beautifully analysed the implications of his discovery (along with Watson) of a molecular basis of inheritance. The central upshot: the most important biomolecules – the proteins (the workhorse molecules of biology) – have their function controlled in an indirect way from the source code, deoxyribonucleic acid (DNA). This indirectness is now being valuably challenged by chemists and biologists – we have a vision of a biology that may be more directly tuned at the molecular level, a Synthetic Biology. This field, and focused examples, can be used to illustrate how properly considered environment might influence outcomes in far-reaching research.

The principle of vaccination has been with us, in essence, for centuries. Nonetheless, striking goals remain, amongst them development of vaccines for many pathogens that lack a 'cure', such as HIV. Proteins on the surface of pathogens can be analysed structurally ("visualised") through various methods. By identifying those that are important to the pathogen, such as the HIV-coat-protein gp120, we can now envisage mimics. These mimics, given to a patient, might elicit antibodies that recognise key features. This use of mimics 'trains' host immune systems with a potential to recognise and neutralise pathogens. By enabling the creation of such mimics, Synthetic Biology can address such important goals, whilst also testing fundamental hypotheses regarding the molecular nature of Immunology. Such work 'stand[s] on the shoulders of [many] giants'; a timeline of innovation stretches back to the late 18th century and to Jenner, who used intact and mock pathogens for such mimicry. Although, in the early 20th century, this process was partially refined (using instead fragments of pathogens), in many respects currently licensed vaccines are essentially similar in design and strategy. In time we hope that we will be able to apply modern chemical assembly to Synthetic Biology to fully 'design' mimics as vaccines. However, until that time, examples of the current state-of-the-art are illustrative of both potential and of how environment will be instrumental in the development of this future science.

These advances will test our existing approaches. To my mind, a leading example is a vaccine called *QuimiHIb*, sold by Heber Biotechnology. It is used to treat *Haemophilus influenzae* type b (Hib), a pathogen that, before the introduction of Hib vaccines in the late 1980s, was the leading cause of bacterial meningitis in children in the United States of America (since reduced by >95%). Notably, use of the vaccine in developing countries has been slow due to cost and availability. The World Health Organization estimates that in the developing world Hib kills ~350,000 pa, mainly under five-years-old. Heber is a company that few will have heard of; it is Cuban and the model that led to *QuimiHib* is unconventional.

One key portion of *QuimiHib* is entirely synthetic – rather than being isolated from pathogens, it has been chemically assembled before incorporation into the vaccine. It is thus the first of its kind [Verez-Bencomo et al, *Science*, 2004, 305, 522] and was developed by an academic team (led by Vicente - Bencomo-Verez) in Havana in collaboration with a Canadian chemist (René Roy). The 99.7% success rate of *QuimiHib* led to its direct incorporation, in 2004, into Cuba's national vaccination programme.

What were the elements of success that led to such unprecedented translation? Vision was necessary: national centres of excellence were supported (eg CIGB, Finlay Institute) at a bold level given the corresponding national GDP.

There was pressing societal need: only 2% of the world's children were protected by the prior (pre-2004) Hib-vaccination regimes. Prevailing legislative backdrops created an incumbent necessity to avoid developed-world spin-out routes or interaction with large pharmaceutical companies – this created the need for a disruptive business model. *Verez-Bencomo* evoked the associated ethos of academic and social courage for the resulting national collaboration rather than market-driven competition: "It's a collective achievement of the accumulated intelligence of our country". In the backdrop of the UK's climate of 'impact assessment' it is interesting to note that many typical 'metrics' of output were met by Heber: >60 patents, technology transfer, joint industrial projects, extensive exports. Yet Heber's sales are measured in the tens of millions of dollars, a fraction of competitor operations in the developed world: "Our objective is not to make money. Of course, we can't give the vaccine away. We must sell it. But money isn't the objective of our biotech industry, it's the means. We're substantially different from [transnational corporations] TNCs which serve under their own banners, because we work under the same banner as our country and share social and human objectives rather than purely financial ends." *(Carlos Manuel Mella Lizama, Heber Biotec)*.

Could this happen elsewhere? One can argue that few countries possess similar (correctly?) integrated systems combining fundamental discovery with appropriate need and ability: in this scenario, advanced fundamental scientific enquiry plus effective socialized medicine; however, in many cases, the UK thankfully does.

Could, therefore, such models emerge in the UK? Synthetic Biology is just one science that could provide a useful disruptive influence (a novelty that demands a reassessment of current systems) that would address current or future crises. What would be needed for an environment that would support it or other parallel disruptive models in other disciplines? It would be trite and intellectually lazy to focus simply on increased resource or even changes in associated regulation. These are important but only part of the issue. I would argue that we also need to consider three things.

Firstly, a long-term and fresh view of the value of fundamentals in science is essential. This may require investment in models that will yield only very distant results e.g., vaccine investment in 1970s treats disease in 2004. We should strongly avoid 'pork barrel' funding in response to lobbying that might (and recently has) led to knee-jerk support of certain narrow scientific topics, no matter their immediate cosmetic attraction. Haldane principles have valuably guarded the UK's intellectual integrity and rigour. Bernal [Bernal, J.D. (1939) *The Social Function of Science.* London: Routledge] and Zuckerman's points on the 'function of science' are equally well-taken; however, all-too-often a false opposition is created between social good and researchers' freedom. We must trust in expert vision, through responsive-mode, peer-reviewed, bottom-up solutions to a challenge and then (plurally) support it. Since creativity can be equated, in some measure, to levels of individuality as well as expertise it should not be micromanaged: we need to nurture future experts, not generate armies of trainees. Moreover, sciences such as Synthetic Biology that exploit and explore multiple fundamental topics are not handled well by organisational 'silos' – they will break these moulds. We may, therefore, need to question some existing frameworks here in the UK (eg BBSRC+EPSRC+MRC+NERC+STFC+MHRA…) and elsewhere (eg NIH+NSF+DARPA+BMGF+FDA…).

Secondly, we should aim to more broadly identify how such creativity adds value and where this value lies. We should stop confusing pre-competitive research with competitive; the hallmarks of success are very different. We should learn lessons about the 'icons' of technological impact eg *QuimiHIb cf Avastin* – what have been the true, associated, global benefits and efficacies. As a nation, for example, we should perhaps be proud that we have grasped the nettle of this analysis in some cases (eg QALYs). We will need to learn the lessons of historical national success and failure (eg Li-ion batteries, monoclonal antibodies are pertinent to the UK). We should create an environment as a 'midwife' to these ideas rather then falsely induce their birth. Boston, MA, oft-cited as an ideal, has strengths that are largely passive (simply clustered). Let us populate that supportive landscape with appropriate people; the model of the CEO as a 'hero' has served many smaller companies poorly and we should encourage the emergence of some genuine *Masters of Business Administration*. This will also need us to clearly distinguish innovation from entrepreneurship. Here, by recognising, that value is not tantamount to monetary reward for many innovators, we will better understand their

motivations. In turn, this will allow us to reward, for example, a desire to add value to the community by creating a better environment for further innovation. Few currently in academia chose their profession for the money.

Finally, all this may necessitate alternative models for addressing pressing challenges (again there are pertinent UK narratives eg Penicillin's development by Florey, Chain and Heatley). We may need to acknowledge that certain existing institutional models are creaking or even broken eg large pharmaceutical companies as the primary 'drivers' in medicinal research. Aspects of current intellectual property legislation make it a blunt tool. The role of naked competition in solving large-scale problems may need to re-evaluated in the light of 'national collaboration' or distributive alternatives.

It might be said that far from being an alternative perspective the 'Havana model' is instead one innovative solution that could be taken to fresh and exciting heights. In this context, I wistfully note that the individual (Crick) who has been a scientific inspiration for my own group's perspective on this burgeoning scientific frontier has also been chosen as the totem for the UK's largest and most bold centre of excellence, which will open in the heart of London in the coming decade. With vision, courage and support, the stage is therefore, in some part, potentially well set.

IS SCIENTIFIC FREEDOM THE ELIXIR OF CIVILISATION?

UK'S APPROACH TO RESEARCH DOES NOT LIMIT THINKING

Professor David Delpy
Chief Executive and Deputy Chair, Engineering and Physical Sciences Research Council

The UK has a strong and vibrant research base which continues to produce some of the world's most important scientific discoveries and talented academics, as well as attracting inward investment from global businesses. The UK has only one per cent of the world population but invests in five per cent of the global research and produces 14 per cent of the world's most-cited scientific papers. [1]

Government research funding, allocated through the UK's research councils, has consistently supported innovative scientific, sociological and technological developments that have both pushed at the boundaries of conventional thinking and brought change to the everyday lives of people at home and across the world.

However, despite this pedigree, some hold the view that the way research funds are allocated means that imaginative projects are held back. They maintain that the process of peer review is inherently too conservative in approach and that therefore discovery-led research is less likely to get approved.

This is far from reality. A recent review [2] of Nobel prize-winning research showed that over 50 per cent had been funded through government sources and agencies which will have been through peer review.

A relevant example is the work of Sir Andre Geim and Sir Konstanin Novoselov, Professors at the University of Manchester, who were awarded the Nobel Prize for Physics for their work with the revolutionary material graphene, which has the potential to replace silicon in integrated circuits and a host of other applications.

The success of Geim and Novoselov would not have been possible without long-term and strategic funding, which began 10 years ago.

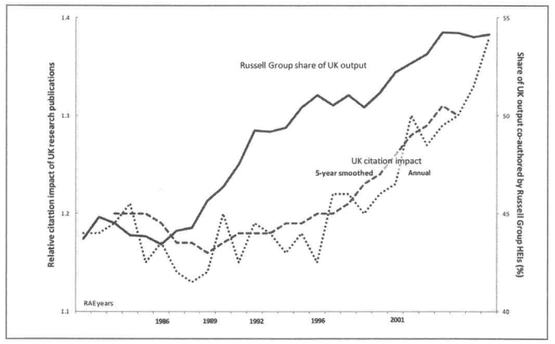
Sir Andre says: "The EPSRC grants that got us started supported curiosity-driven projects, which are generally not expected to have application, certainly not in anything other than the very long term.

"Graphene research is still a very new area, so we are still at the stage of assessing applications for the material – but already the initial investments have been returned in taxes, and in 10 years' time the government will have its investment repaid a thousand times over."

The presumption that applications for funding to carry out discovery-led research fare worse than those for applied research is also baseless. Statistics collected by EPSRC show researchers who succeed in applying for funding tend to be successful in both discovery-led and challenge theme-led research because their projects are excellent per se.

There is a high level of overlap between the populations of researchers supported through both discover-led and challenge-led modes. Between 1999 -2008 the majority of EPSRC research funding (62%) was allocated to researchers who received both types of funding. Among the top researchers, those who consistently submitted successful applications for funding, 67% were successful across both modes and accounted for 84% of EPSRC funding.

The relative citation impact of the UK research base (1981-2007)[5]



Likewise, it has been suggested that an increased focus on the commercial application of research is detrimental to the health of a research base. Jerry and Marie Thursby [3] looked at this very claim in relation to the effects of the Bayh-Dole Act on basic research in the US. The Act ensured that the intellectual property contained in research rested with academics and prompted a worry that only applied research projects would be pursued.

They concluded that at the eight major US universities, while there was growth in applied research, the level of basic research also rose.

Similar concerns were voiced about the introduction of the need to demonstrate the impact of research and inclusion of the criterion of national importance in applications for funding. The research councils and government have monitored relevance of research to beneficiaries since 1994. The Research Assessment Exercise shows that the quality of research has consistently risen over the 17 years since then and independent comparisons to other countries show citation rates and impact as consistently high, second only to the USA. [4]

The Natural Environment Research Council commissioned Evidence Ltd to undertake bibliometric analysis in 2008 [6], it showed impact was very similar across research funding modes. The highest quality consistently came from the funding of fellows and in the last year of analysis (2005) directed mode grants had a higher citation impact than responsive mode.

A similar analysis of the impact of EPSRC-funded research in 2009 found no significant difference in citation performance for papers arising from 'Responsive' and 'Targeted' funding modes. The proportion of papers highly cited (cited ≥ 4 times the relevant world average) was 9.2% and 8.6% respectively. The overall citation impact, 1.6 times the world average, was the around the same for both funding modes. [7]

Maintaining novel approaches and creativity in research is absolutely essential to the long term future of our research base. The scientific community is monitoring this through the peer review system to ensure creativity flourishes.

In an EPSRC analysis of applications presented to peer review panels since September 2009 reviewers reported that there was no drop in the level of adventure or creativity of those applications receiving funding.

The UK's reputation for high quality researchers and research facilities brings valuable investment into the country. There is a high incidence of multi-national organisations choosing to co-locate their business's R&D with relevant UK university research departments. [8]

Data from the OECD shows international business invests more in research and development based in the UK than anywhere else. Over 20% of business R&D in the UK is funded with investment from abroad. [9]

A recent report [10] commissioned by the Department of Business Innovation and Skills says that "while the UK spends far less in absolute terms on research than the US, China, Japan or Germany, recent trends indicate that it is becoming even more efficient than all four in terms of output per unit spend. The UK is also becoming more efficient over time in terms of output per researcher and per unit of research spend.

The UK is the clear leader among all eight comparator countries (Canada, China, France, Germany, Italy, Japan, UK, US) on citations per unit spend on Gross Expenditure on Research and Development."

It is clear that the UK punches above its weight in terms of research quality and is increasing its reputation in fields in which it already has strength. To maintain this high reputation and investment income the research community needs to continue to use its robust, proven systems to monitor both the quality of the research it funds and ensure that new ideas have a healthy environment in which to grow.

Footnotes

1 International Comparative Performance of the UK Research Base – 2011 by Elsevier on behalf of the Department of Business Innovation and Skills http://www.bis.gov.uk/policies/science/science-innovation-analysis/uk-research-base

2 Tatsioni, A., Vavva, E., Ioannidis, J.P.A. Sources of funding for Nobel Prize-winning work: public or private? FASEB J. 24, 1335–1339 (2010). www.fasebj.org

3 Has the Bayh-Dole act compromised basic research? Research Policy (2011) Volume: 40, Issue: 8, Publisher: Elsevier B.V., Pages: 1077-1083 ISSN: 00487333

4 International Comparative Performance of the UK Research Base – 2011 by Elsevier on behalf of the Department of Business Innovation and Skills http://www.bis.gov.uk/policies/science/science-innovation-analysis/uk-research-base

5 Funding selectivity, concentration and excellence - how good is the UK's research? Jonathan Adams and Karen Gurney - March 2010 Hepi http://www.hepi.ac.uk/466-1793/Funding-selectivity,-concentration-and-excellence—how-good-is-the-UK's-research.html

6 NERC Citations Study 2008 NERC Research Outputs Database 2003-2005: Bibliometric baselines September 2008 http://www.nerc.ac.uk/about/perform/documents/citations-study-2008.pdf

7 EPSRC Citations Study 2009 Evidence, Thomson Reuters www.epsrc.ac.uk/SiteCollectionDocuments/Publications/Other/citationstudy2009.pdf

8 University Research and the Location of Business R & D Abramovsky L., Harrison R. and Simpson H. (2007) The Institute for Fiscal Studies WP07/02 http://www.ifs.org.uk/publications/3829

9 OECD main databases

10 International Comparative Performance of the UK Research Base – 2011 by Elsevier on behalf of the Department of Business Innovation and Skills http://www.bis.gov.uk/policies/science/science-innovation-analysis/uk-research-base