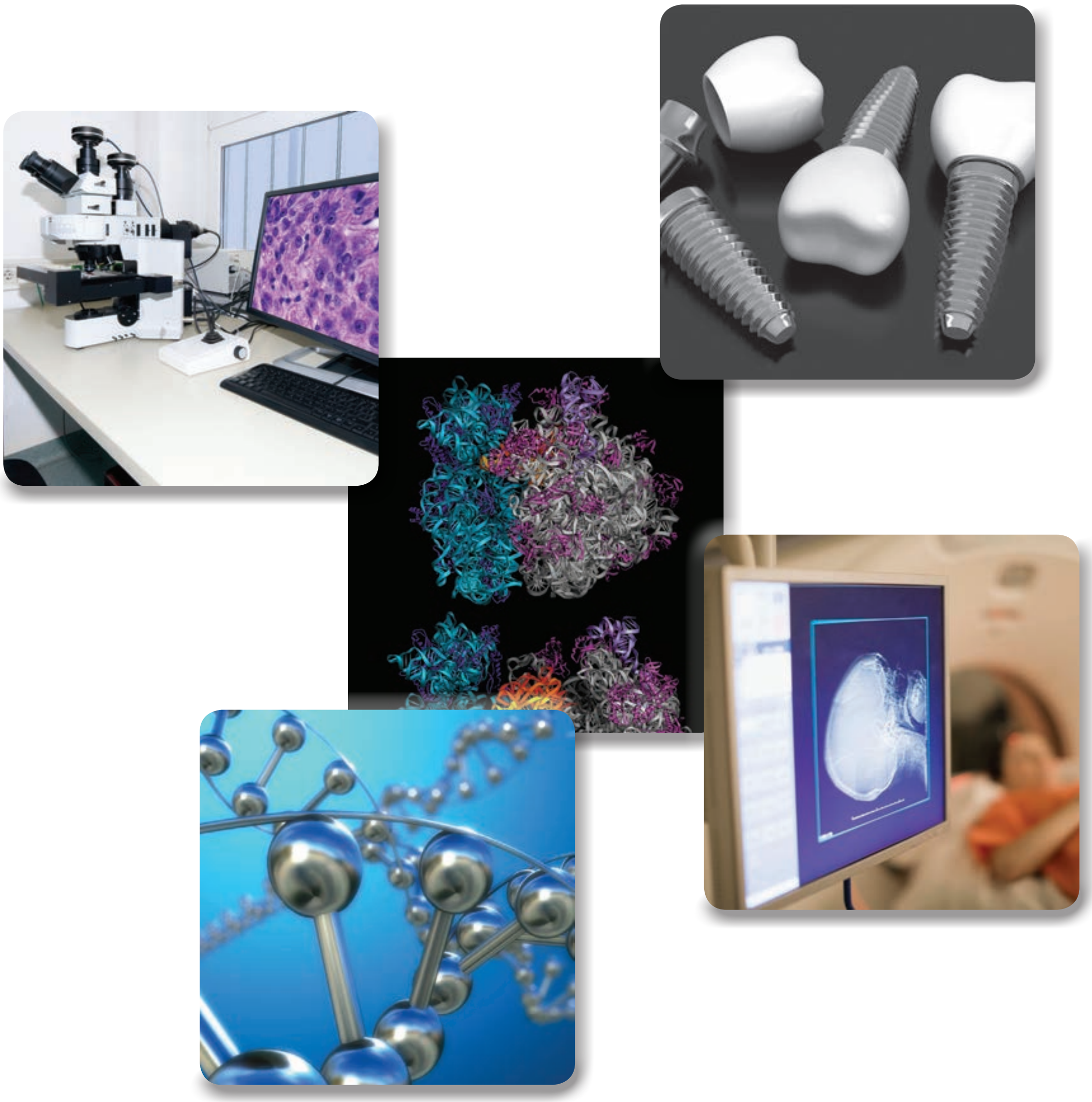
The importance of engineering and physical sciences research to health and life sciences



EPSRC
Engineering and Physical Sciences
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Foreword

At the end of 2012 I was asked by the Engineering and Physical Sciences Research Council (EPSRC) to chair a small independent review group to look at the relationships between engineering and physical sciences (EPS) research and health and life sciences (HLS). We all recognised from the outset that this is something of a false dichotomy; in reality research is increasingly an integrated activity. However, this is not always reflected in the structuring and resourcing of our research base, so we adopted this nomenclature as a form of shorthand, to enable us to focus on the issues in this area.

In undertaking this review we looked at a range of material and evidence, for example interdisciplinary institutional structures and ways of working that help EPS/HLS interactions. We also discussed future research challenges at the EPS/HLS interface.

Our overriding conclusion is that engineering and physical sciences research, including mathematics, statistics and computer science, has played a major role in advancing health and life sciences and will be increasingly important in the future. Yet this view is one that until now has not necessarily been given clear recognition. We strongly believe that it is vital that the UK continues to invest in world class EPS if we are to continue to see major advances in HLS. In addition, this interaction between EPS and HLS is a long-term agenda which requires on-going dialogue involving all the key stakeholders in order to address the challenges facing us in the future.

The group have identified a number of high level key recommendations, which include the importance of working across disciplinary boundaries and the value of interdisciplinary and challenge-driven research. These recommendations are the views of the review group and we would expect extensive engagement with all appropriate stakeholders in order to take these forward.

The case study graphics show that EPS advances have had a significant impact in HLS over the past 50 years. In addition, the forward-looking think pieces, for which we thank leading experts in their fields, identify important future challenges. These challenges range from the development and application of advanced materials that can be applied in healthcare, innovative technologies for surgery, to future challenges associated with drug discovery and feeding the world's ever growing population.

Finally, I would like to thank the members of the review group for their valued contributions during this stimulating project.

Professor Patrick H Maxwell FMedSci
Review Group Chair
Regius Professor of Physic and Head of the School of Clinical Medicine
University of Cambridge

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Introduction

> ***"Life science – and the UK's role in it – is at a crossroads. Behind us lies a great history of discovery, from the unravelling of DNA to MRI scanning and genetic sequencing. We can be proud of our past, but this government is acutely aware that we cannot be complacent about the future."*** Prime Minister David Cameron

This report considers the importance of the role of engineering and physical sciences (EPS) in health and life sciences (HLS) research and explores how the dependence is likely to develop in the future, based on likely future scenarios and the implications for ensuring that the UK has sufficient capability in key areas of EPS.

The government places a high priority on medical/health and life sciences (HLS) research, as evidenced by its Strategy for UK Life Sciences[1] and significant investments over the last few years. However, what is often less apparent is the extent to which HLS research is dependent on advances in engineering and physical sciences (EPS) both directly, for example through medical engineering, and indirectly through development of the technologies, materials, advanced data management, statistical analyses and advanced instrumentation that enable cutting edge breakthroughs.

The Engineering and Physical Sciences Research Council (EPSRC) invited a small group of experts across a range of HLS-related fields to join a review group[2]. The group met three times, in April, June and September 2013, to discuss the main issues, consider evidence and identify some key recommendations. They drew on their expertise to provide advice on the strategic direction of the review, advising on the information generated by the review and developing recommendations and conclusions. The group considered the following key questions:

- What role has EPS played in key HLS developments?
- What role will EPS play in the HLS areas which are likely to be the most fruitful for the UK over the next 10-20 years?
- How can the UK ensure that it has sufficient capability in key areas of EPS to be sure of success in these highlighted areas of HLS?

The group considered a broad range of supporting information to inform their discussions: a brief overview of the main evidence is provided below.

[1] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf

[2] Full membership and terms of reference for the review group are at Appendix A.

Evidence

One way of exploring the relationship between EPS and HLS disciplines is through analysis of publications and citations. A study was undertaken by the Centre for Science and Technology Studies at Leiden University, which demonstrated that one in ten publications from across all areas of EPS and HLS address interdisciplinary topics at the EPS/HLS interface. Figure 1 shows the main research areas with significant levels of publications and citations by both HLS and EPS researchers. These are shown by the coloured dots; the grey dots show research clusters across all science and engineering areas. It is interesting to note that the number of publications in Medical Statistics and Informatics is increasing at a significantly faster rate than the other areas. This reflects the major developments in computing power which have led to the key areas of bioinformatics and genomics, where huge amounts of biological data are used to enhance our understanding of the genetic basis of disease and drug response. This is one of a number of areas in which the UK performs well in terms of highly cited papers; other areas of strength include medicinal chemistry, natural product synthesis and genomics/proteomics.

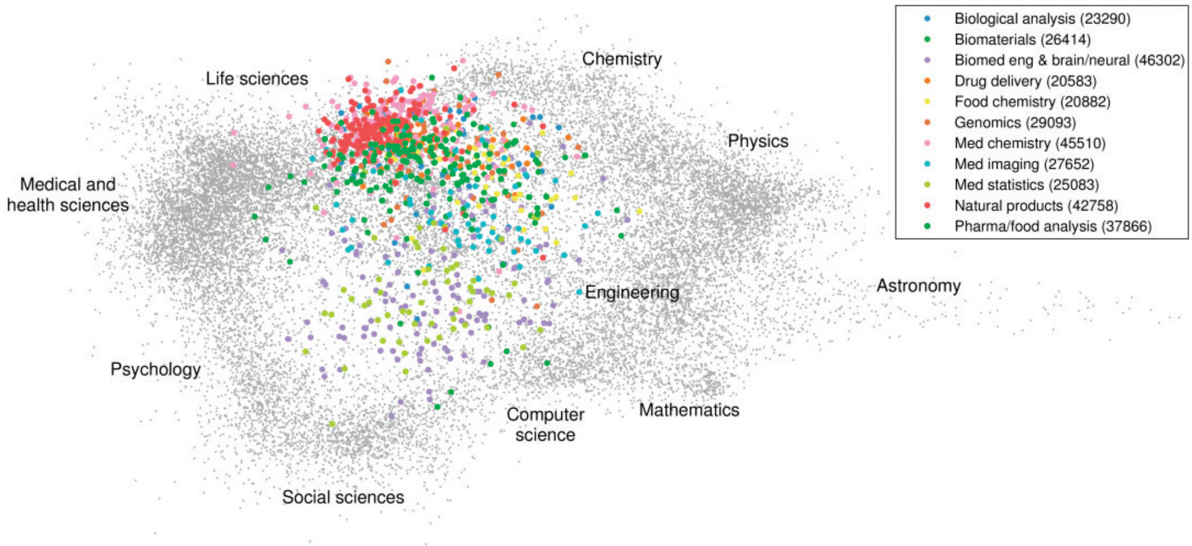


Figure 1: Map of research clusters showing those at the interface between EPS and HLS

Further evidence comes from considering the role of EPS in major discoveries, such as those recognised by Nobel Prizes (see below).

Nobel Prizes – evidence of the inter-relationship at the highest level of science

Since 2000 all except one of the Nobel Prizes for Chemistry and half of the Nobel Prizes for Physics have been awarded for discoveries with life science applications

During the last 35 years, 11 of the Nobel prize-winners for medicine have had a background in chemistry, physics or engineering.

- Chemistry Prizes have been awarded for discoveries with a range of applications including improving production of pharmaceuticals, making artificial muscles, limbs and nerves (conductive polymers) and enabling tagging of proteins to observe disease processes such as cancer (green fluorescent protein).
- Physics Prizes have recognised key developments with applications in medical imaging, sensors and ophthalmology, whilst graphene-based nanomaterials offer opportunities for tissue engineering, molecular imaging and drug delivery applications.

The importance of EPS in breakthrough discoveries is also evident in a range of case studies that were assembled for this report, which summarise in graphic form the impact of synchrotrons, microscopy, DNA sequencing, biomaterials and magnetic resonance imaging.

Another aspect to consider is the level of research investment in relevant areas. Whilst recognising that there are a number of sources of funding, within the constraints of this review we focused on the EPSRC research and training portfolio[3]. Over £2 billion, or around 25 per cent of EPSRC's research investment over the past 20 years, is relevant to health or life sciences, with this proportion increasing to more than a third of spend on research fellowships. The most significant areas of investment by value are:

- Medical imaging (including medical image and vision computing)
- Clinical technologies (excluding imaging)
- Biomaterials and tissue engineering
- Sensors and instrumentation
- Chemical biology and biological chemistry
- Analytical science

In addition, there are other areas of considerable relevance, for example:

- Mathematical science underpins much of medical imaging and provides support for clinical trials and biomedical statistics. Statistics is vital for understanding and extracting information from large data sets found in biological systems and bioinformatics as well as ecology, epidemiology and population studies.
- Process engineering, fluid flow, powder technology and reactor design have all contributed to new and improved drug production.
- Research in the built environment has improved the design of hospitals to reduce infection.
- Information technology underpins a range of assistive and mobile technologies in healthcare.

In summary, it is clear that engineering and physical sciences have made significant contributions to a wide range of advances in health and life sciences, and that a significant proportion of government-funded investment in EPS research is at this interface. In the next section we explore how the relationship between EPS and HLS is likely to contribute to meeting major challenges over the coming 10-20 years.

[3] A summary of this analysis is at Appendix D.

Looking ahead – opportunities for the future

As part of this review the panel identified areas of health and life sciences which are likely to become increasingly important in the future and where the UK is well-placed to make a significant contribution. Experts were invited to provide forward-looking think pieces, setting out their visions of the challenges and opportunities associated with these areas, and highlighting in particular the role that engineering and physical sciences would play in enabling the breakthroughs to occur. The main points are summarised below; the think pieces are included later in the report.

Sustainable food production (Dr David Lawrence, Non-Exec Director, Syngenta)
Feeding the world sustainably is recognised as a major challenge: globally food production will need to grow by at least 50 per cent and perhaps as much as 75 per cent. This will only be possible with significant research-based innovations in areas such as crop protection (e.g. through safe herbicides and insecticides), improving crop take-up of key nutrients such as nitrogen and phosphates, improving water recycling in agriculture and understanding and applying best practice in agricultural settings. Developments will rely heavily on EPS research in areas such as: **catalyst technology, sensor technology, soil chemistry, advanced informatics and chemical synthesis**.

Brain mapping (Professor Steve Furber, Professor of Computing Engineering, University of Manchester)
The economic cost of brain disease exceeds the combined cost of heart disease and cancer in developed countries. Computing research to increase our understanding of how the brain processes information will contribute to improving the cost-effectiveness of developing new drugs to combat brain disease; understanding how the brain processes information will require **research into areas such as biologically-inspired image sensors, models of computation that mimic processing techniques in biological nervous system and improving fault-tolerance in computer systems**.

The future of drug discovery (Professor Patrick Vallance, President, Pharmaceuticals R&D, GlaxoSmithKline)
In the last two decades medicines have turned HIV from a death sentence to a chronic disease with near normal life expectancy, led to the cure of certain types of childhood cancers, radically altered the outlook for breast cancer and many other cancers and greatly improved the lives of millions of people with chronic disorders. To accelerate the revolution in healthcare, capabilities in the engineering and physical sciences must be further developed, for example in areas such as **informatics** (allowing, for example, '**in silico**' **prediction of drug effects** and minimising testing), **tissue engineering** (**testing of printed organs on chips**), next-generation chemistry (allowing more targeted therapy including production of bi-functional molecules) and **high resolution molecular imaging of drugs in the body**.

Physical devices and surgery (Professor The Lord Darzi of Denham, Professor of Surgery, Imperial College London)
Since the start of the 20th Century, advances in healthcare have transformed human health – life expectancy has doubled in this time and surgery and medical devices have made major contributions to this progress. We face significant healthcare challenges in the coming decades including the threat of non-communicable diseases such as obesity and diabetes, burgeoning healthcare expenditure and the need for cost-effective prevention, as opposed to cure. The challenge will be to create new and disruptive treatments and diagnostics that are both sympathetic to humans and their physiology and intelligent through monopolising information from the world around and patient specific data in order to make better health decisions for clinicians and patients. It will require the parallel advancement of cutting edge **robotics, micro-processing, computer technology, miniaturisation and sensing technology**, with the goal of creating bio-compatible technologies and devices for integration with humans.

Big data, genomics and healthcare (Professor Sir John Bell, Regius Professor of Medicine, University of Oxford) Rapid advances in big data, genomics and mobile health are transforming the global healthcare market. Much of the advances in these areas will rely on the skills and knowledge from engineering and physical sciences. Big data will enable the analysis of complex healthcare data, to the extent that medical research and health care delivery is likely to be completely different in 20 years. The ability to use big data in conjunction with the significant EPS-led innovations in genome sequencing will help decipher a range of diseases, including cancers, arthritis and vascular diseases. Doctors will be more able to prescribe with precision the best health treatments and preventative care available, that is bespoke to an individual's unique genetics and circumstances. But that will only be possible with significant input from **data scientists**, **computer scientists and statisticians** working with health experts to determine how to analyse and interpret the data effectively. Likewise, a wider take up of 'mobile health', which will shorten hospital stays, enable patients to have rehabilitation at home and improve patients' health, will require further advances in EPS areas such as **sensors and detection systems, miniaturised analytical devices, information processing and communications technologies**.

Maximising the likelihood of success

In order to gain insight into factors that might influence success at the interface, the panel reviewed the structures of selected organisations, with a focus on the range of different models and the features that made them successful. This was informed by a study which looked at research institutes and universities in the UK and overseas[4], including the following organisations:

- Howard Hughes Medical Institute, Janelia Farm, USA
- European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
- Laboratory of Molecular Biology (LMB), Cambridge, UK
- European Bioinformatics Institute (EMBL-EBI – part of the European Molecular Biology Laboratory), Hinxton, UK
- Broad Institute, Boston, USA

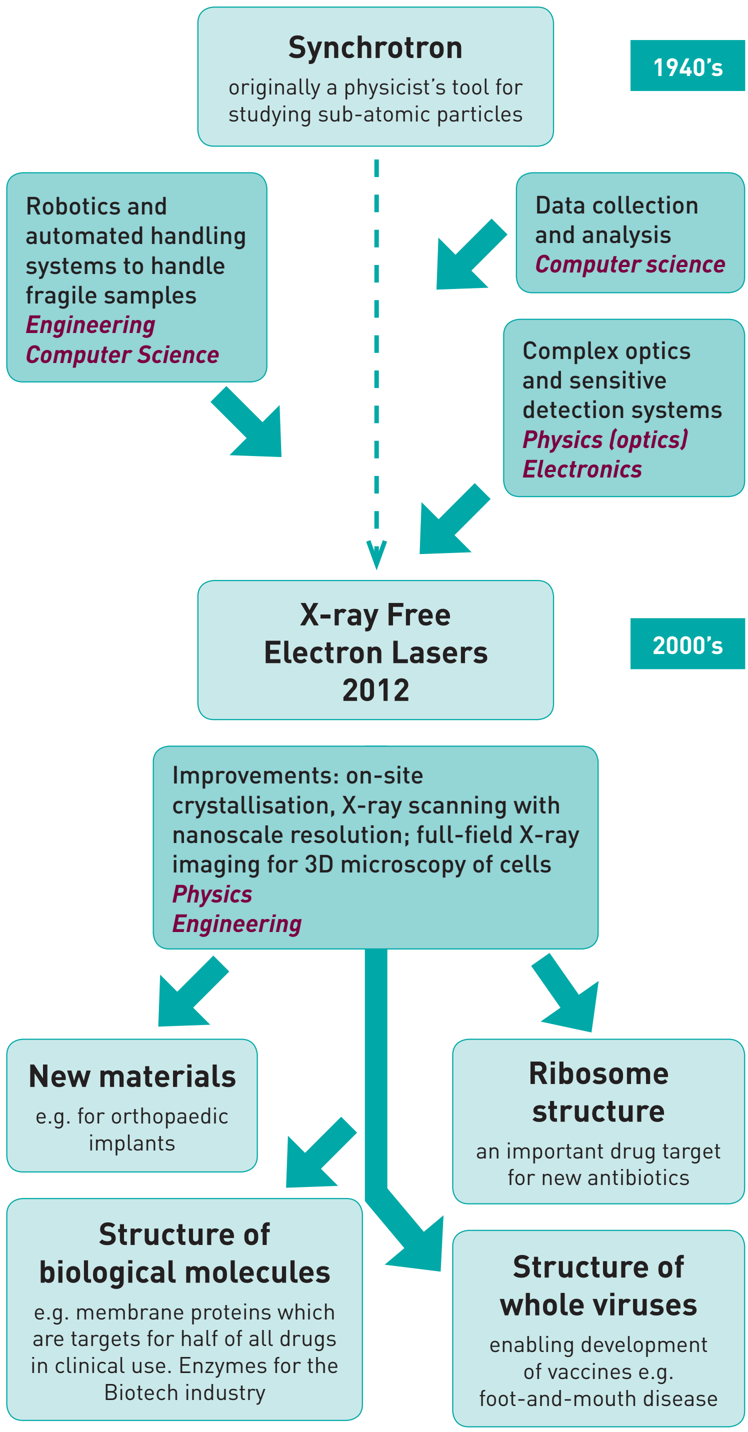
The key messages which emerged were:

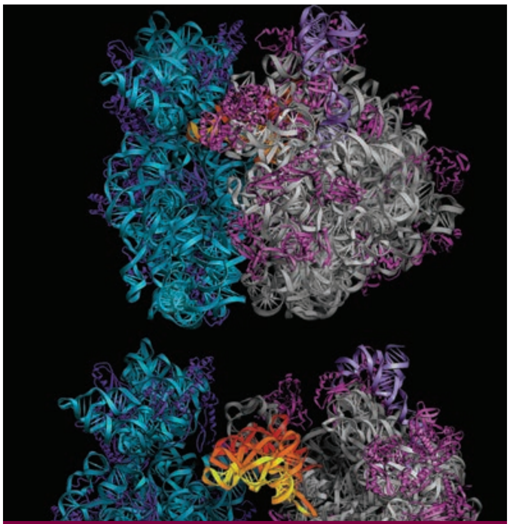
- The need to focus activity around key challenges and bring to bear the most relevant skills, regardless of discipline 'label'.
- The importance of organisational culture.
- Access to flexible funding to underpin dynamism.

[4] The executive summary of this study is at Appendix C.

Case study: Synchrotrons

Synchrotrons are a key tool for studying the detailed structure of complex biological molecules and other materials; they were developed by physicists, computer scientists and engineers.





Pharmaceutical companies and academic researchers are making increasing use of synchrotron X-rays to determine the 3D structure of complex biological molecules such as proteins. This will help in the design of targeted drugs for diseases such as Alzheimer's and in understanding the mechanisms behind cancer.

Synthetic vaccines

Virus crystals are very small and fragile, making them difficult to study. Diamond is the only place in the world that can allow analysis of dangerous viruses at room temperature without physical handling. UK researchers used Diamond's resources and their expertise in structural analysis and computer simulation to visualise the foot-and-mouth disease (FMDV) virus. This allowed them to design a very precise copy for use in a synthetic vaccine which will be easier to produce and more stable to transport than the current versions.

New antibiotics

The structure of the ribosome, an important drug target for new antibiotics, particularly against multi-drug resistant strains, was determined using a synchrotron: Venkatraman Ramakrishnan of the Laboratory of Molecular Biology (LMB) was awarded the Nobel Prize for Chemistry in 2009 for this work.

Improved implant materials

Orthopaedic implants made of metal alloys and polyethylene can fail and cause discomfort. Researchers are using the Diamond Synchrotron to investigate the molecular processes that occur during the irradiation of polyethylene which offers a way to produce stable, better performing implants.

Policy implications

The review group applauds the UK government's recognition of the importance of research in health and life sciences (HLS). To achieve the UK's potential in HLS it is also important to invest in other disciplines such as engineering and physical sciences, from which many new developments in HLS originate. Engineering and physical sciences (EPS) research has played an important role in key areas of HLS and will continue to play a vital part in the future in tackling major challenges, such as those associated with an ageing population and the sustainable provision of food and development of cost-effective medicines.

In his introduction to the government's *Strategy for UK Health and Life Sciences*[5], David Cameron noted that: *"We understand that the game has changed – and that the UK must change with it. This country has all the ingredients to be an outstanding location for medical innovation: an integrated National Health Service, unlike any other; a highly competitive tax and investment framework; and an unrivalled science base, with four of the world's top ten universities here in Britain."*

The review panel applaud the government's recognition of the importance of health and life sciences, and its commitment to maximise the benefits that can be realised, in terms not only of the health and well-being of the population, but also in contributing to the sustained growth of the UK economy through the strength of sectors such as pharmaceuticals and medical technologies. This commitment has been clear through the significant new investments being made, including for example, providing over a quarter of a billion pounds for the flagship Francis Crick Institute.

To make the most of these opportunities, the panel note the importance of embracing and supporting the breadth of research from which biomedical breakthroughs emerge. In particular they want to highlight the essential role played by engineering and physical sciences. It is interesting to note that Francis Crick began his scientific career in physics, before making the transition to focusing on biological problems, including the fundamental question of how genetic information could be stored in molecular form, leading in 1953 to the proposal of the double-helical structure for DNA.

Over the last half century there have been various waves of technological advances in instrumentation, computation, and analysis which have enabled breakthroughs in key areas such as molecular biology, medical imaging and drug discovery. This includes analysis of synchrotron data, light microscopy and DNA sequencing; some illustrative examples are provided in this report. During this study we had feedback from individuals at internationally prominent institutes who were unanimous in agreement that the vast majority of cutting edge biology/health sciences results to have emerged from their labs have only been made possible by preceding advances in physics, chemistry, computing, mathematics, materials or engineering.

> ***"In order to conduct efficient DNA sequencing it first required chemists to put in place the key step of being able to synthesise dideoxynucleotides and thanks to new computing techniques it is now possible to see the side chains of alpha helices in electron microscopes. These techniques and others provide new tools for biologists, which act as catalysts, opening up huge swathes of previously inaccessible new biological discoveries."*** Sir Hugh Pelham, Director, Laboratory for Molecular Biology

[5] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32451/11-1428-investing-in-uk-health-and-life-sciences.pdf

And it's not just the provision of tools and instruments: EPS approaches and developments have changed the way biomedical researchers think. For example, the advances in computation and informatics have enabled life scientists to develop new approaches based on huge datasets, which in turn have opened up new avenues of discovery.

The challenges and opportunities for the future are significant; for example, the sustainable and secure provision of food for a growing global population; efficient ways of developing and producing new, more effective medicines and therapeutic treatments, which can be manufactured with minimal adverse environmental impact; developing individually tailored approaches to healthcare based on the genetic profiles of individuals; exploiting the potential of nano and micro-scale materials and devices for minimally invasive diagnostics and treatments. In all these cases, there is a clear role for engineering and physical sciences: the think pieces included in this report highlight this more fully. For example, future drug discovery will be dependent on:

- **Bio-informatics** to allow the analysis of large databases of clinical information.
- **3-dimensional bioprinting** of human tissue for screening drugs.
- **New synthetic chemistry** which can be quickly industrialised.
- **New materials** for long-term drug delivery systems.
- **Bio-electronic medicines** – using modulation of nerve signals to regulate chronic diseases such as diabetes.
- **High resolution molecular imaging** to assess drug distribution at the cellular level.
- Advances in **flow chemistry, catalysis and continuous processing**.

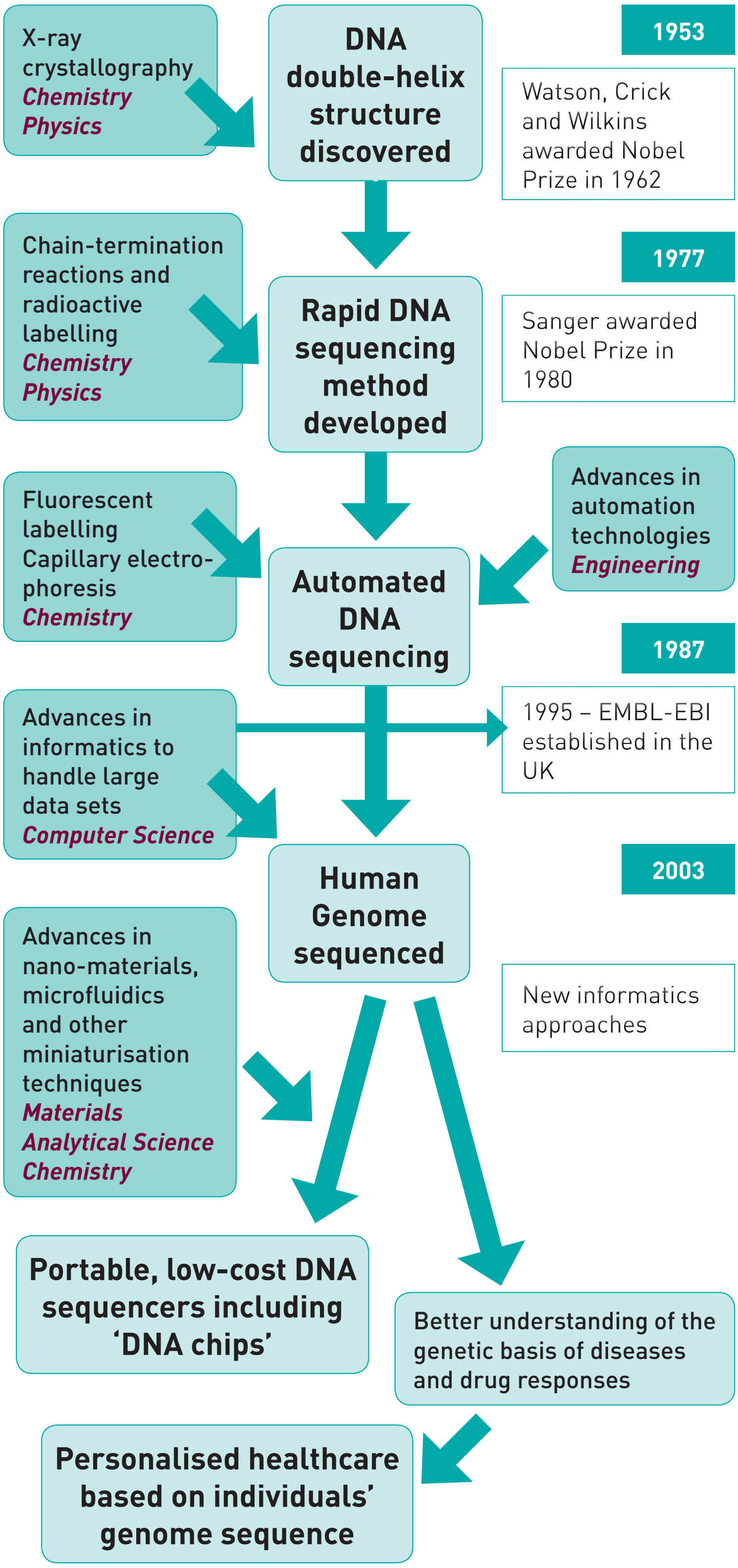
A key conclusion is that to fulfil its vision for the UK to be an outstanding location for research and innovation in health and life sciences, the government must nurture not only the biomedical disciplines, but also the full spectrum of disciplines on which HLS draws, including mathematics, physical sciences and engineering. Success will be very limited without an integrated approach involving physical scientists, engineers and life scientists working together on the key research challenges of the future.

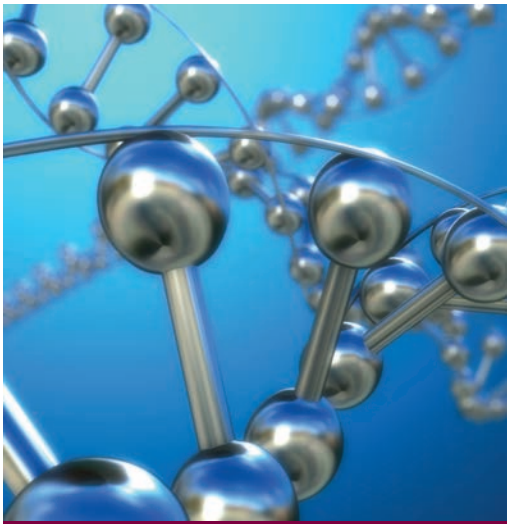
> ***"Biomedicine is becoming progressively more dependent on other scientific disciplines, including physics, chemistry, engineering and computational sciences. To succeed in this changing environment, we must develop ways of working that are receptive to new techniques and approaches and unconstrained by traditional disciplinary boundaries."*** From the Strategy of the Francis Crick Institute[6]

[6] http://www.crick.ac.uk/media/131115/tfc_full_document_for_web_single_pages.pdf

Case study: DNA sequencing

The advent of rapid DNA sequencing methods has greatly accelerated biological and medical research and discovery.





In April 1953, James Watson and Francis Crick published the structure of the DNA-helix, the molecule that carries genetic information from one generation to the other. Their discovery was the result of a combination of experimental (x-ray crystallography) and theoretical approaches.

Sanger's team at Cambridge developed a rapid DNA sequencing method using chain-termination inhibitors which was widely used for the next 25 years.

In 2003 an international team of researchers, including UK scientists funded by RCUK and the Wellcome Trust, completed the DNA sequencing of the human genome.

The opportunities this offers include: genotyping of specific viruses to direct appropriate treatment; identification of oncogenes and mutations linked to different forms of cancer; the design of medication and more accurate prediction of their effects; advancement in forensic applied sciences; biofuels and other energy applications; agriculture, livestock breeding, bioprocessing; risk assessment; bioarchaeology, anthropology and evolution.

The major current sequencing technology was developed by academic researchers at Cambridge and commercialised by the company Solexa (subsequently acquired by Illumina in 2007). Another UK-based company, Oxford Nanopore, is developing portable, low-cost, DNA analysis sequencing devices by exploiting breakthroughs in the chemistry and physics of nanopores.

Key recommendations

Recommendation one: Funders and research organisations should actively foster work at the interdisciplinary interface. This should build on experience of successful approaches in the UK and overseas, which suggest that while there is no simple recipe, creating the right scientific environment is critical and that important ingredients are inspirational leadership, a clear mission, flexible funding and an organisational culture which encourages 'non-silo', 'trans-discipline' thinking.

There are many very good examples of successful interdisciplinary research activities involving physical and life scientists working together. High-profile examples include the European Molecular Biology Laboratory (EMBL), Janelia Farm Research Campus (part of the Howard Hughes Medical Institute), the BROAD Institute, and in the UK, the Laboratory of Molecular Biology (LMB) and the European Bioinformatics Institute (EBI). In addition, UK universities demonstrate a rich variety of approaches for delivering research spanning traditional discipline boundaries. These range from university-spanning 'institutes' to small, tightly focused centres. The panel noted that, in terms of structure, it was quite clear that there was no 'one-size-fits-all' solution. However, they identified some aspects which appear common to successful interdisciplinary activities.

Success features:

- Strong, inspirational leadership is crucial to create and encourage a strong culture of interdisciplinary working; the culture of a group or organisation relies heavily on the way in which the leader or senior team demonstrate their appreciation of complementary skills brought by others.

- There needs to be a clear vision or mission, which allows all researchers to see how their work and skills can contribute, whilst allowing a common language and set of activities to develop – this may be focused around one or more big challenges (such as the Broad Institute), or around the delivery of a key service to others (EBI) and/or the advancement of knowledge in a specific area (LMB). There are also good examples of this focus on a key challenge in industrial research teams.

- Flexible funding is essential to enable activities to be refocused dynamically as results emerge. There needs to be opportunities to change research direction or to move flexibly from fundamental discovery through to translation and real-world application. Long-term support for high quality interdisciplinary research, scrutinised by peer review, should be the preferred route, with regular review points to ensure that quality is maintained.

Approaches to interdisciplinary activity

The study of existing interdisciplinary centres and activities reinforced the view that there is no single solution in terms of structure. The view from internationally prominent institutes was that it was more effective to set up a physical entity with groups of researchers formed around a particular challenge than to set up discipline based departments. The opposite view was held by centres within universities where interviewees were clear that forming around a grand challenge gave focus, but that they needed to remain in a 'home' department to enable their subject area expertise to grow and contribute to advances in the 'core' of their discipline. These interviewees were concerned that co-locating all researchers into a single facility would just create a different type of silo.

The panel agreed that interdisciplinary institutes are excellent for collaborations and for training people (including students), but they are not the only way of ensuring good interdisciplinary research. Many centres are badged as life sciences even though they are actually fully interdisciplinary. The physical proximity of different disciplines is important (but not essential) to interdisciplinary working. Strong collaborations have been enabled through the development of the internet: this is particularly true with 'dry' research e.g. computational and mathematical approaches to biology. Some interdisciplinary institutes have benefitted by not being located in the most obvious locations: the panel noted that it is sometimes beneficial for interdisciplinary institutes to be located away from their obvious 'home' environment in order to break traditional paradigms and encourage new interdisciplinary working. Examples include the Structural Genomics Consortium in Oxford, the Manchester Institute of Biotechnology and the Laboratory for Molecular Biology in Cambridge.

The relationship between size and interdisciplinary success is unpredictable. Some smaller universities may not have the critical mass to develop substantive interdisciplinary EPS/HLS centres, both in terms of a) the number and range of staff expertise; and b) availability of appropriate infrastructure. However, some of these can be better environments for interdisciplinary research. This is because in some large organisations, it can be difficult to drive new initiatives to a successful outcome, as the complexity of internal partners and the 'shock' of trying to implement a radical initiative means that compromises are often required that dilute the interdisciplinary objectives. Smaller HEIs may also be more likely to develop successful external partnerships.

It was noted that it can be a challenge to integrate 'wet' and 'dry' or 'experimental' and 'computational' research. Evidence from the EBI suggested that over the last five years the way in which this happens has changed significantly for the better. For example, computational researchers are now involved right at the start of projects to ensure that experiments are designed and modified to ensure data quality and integrity. This reflects an increasing recognition that as the research problems become more complex, many of the tools and instrumentation need to be developed as an integral part of the research endeavour, rather than an off-the shelf service that can be used as required.

The panel agreed that to meet future challenges it would be necessary to enhance and extend the culture of interdisciplinary working further through the use of innovative approaches as well as through ensuring that the composition of peer review, promotion and interview panels is appropriate for fostering interdisciplinary research.

It is encouraging to note that the importance of this approach is recognised in the strategy of the Francis Crick Institute, the UK's new flagship biomedical research centre, which states: "*Increased interactions between biological and physical sciences will pay dividends to both sides, introducing new data, methodologies, concepts and perspectives and stimulating the development of novel approaches to problems*."[7]

[7] http://www.crick.ac.uk/media/131115/tfc_full_document_for_web_single_pages.pdf

Recommendation two: Effectiveness at the EPS/HLS interface depends in part on focussing effort on the right challenges. Funders and research organisations should play a major role in identifying and defining important challenges, assembling effective teams to tackle these challenges and providing sufficient support for them to do so. However, these challenge-driven approaches should not exclude support for curiosity-driven research.

Many significant breakthroughs have arisen through a response to clearly defined challenges, from determining the structure of DNA, to sequencing the entire human genome. This challenge-driven approach is often adopted in industrial R&D; for example, drug discovery labs are usually focused around specific diseases and/or molecular targets.

The review group identified a range of key research 'challenges' that have an important EPS/HLS component: some of these challenges are major health challenges that EPS should contribute to, for example:

- The changing demographics in the UK (ageing population) and its impacts on healthcare.
- Health challenges arising from changing diet and lifestyles, such as obesity, fatty liver disease, etc.
- The needs of developing nations in particular to improve preventative health care, e.g. the need for more people with fewer formal qualifications to provide health support using innovative technologies.
- New therapeutics to tackle neurodegenerative diseases.

Other challenges are more specific ones that the EPS community can address, for example:

- Multiple drug resistance of disease-causing microorganisms.
- Implants that will last the lifetime of the patient.
- Developing our understanding of brain function.
- Requirements to develop new more efficient personalised therapies: maximising the effectiveness of procedures and interventions (including regenerative approaches) whilst minimising cost.

These examples illustrate the range of challenges, including the variety of drivers and timescales associated with them. Funders, such as research councils and charities, have the power to bring together academics and to create momentum in research via targeted funding calls that stimulate collaborative and interdisciplinary research focused around key challenges, such as those listed above.

Complementing the challenge-driven approach is the need to balance support and resources for curiosity-driven research. These two approaches should not be mutually exclusive. The Broad Institute, a collaboration between Massachusetts Institute of Technology (MIT) and Harvard University, is an example of a centre that encourages blue-skies research as well as having a focus around a few key challenges.

The Broad Institute is committed to meeting the most critical challenges in biology and medicine. It supports a wide variety of projects that cut across scientific disciplines and institutions which collectively aim to:

- Assemble a complete picture of the molecular components of life.
- Define the biological circuits that underlie cellular responses.
- Uncover the molecular basis of major inherited diseases.
- Unearth all the mutations that underlie different cancer types.
- Discover the molecular basis of major infectious diseases.
- Transform the process of therapeutic discovery and development.

Case study: Microscopy

The development of microscopy revolutionised biology and remains an essential technique in the life and medical sciences.

1674

Simple microscope
for viewing biological specimens

Phase contrast microscopy
study of the cell cycle in living cells

Dutch physicist Fritz Zernike awarded Nobel Prize in 1953

Development of lasers
Physics

1970's

Fluorescence microscopy
targeted staining of different biological structures or molecules

Chemical labelling techniques
Chemistry

Gene fusion to link GFP expression to the target protein
Molecular Biology

Fluorescence microscopy using green fluorescent protein (GFP) allows study of protein function in vivo

Development of infra-red/pulsed lasers
Physics

Two-photon microscopy
imaging of living tissue up to a high depth (i.e. 1mm)

Serial Time Encoded Amplified Microscopy (STEAM) used for biomedical applications that requires high image acquisition rates including laser surgery

Multiphoton microscopy
high-resolution, 3D imaging of live brain

Microscopes have been used for several hundred years to view samples and objects that cannot be seen with the unaided eye. However, the developments in microscopy have been particularly dramatic over the last 50 years with the rise of fluorescence microscopy, which is of critical importance in the modern life sciences. The main fluorescent labelling techniques include chemical staining of cellular structures, to label DNA, use of antibodies conjugated to fluorescent molecules and fluorescent proteins, such as green fluorescent protein. These have been developed using the molecular biology technique of gene fusion, a process that links the expression of the fluorescent compound to that of the target protein. Genetically modified cells or organisms directly express the fluorescently tagged proteins, which enables the study of the function of the original protein in vivo.

Using a scanning point of light instead of full sample illumination, confocal microscopy gives slightly higher resolution and significant improvements in optical sectioning. Confocal microscopy is, therefore, commonly used where 3D structure is important.

Cornell researchers have demonstrated a new way of taking high-resolution, three-dimensional images of the brain's inner workings through a three-fold improvement in the depth limits of multiphoton microscopy. Pushing these depth limits is important for basic science and eventually could prove useful clinically. Diseases like Parkinson's and Alzheimer's are associated with changes deep inside the brain, and finding the cures could be helped by this approach.

Recommendation three: The UK should build human capacity that can operate effectively across discipline boundaries in order to maintain our leading role in health and life sciences. As well as focusing on high quality doctoral level training for interdisciplinary research, research organisations and funders need to work together to maximise career opportunities for EPS and HLS trained researchers within interdisciplinary environments.

The increased emphasis on tackling key HLS challenges and adopting more interdisciplinary approaches will require increasing numbers of skilled researchers who can work effectively with others from a range of disciplinary backgrounds.

It was agreed that it was important to nurture and develop early career researchers to be able to operate in multidisciplinary environments. The panel noted that there are already good examples of effective doctoral level training focused specifically on developing interdisciplinary skills, for example, the life sciences interface doctoral training centres supported by the EPSRC in areas such as bio-nanotechnology, medical imaging and bioinformatics, targeted therapeutics, tissue engineering and regenerative medicine and neuroinformatics. The use of these doctoral training centres to train a new generation of researchers in these skills had been highlighted as making a real difference to how researchers thought about their subjects and research questions. For example, the Head of the Centre for Biological Engineering at Loughborough expressed the ease with which these centre-trained students can interact with peers outside their discipline specialism by saying that they 'had grown up multilingual'.

The vision is to create a new cadre of healthcare professionals by having health and EPS professionals train and work together. The aim is to assist a culture shift. Aspects could include:

- Research councils working together to co-fund more centres for doctoral training, especially MRC and EPSRC with a focus on emerging areas of clinical need.
- Exchange fellowships between HLS and EPS laboratories.
- Sponsorship of integrated multidisciplinary training for medics, scientists and engineers.
- Continuing professional development focused on the latest technological developments.

Beyond doctoral training, there needs to be a continuing emphasis on encouraging greater 'permeability' of research careers, for example, through movement across disciplines as well as through involvement in multidisciplinary teams. An important barrier is that physical scientists may find it hard to see how they can gain career enhancement whilst working in a life sciences environment. A number of the leading international centres included in the study reported difficulties in hiring those skilled in engineering/physical science disciplines as there was a perception that these skills would simply be used as a service to biologist/medical colleagues and that such researchers would not advance their careers in their 'home' discipline as quickly. In most cases this appears to be mainly a barrier of perception (e.g. EMBL reports that physical scientists have done very well). However, it is clearly important to ensure adequate challenge and opportunity for all the scientists involved, and also that the achievements of researchers in interdisciplinary areas are fully recognised.

Recommendation four: The role of engineering and physical sciences should be integrated into the UK strategy for life sciences. Government departments such as BIS and the Department of Health need to ensure that they fully engage with relevant stakeholders in developing and delivering a shared vision for this interface.

The creation in January 2007 of the Office for Strategic Co-ordination of Health Research (OSCHR) following the Cooksey Review has enabled better coordination of health research strategy and funding. In addition to the cross-departmental role of OSCHR, the government's Office for Life Sciences (OLS) has a complementary responsibility to work with other government departments (Health, Energy & Climate Change), UKTI, the NHS and others to foster the sustainable long-term growth and global competitiveness of the UK life sciences sector.

The UK has one of the strongest and most productive life sciences industries in the world, contributing to patient well-being as well as supporting growth. UK life science industries generate turnover of over £50 billion and employ 167,500 in over 4,500 companies[8]. In December 2011 the government launched its ten-year *Strategy for UK Health and Life Sciences*, which sets out a long-term vision to re-establish the UK's global leadership in life sciences, and support the growth of British life science companies. The aim is to achieve an integrated healthcare economy in which the different elements of the UK sector (fundamental research, clinical research, industry and the National Health Service) are able to work much more closely together to accelerate healthcare innovation.

Engineering and physical sciences play an important role in many areas of the strategy, for example key developments in medical imaging, regenerative therapies, novel drug design and delivery, medical instrumentation and implants will all be dependent on EPS research and researchers. The panel agreed that it is vital that this role is recognised in the development and implementation of strategies for health and life science, through appropriate representation and engagement with key bodies such as OSCHR and OLS.

They also agreed that there is scope for greater integration at the operational level. For example, engineers could become more involved at the point of delivery of health research. Although medical and hospital organisational structures can be difficult to navigate, more interchange of ideas and approaches between clinicians and engineers would be beneficial. Clinicians have a natural focus on the medical aspects of an issue and may not recognise the opportunities for EPS to transform aspects of the clinical environment. Notably, there is potential for greater integration of basic informatics research with applications in the clinical setting. Currently computers in hospitals are used most intensively in the development and analysis of medical imaging, but it is clear that there is huge scope for increased use of ICT in addressing health challenges.

The group also felt that there was a significant opportunity to increase the EPS research undertaken within the NHS. They suggested that real benefits could arise from short sabbaticals for EPS trained researchers to spend time in hospitals to help encourage NHS/medical staff and EPS staff to collaborate – creating a rich environment for identifying and addressing research challenges.

[8] https://www.gov.uk/government/organisations/office-for-life-sciences

Case study: Biomaterials

Biomaterials are used every day in dental applications, surgery and drug delivery. They are the combined product of medicine, biology, chemistry, tissue engineering and materials science.

First man-made material to bond to living tissues (Bioglass)

1960's

First total hip replacement
(using polyethylene and stainless steel)

Scientific advances in biomaterials and biomimetics environments
Materials
Chemistry
Biology

Development of bio-compatible materials
Precision engineering of implants
Materials Science
Engineering

Tissue engineering development of biological substitutes that restore, maintain or improve tissue function

Implants to replace or repair: heart valves, joints, bone, tendons/ligaments, blood vessels

Bioartificial organs e.g. artificial pancreas or liver

Regenerative Medicine using stem cells to produce tissues

The Future
Further research advances in cell and developmental biology, materials science, engineering and bio-informatics

Development of fully functional human replacement tissues and organs

The first total hip replacement was in 1962. Sir John Charnley used a plastic cup (made from High Molecular Weight Polyethylene) and a metal 'ball' for the head of the thigh bone. The bone cement that he used was originally developed for making dentures, but is also suitable for fixing prostheses, and is still used in over 80 per cent of hip and over 90 per cent of knee replacements. In the same decade, the first generation of bioceramic material was developed. Known as Bioglass®, it was the first class of man-made materials with the unique ability to bond with bone and connective tissue making it suitable for clinical applications in the repair of bones, joints and teeth. Later it was discovered that a liquid form of Bioglass could enhance the healing process.

In the 1990's, backed by EPSRC funding, medical materials engineers Professor Bill Bonfield and Dr Karin Hing, at Queen Mary, University of London, pioneered a form of bone graft with enhanced structure and chemistry to boost healing. The research led to the formation of ApaTech, a highly successful orthobiologics company to produce the material commercially - today it is used by surgeons worldwide.

Materials that can mimic soft tissues such as skin, nerves, cartilage and tendons are also being designed and engineered thanks to the concerted efforts of chemists, materials scientists and bioscientists. For example,research on polymers at Sheffield University led to the development of MySkin, a dressing for severe burns made from flexible silicone coated with a chemically controlled plasma polymer film. Launched in 2005, it is now being tested on diabetic foot ulcers.

In 2011 researchers at the University of Leeds developed a peptide-based fluid that, when painted onto a tooth that shows signs of decay, helps it to regenerate by inducing the mineral deposition process required for repair of tooth decay. Also in 2011, surgeons in Sweden carried out the world's first synthetic organ transplant using a windpipe 'grown' from the patient's stem cells. The replica organ was designed and developed by EPSRC-sponsored scientists: the team used 3D computed tomography (CT) scans of the patient to craft a perfect copy of his trachea using a glass mould, from which they developed a replica 'scaffold' using a novel polymer.

The continued success of tissue engineering, and the eventual development of true human replacement parts, will grow from the convergence of engineering and basic research advances in tissue, matrix, growth factor, stem cell, and developmental biology, as well as materials science and bioinformatics.

Recommendation five: As part of the process to promote and encourage interdisciplinary research at the EPS/HSL interface, we recommend that key stakeholders give detailed thought to how interdisciplinary research and the environment in which it occurs can best be measured.

The importance of interdisciplinary collaborations in enabling and delivering innovative world class research is a crucial issue at the EPS/HLS interface. To achieve a greater level of interdisciplinary working requires regular monitoring and sustained scrutiny from relevant stakeholders. Measurement of performance frequently has an influence on behaviour and outcomes. In order to foster interdisciplinarity, improved measurements need to be put in place. This should occur in conjunction with the regular reviews proposed in recommendation six. It is recognised that this will not be simple: an agreed definition of interdisciplinary research will be needed as a first step. Funding bodies should work together to ensure that there is an agreed methodology for quantifying interdisciplinarity in research proposals, awards and research outputs.

The importance of interdisciplinary research is recognised in the 2014 Research Excellence Framework (REF), which claims to promote equity of all types of research and research output across all disciplines. The REF aims to identify excellence in research including interdisciplinary research, without distorting the activity that it measures or encouraging or discouraging any particular type of research activity, other than providing a general stimulus to enhancing the overall achievements of the UK research base. The REF allows institutions to provide information about how they support interdisciplinary research so that recognition can be given to where this has enhanced the vitality and sustainability of the research environment or the contribution to the wider research base. The increasing recognition of interdisciplinary research in the REF over the Research Assessment Exercise is a positive step; however there is a pressing need to improve the identification and collection of appropriate measures of interdisciplinary research to stimulate this important area.

Whilst there are many published tables that address a range of measures of HEI's, the review group is unaware of a table that focuses on the interdisciplinarity. UK university rankings use a range of criteria such as student satisfaction, teaching excellence, peer assessments, research quality, graduate unemployment rates, library and computing spending and student satisfaction. International university rankings include indicators such as academic and employer reputational surveys, research and teaching income, publication citations and prize winners. A measurement of interdisciplinarity could be an important addition to these league tables.

Recommendation six: Key stakeholders should review activity and opportunity at the EPS/HLS interface on a regular basis. These reviews should challenge the status quo and aim to catalyse more effective coordination between EPS and HLS.

The continued development of the EPS/HLS interface is a long-term agenda which requires on-going strategic input from all of the key stakeholders. The landscape is complex, involving many different organisations and activities, including government, public and third sector funders and research organisations, industry and regulatory bodies. The panel noted that there is a rich spectrum of research and training activity within the UK, much of it based on partnerships between key players. Examples include:

- **UK Regenerative Medicine Platform** – established by BBSRC, EPSRC and MRC in 2012 to address the technical and scientific challenges associated with translating promising scientific discoveries in this area towards clinical impact. As part of the first phase four interdisciplinary and complementary research hubs have been established in: cell behaviour, differentiation and manufacturing; stem cell engineering and exploitation; imaging technologies; and smart material approaches for therapeutic delivery.

- **Wellcome Trust/EPSRC medical engineering centres of excellence** – focused around the themes of medical imaging, osteoarthritis, human joint and cardiovascular health, and personalised medicine, these centres provide an environment for mathematics, physical science, engineering and medical research to come together, to encourage exploratory research and the translation of that research into products that can improve healthcare.

- **The Biomedical Catalyst** – a funding initiative jointly run by the Technology Strategy Board and MRC which opened for applications in April 2012 and was designed, in Prime Minister David Cameron's words, to get "*the best ideas through the proof of concept stage, so we can get them into clinical development and get our entrepreneurs selling them around the world*".

- **The Centre for the Advancement of Sustainable Medical Innovation (CASMI)** – a partnership between Oxford University and UCL, created to develop new models for medical innovation. The centre aims to address the issues that have led to current failures in the translation of basic bioscience into affordable and widely adopted new treatments. CASMI brings together a broad range of academic disciplines and other stakeholders, including patient groups, industry, regulators, policymakers and clinicians, to tackle problems at a systemic level, designing socially and economically sustainable solutions that are acceptable to all.

- **Synthetic Biology Innovation and Knowledge Centre (SynbiCITE)** – launched jointly by EPSRC, BBSRC and the Technology Strategy Board in 2013, SynbiCITE 's role is as an industrial translation engine that can integrate university and industry based research in synthetic biology into industrial process and products. The centre involves researchers from 18 universities and academic institutions across the UK, as well as 13 industrial partners, including the research arms of Microsoft, Shell and GlaxoSmithKline.

- **Interdisciplinary research collaborations** – centres of internationally-acknowledged scientific and technological excellence, with sufficient critical mass to make a real impact in areas of key future industrial relevance to the UK. The collaborations are funded by EPSRC through long-term grants and generally involve several universities together with industrial partners. New centres have recently been established in: early-warning sensing systems for infectious diseases, 'Touch and tell' optical molecular sensing and imaging, and sensor platforms for healthcare in a residential environment.

- **Cancer Research UK-EPSRC cancer imaging centres** – four centres were established in 2009 to develop new imaging techniques and uses for existing advanced imaging technologies, including imaging equipment to allow scientists to watch cells in action by tracing radioactive markers injected into a patient's body. These techniques will enable doctors to see therapies at work and identify at an earlier stage which treatments work best for individual patients. An additional funding boost for five years was announced in October 2013. This latest funding will bring together scientists, engineers and clinicians to develop new imaging techniques and applications which will help clinicians learn more about how tumours feed and grow, how cancer cells signal to one another, tumour blood supply, the environment surrounding tumours and molecular and genetic signatures.

Whilst these collaborative activities are encouraging, the panel considers that there is much more scope for future coordination of EPS and HLS, and that this will be necessary to ensure that the UK is well placed to deliver on the health/life sciences related challenges. They recommended that a periodic review should take place, of the extent to which an integrated, multidisciplinary approach is being adopted, both in the delivery of research, training and innovation in key areas, and in the development of strategy. The panel felt that this recommended 'stock-take' should be undertaken jointly by the key stakeholders and would provide an opportunity to reflect on the effectiveness of the engagement and identify areas where actions could be taken to further enhance it.

Case study: Magnetic resonance imaging

Today's MRI scanners are the product of research from physics (superconducting magnets) and chemistry (contrast agents to improve images) to computer science (software to produce and analyse images) and engineering (scanner construction).

Superconducting Magnets (UK advances in particle physics technology pioneered early superconducting magnets, vital for the development of MRI scanners)
Physics

Early imaging techniques
Physics
Computer science

MRI
structural analysis of soft tissue

Sir Peter Mansfield received a Nobel Prize in 2003 for developing MRI

1970's

Software (Vector Fields)
Computer science

Echo-Planar Imaging (EPI) allows faster imaging
Physics

1977

Advances in image analysis
Physics
Computer science

Functional MRI (fMRI)
Studying dynamic processes in living organisms e.g. imaging brain function

1993

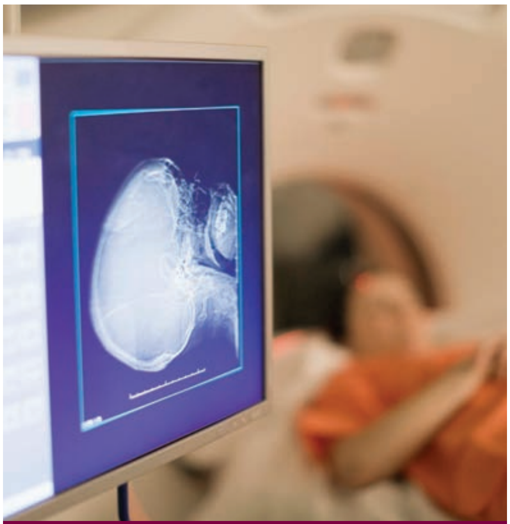
Advances in detector technology and image analysis
Physics
Computer science

Development of contrast agents, probes and tracers (e.g. nanomaterials for diagnosis and targeted therapy combined)
Chemistry
Materials

MRI-guided intervention
used, for example, in the diagnosis and treatment of cancers

The future

Fusion of MRI images with others derived from complementary techniques
high sensitivity diagnosis and monitoring of treatment – especially for cancer, spinal problems and brain disorders



MRI revolutionised medical imaging by producing detailed images of soft tissues for the first time; previously imaging relied on X-rays and ultrasound. UK researchers were key to its development, including Raymond Andrew (Bangor, Nottingham) and John Mallard (Aberdeen), who led the team which developed and tested the MRI body scanning machine and brought its wide spread use to the medical profession. In 1983 the University of Manchester Medical School installed the first commercial MRI scanner in Europe.

The development of Echo-Planar Imaging improved imaging speed – by 1987 it was possible to perform real-time movie imaging of a single heart cycle.

Functional MRI allows doctors to study brain activity during development, following injury and in brain disorders such as Schizophrenia and Alzheimer's disease.

'Motion-tolerant' image analysis enables 3D images of foetuses moving in the womb; it will improve care for very small and premature babies and allow the testing of new therapies for treating brain damage.

Combining MRI images with those from other techniques such as Single Photon Emission Computed Tomography will make it possible to look at the structure and function of an organ simultaneously.

Cancer – MRI is used to assess how tumours respond to different treatments and may be used to assess patients' suitability for radiotherapy.

Neuroscience – latest developments allow MRI to monitor blood flow in the brain to pinpoint specific functions such as language production.

Looking to the future – the vital role of engineering and physical sciences in key health and life sciences developments

As part of this review the panel identified areas of health and life sciences which are likely to become increasingly important in the future and where the UK is well-placed to make a significant contribution. Experts were invited to provide forward-looking think pieces, setting out their visions of the challenges and opportunities associated with these areas, and highlighting in particular the role that engineering and physical sciences would play in enabling the breakthroughs to occur.

Sustainable food production: Meeting the global challenge

Dr David Lawrence, Non-Executive Director of Syngenta AG, Chair of the Syngenta Science & Technology Advisory Board

Feeding the world sustainably is recognised as a major challenge: globally food production will need to grow by at least 50 per cent and perhaps as much as 75 per cent. This will only be possible with significant research-based innovations in areas such as crop protection (e.g. through safe herbicides and insecticides), improving crop take-up of key nutrients such as nitrogen and phosphates, improving water recycling in agriculture and understanding and applying best practice in agricultural settings. Developments will rely heavily on engineering and physical sciences research, for example:

- **Catalyst technology** to reduce energy demands for nitrogen-fixing.

- **Sensor technology** to tailor the application of water and key nutrients such as nitrogen and phosphate only when crops need it.

- **Soil chemistry** to optimise mineral nutrition, so that as much as possible of the applied nitrogen, phosphate and other minerals gets taken into the crop.

- **Advanced informatics** to enable tailored treatments for crops and animals based on increased understanding of the effects of key variables.

- **Chemical synthesis** to design and synthesise new, highly effective and safe active compounds for protecting crops and optimising yields.

Those living in the wealthy countries of the west have had an unprecedented last one hundred years. Food has been increasingly plentiful and diverse, its quality has increased not just in nutrition, but also in visual appearance. At the same time the proportion of income required to pay for it has declined. The readily availability of good, wholesome food, together with improved hygiene and antibiotics, has resulted in a very significant increase in life expectancy.

This success has been possible only through many innovations in the physical sciences. However, everything that has been achieved is at risk over the next decades. Much grain is used to feed animals, so in theory if everyone became vegetarian the pressure on crops would be lower, but realistically this is not going to happen. Global population is certain to grow 40-50 per cent and, indeed, meat eating is increasing where population is growing fastest. Also, hopefully, society will finally manage to eliminate hunger amongst the poorest. Overall food production needs to grow by at least 50 per cent and perhaps as much as 75 per cent if everyone is to be fed. In addition, it is clear that some of the present gains have only been achieved though unsustainable use of resources, and agriculture and food production has contributed to greenhouse gas emissions which bring an additional challenge in adapting crop production to a changing climate. Feeding the world equitably and sustainably is clearly going to be possible only with many more innovations. Unfortunately, the rate of productivity gains has noticeably slowed this century and the recent rises in food prices give a hint to the consequences of failing to increase productivity.

It used to be said that man's most common activity, other than sleeping, was weeding. In fact it was not men, but women and children who did it. The introduction of mechanisation, and then even more of chemical herbicides has completely changed this situation, enabling huge urbanisation and dramatically improved education and lifestyles for women. It is inconceivable that we could feed the world without good weed control: it would reduce yields by at least 20 per cent at a time when we need an increase. However, resistance is reducing the effectiveness of existing herbicides and the last new major mode-of-action was discovered way back in the 1980's.

It is well known now that human pathogens are becoming resistant to antibiotics, and that there is an urgent need for new ones. What is less well known is that the situation is exactly the same with plant fungicides and antibiotics used to control animal diseases. Insect resistance is also creating a similar need for new control chemicals in agriculture and animal husbandry.

Together, it is estimated that without herbicides, insecticides and fungicides, crop yield would decrease by at least 40 per cent. There is an easy idealism which believes that it is possible to live without these tools. However, the only alternative to herbicides is either manual weeding or complex automated machinery which needs to be able to distinguish a weed from a crop and then remove it. This is itself an area worth of innovation in physical sciences, but one unlikely to be a panacea. Although there is little natural resistance to insect pests within the plant genomes, there is indeed resistance to fungi. However, yield losses of 10-20 per cent without fungicides are on genetically resistant plants: without this resistance, losses can be total. Historically this can be seen with potato blight, which caused the Irish potato famine, and where the impact is limited through chemical fungicides. Only the combination of technologies gives close to total protection. Climate change is changing the pattern of plant pests of all sorts, and enabling new species to become problems. The challenge, of course, is not just to find effective actives, but ones which can be used without causing damage to people or the environment.

The capacity to design new, highly effective and safe actives is one which has eluded biological chemists over the last century of enormous progress in chemistry. Advances in science have certainly made optimisation faster and allowed the selection of safer molecules, but finding active, novel structures remains largely a matter of serendipity even with the latest technologies. The challenge, however, is one which needs to be conquered in food production as well as medicine: failure in either field potentially has very serious consequence for everyone.

Almost all of the protein in our bodies comes, directly or indirectly through the processing of fixed nitrogen in plants. Most of this comes from chemical fixation, either after direct application of synthetic fertiliser to plants, or through recycling previously incorporated plant nitrogen in animal manure. Fixing this nitrogen takes around four per cent of the world's total energy usage, around 15 per cent of the world's natural gas. In addition, significant amounts of the fixed nitrogen applied to soils can be lost through leaching or through the action of soil bacteria, releasing the powerful greenhouse gas nitrous oxide. We cannot survive without the protein in our diet, but it is equally clear that we need to improve the efficiency of fixing, recycling and applying nitrogen to crops. Process development has cut the energy cost of nitrogen fixation, but the Haber process itself remains largely unchanged. There are great opportunities to reduce energy demand and reduce greenhouse gas emissions, for example, through the application of the latest catalyst technology, where there is very recent evidence of academic success, and through sensor technology to tailor the application of nitrogen only when the crop has need of it.

The other major challenge in plant nutrition concerns phosphate. Again, almost all of the phosphate in human biochemistry has come ultimately from plants. The problem isn't that there is a lack of phosphate, but that most of it is present in low grade ores. The supplies of high-grade ores are forecast to run out in 200-300 years. In effect, what current agriculture does is to take pure phosphate and any which the plant does not absorb runs into oceans, making it hard to recover. Surprisingly, the behaviours of phosphate in soils are poorly understood. Some soils bind it tightly, making it unavailable, and in general the only safe recommendation for farmers involves overdosing on many soil types, wasting rich phosphate reserves and resulting in hard-to-recover phosphate in sea water.

In fact, this is just the most obvious example of how little we understand about soil. It is well known that soil microflora can have a significant effect on plant growth, but very little about the mechanisms through which this is achieved, except that there is evidence that some minerals can only be accessed by plants after they have been absorbed into the microflora. Metagenomics is beginning to characterise the species present, but there is a big gulf in the understanding of soil chemistry and how this interacts with those organisms. Only by gaining such understanding will it be possible to optimise mineral nutrition, so that as much as possible of the applied nitrogen, phosphate and other minerals gets taken into the crop and as little as possible leaches to ground water or released into the atmosphere.

Soil structure also has an important effect on water availability for plants. Around 70 per cent of the world's potable water is used in agriculture, and there does not seem much chance of dramatically reducing water usage in plant growth, as it is used as the source of all of the hydrogen, as a transport mechanism for minerals from roots to leaves and above all to cool the photosynthetic apparatus of the leaves. There are huge opportunities to improve the efficiency of water recycling from agriculture and in using advanced sensors to ensure that water is provided to plants only when required and when the plant is capable of absorbing it.

Future food security requires innovations in effect molecules, new catalysts, smart sensors and new purification and recycling methods. But there is also a need for advanced informatics. There are very significant variations in productivity, energy efficiency and greenhouse gas emissions between operations which on the face of it seem to be using the same tools in the same way. The average yield of most crops, for example, is typically only around half of the record yields and even these are below calculated theoretical maximum yields. Surprisingly this cannot just be ascribed to climate, geography or investment, but seems to have a large component of understanding and applying best practice. To date, little data has been systematically collected and analysed. Precision agriculture companies are starting to collect data and gain understanding of how variables vary across a field or a herd of cattle, and adapt treatments to ensure that they are applied where needed, but are not wastefully used where they are not. A few consortia, such as the Keystone Alliance for Sustainable Agriculture, have started to collect data across agricultural enterprises, monitoring variables such as water and energy use and soil health as well as productivity, then analysing it and feeding it back to their contributing members to share and extend best practice.

Brain mapping and the opportunities in healthcare and beyond

Professor Steve Furber, Professor of Computing Engineering, University of Manchester

Summary

The economic cost of brain disease exceeds the combined cost of heart disease and cancer in developed countries, yet many pharmaceutical companies are not investing in this area. Computing research to increase our understanding of how the brain processes information will improve the cost-effectiveness of developing new drugs to combat brain disease. Progress is likely to depend on advances in understanding that will emerge from large-scale projects such as the recently announced EU-funded Human Brain Project, a ten year collaboration that will simulate a complete human brain in a supercomputer using biological data.

Understanding how the brain processes information will rely on ICT research into:

- Neuromorphic computation that mimic processing techniques in biological nervous systems.
- Improving processors that run multiple instructions at the same time.
- Improving fault-tolerance in computer systems that help to overcome the challenges of increasingly unreliable components on computer chips.
- Biologically-inspired image sensors that will be much more advanced and energy-efficient than current imaging systems.

Introduction – the current state of play

The human brain remains as one of the great frontiers of science: how does this organ, which is so crucial to our existence, do its job? How is information represented, stored and processed in the brain?

We know that the brain is composed of some 85 billion brain cells or 'neurons', and that these cells grow projections whereby they can 'choose' which neighbours they interact with. These interactions are largely in the form of 'spikes' – electro-chemical impulses that pass from one neuron to the next through complex connections called 'synapses', and that our personality and memory is somehow defined by how these connections formed and adapted as a result of our genes, development and subsequent experience. Spikes are not the whole story: there are neuromodulators and gap junctions too. And neurons are not the whole story either: they are outnumbered in the brain by glial cells, whose role in brain dynamics is still the subject of debate and conjecture.

Research activity related to the brain is vast and diverse. Publications on neuroscience alone exceed 100,000 per year. A great deal is known about the basic component of the brain - the neuron - and the general structure of the brain. Wet neuroscience delivers ever more experimental data about individual neurons and small networks. Within the neuron, there is increasing data on proteins, channels, cellular machinery, and genetic impact on these systems. Brain imaging gives ever more data on coarse-grain brain activity, to the extent that scanners can read out what a subject is seeing or thinking. Mind reading is now a practical reality, albeit at a rather low resolution!

What is missing is any real understanding of the intermediate scales between the tens or hundreds of neurons accessible to wet neuroscience and the millions of neurons visible to brain scanners. The only instrument capable of 'seeing' these intermediate scales, where all of the important information representation and processing take place, is the computer model. Computational neuroscience is a very diverse area of research, with many opinions over the right level of abstraction of the neuron and the synapse. The area advances through a combination of theory, hypothesis, ever-more detailed data from wet neuroscience, embodiment in neurorobotics, and so on.

Computational neuroscience is limited in the scale of network that can be modelled by the availability and characteristics of available computer platforms. Even the fastest high-performance computers have limited capability to model large-scale spiking networks in real time because of the nature of their communications infrastructure, and access to such machines can be expensive. This has led to the development of more efficient, most cost-effective 'neuromorphic' computational platforms.

The next ten years

There is a global sense that the time is right to launch a full-frontal attack on the brain. This is a scientific Grand Challenge, with no guarantee that a reasonably complete understanding of the brain will emerge within ten years, but success is far more likely if existing fragmented activity is federated into a much more coherent whole. In addition, computer technology is approaching the level of performance required to make whole-brain modelling feasible – this is generally estimated to be at or beyond exascale (ten operations/s).

Recent initiatives have pointed towards the need to bring overriding coherence to brain research, which is currently very fragmented:

- The EU €1 billion ICT Flagship Human Brain Project launched in October 2013, bringing large resources to federating existing neuroscience data and mapping that data into large-scale HPC and neuromorphic models.

- The US Obama Brain project, $100 million so far, but $3 billion anticipated.

At a recent meeting in Heidelberg (October 2013) between the EU and US programmes a number of issues came to light, foremost among which was the differences in emphasis across the Atlantic. The EU approach is very much science first – understand the brain, and then use that new knowledge to derive ICT applications. In the US there is a much stronger drive towards early applications of the current very incomplete understanding of neuroscience. This is exemplified by IBM's development of a fairly straightforward neuromorphic chip, and perhaps even more by Qualcomm's position that a neuromorphic accelerator on their smartphone chip could be in use by a seventh of the world's population within a year of introduction (Qualcomm ships a billion smartphone chips a year).

The current UK capability

The UK has a broad range of HLS expertise in neuroscience and psychology, and also in related areas in EPS. The EPS capabilities include world-leading brain-modelling computer technology, for example the SpiNNaker machine, developed at the University of Manchester with EPSRC funding, now being offered as a 'Platform' through the EU HBP, and the Cambridge BlueHive FPGA neural modelling platform, developed within the same EPSRC-funded collaboration.

The UK has two of the world's leading suppliers of IP for consumer electronic applications (ARM and Imagination), but although ARM supplies IP used in SpiNNaker, and the Qualcomm and Samsung smartphone chips are based around the ARM architecture, neither UK company appears to share the ambition shown by Qualcomm, IBM and Samsung to be an early provider of brain-inspired computation accelerator technology.

Key EPS/HLS relationships

Progress in understanding the brain will depend critically on the relationship between EPS and HLS. Federating neuroscience data will require sophisticated informatics systems, and testing hypotheses about brain functions will require advanced computing facilities.

The UK has a strong track record in bio and health informatics, with very good connections between relevant EPS and HLS researchers.

What does the UK need to do?

The primary opportunity for the UK is to engage fully with the EU Human Brain Project. Commitment to HBP has thus far been somewhat reserved, but the HBP ball is now in play, and it will be much more efficient to join this game than to set up in competition to it. The UK has significant HBP involvement led by Seth Grant (Edinburgh, SP1 director), Steve Furber (Manchester, SP9 co-director), Alex Thomson (UCL, HBP Open Call leader) and several other participants.

The major gap in the UK (and EU) activity is to match the interest in early commercial applications of neuromorphic technology shown by major US companies (in particular IBM and Qualcomm) and by Samsung. There is a risk that while the EU develops the science the USA and S. Korea will run away with the commercial opportunities.

While the UK has academic research capability in neuromorphic technology, without UK industrial interest the results from that research are likely to be snapped up by overseas companies.

Opportunities and challenges

An increased understanding of information processing in the brain will deliver benefits in several areas:

- **HLS:** improved treatments for brain diseases; improved economics for brain disease drug development (an area that most big pharma have abandoned due to the poor economics of empirical drug exploration in the absence of any real understanding of the brain).

- It is hard to overstate the economic cost of brain disease, which in developed countries exceeds the combined cost of heart disease and cancer. Although there has been recent encouraging news about prospective treatments for Alzheimer's disease, progress with the majority of brain diseases depends on advances in understanding that will emerge only from large-scale projects such as the HBP.

- **EPS:** neuromorphic computation accelerators; new models of computation; better exploitation of many-core parallel architectures; new approaches to fault-tolerance and building reliable systems on unreliable technologies (an area of increasing relevance as Moore's Law inevitably delivers ever-larger numbers of increasingly unreliable components on a chip).

There are a number of promising lines of research that may yield early commercial value. One area of broad interest is in biological models of vision, and early signs indicate that neuromorphic solutions may outperform more conventional engineered solutions based on algorithmic image analysis. Biologically-inspired approaches have yielded several retina-based image sensors that emit spikes in a manner similar to the retina and quite different from frame-based imaging devices that have their origins in transmitting and recording moving images, for example in television, rather than in understanding and acting on those moving images, which is the objective of biology. Further biologically-inspired approaches address the next stage in vision: highly-parallel and energy-efficient convolution of feature detectors across an image to extract salient aspects of the image.

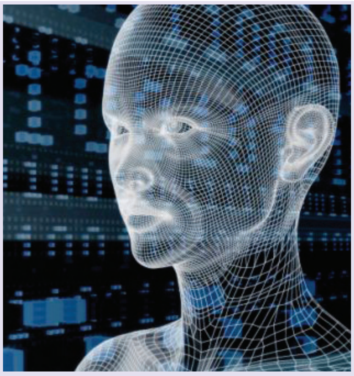
This technology has attracted industrial interest. Qualcomm has been developing neuromorphic systems for image analysis, and Samsung is also investing in this area as part of the trend to replace remote controls for consumer equipment with gesture recognition systems. The day when the smart phone does not simply record through its camera, but also understands and stores the semantic content of what it 'sees', are now not too far away.

Future drug discovery: Accelerating the healthcare revolution

Professor Patrick Vallance (President, R&D), John Baldoni (SVP, R&D) and Graham Simpson (Head, Therapeutic Peptide CPU), GlaxoSmithKline Medicines Research Centre

In the last two decades medicines have turned HIV from a death sentence to a chronic disease with near normal life expectancy, led to the cure of certain types of childhood cancers, radically altered the outlook for breast cancer and many other cancers and greatly improved the lives of millions of people with chronic disorders. Often, this has occurred with a marginal focus on the engineering and physical sciences. In order to accelerate the revolution in healthcare, capabilities in the engineering and physical sciences must be enhanced, integrated and directed to the requirements of future medicines.

In the future, patients, physicians, payers and regulators will become increasingly participative in healthcare, often with competing interests. We are confident that medicines (by which we mean chemical interventions of some form or another) will remain at the front and centre of therapy. However, in order to address the increasing demands from disparate stakeholders, from patients to society, the ways that these drugs are **discovered** (cost, time and precision), **tested** (efficacy and safety) and **manufactured** (access and environmental impact) require attention. Critically addressing attrition, quality and access, in all their dimensions, will require the seamless integration of technology, science and medicine throughout the drug discovery and development process. Well coordinated collaboration amongst experienced scientists, clinicians and engineers, all determined to find the next impactful treatment for patients, will ultimately enable a better healthcare system for all stakeholders. However, a weak link in any of these disciplines diminishes the likelihood of success.



The future patient – drugs and medicines will be at the centre of the patient-focussed healthcare revolution taking place all around us. These examples illustrate the diversity of patients and healthcare situations that will arise. *Example*: **A 35-year old teacher** with aggressive prostate cancer is treated with a targeted nanoparticle therapy which homes to the tumour and delivers toxic chemotherapy without side-effects. *Example*: **A 60-year old charity worker** with Crohn's disease has an implanted device, the size of a grain of rice which selectively suppresses the inflammation in her colon through a targeted modulation of the signals in a sympathetic peripheral nerve that controls the cellular events in the gut mucosa. *Example*: **A ten year old schoolboy** with a congenital auto-immune disease receives treatment derived from his own stem-cells to effectively cure his condition.

The steps in the creation of a medicine can roughly be grouped into three main decision-making stages:-

i. **discovering the medicine** – which *biological target* to pick to affect a particular disease, which drug modality and molecule will allow modulation of that target safely and effectively, and how does that molecule interact with non-targeted biological systems in the body;

ii. **testing the medicine** – how can the therapeutic effect be explored in patients to show whether there is anything worth pursuing further; and if there is, how do we exemplify these positive effects and understand the negative effects in the patient population to be treated;

iii. **making the medicine** – how do we make the medicinal product reproducibly, safely and at suitable scale while limiting effects on the environment in a manner that anyone requiring it has access.

In this paper we focus on two themes – innovation at the interface and integrative training – where there are opportunities for step-change transformations in the drug discovery and development process resulting from the intentional confluence of the physical sciences and engineering disciplines. These will have particular benefit for the UK society and economy. Further, the benefits of this confluence will inevitably benefit other sectors of the economy.

Discovering the medicine

Drug discovery begins with selection of the right target or biological pathway towards which a therapeutic intervention results in effects for patient benefit. The selection of the optimal modality with which to affect that pathway is another key decision. Investigations to understand how that molecule affects other pathways in the body are equally critical for most modalities. Historically, these steps have been grouped in a linear, sequential process; that is, biologists and clinicians select targets, chemists and biochemists design prototype molecules to modulate the pathway and safety scientists ascertain the risks associated with those prototype molecules. Further, historically, much of this work has been done with a belief that animal systems replicate those of humans. This approach is becoming an anachronism.

The very first steps of integrating biological sciences, physical sciences, technology and engineering are happening. Human genomics, epigenetics and various other 'omics' are slowly unravelling the complexity of human biology. Crucially, the results of such studies using real patient data are now providing early readouts that have the potential to validate drug targets in humans. Emerging sophisticated information analytics systems from other sectors are being adapted and integrated with existing healthcare systems to enhance signal detection amongst the noise in human biological data. Screening paradigms are evolving from simple reductionist protein binding determinations to more sophisticated cell based phenotypic screens, with first generation artificial tissues becoming available to create more relevant environments. Chemistry strategies are moving from screening the many to designing the few, and emerging technologies may enable those few to be designed and synthesised in a biology-relevant environment instead of a chemical reactor. The confluence of these and other sciences and technologies will have dramatic impact on all stakeholders in the healthcare value stream. The impact on the challenge of healthcare today, attrition, quality and access, will be significant when intentional focus is directed to creating places where collisions of these biology, physical science and engineering disciplines can occur.

- **Information technology:** Bioinformatic tools will allow the analysis of large databases of publically and privately held clinical information, and will hold the key to mapping of biological pathways with a degree of 'validation' in humans. Today this is becoming real with much more reliable data on phenotype-genotype relationships and with an improved understanding of the epigenome. Much improved cheminformatics will allow integration of the choice of target with molecules to modulate particular nodes on the pathway. At the same time, advances in in silico prediction of drug efficacy, pharmacokinetics and safety, taking advantage of all UK pharma data, will reduce the timelines and ensure that all medicines progressing to trials have negligible toxicity profiles.

- **Tissue engineering:** 3-dimensional bioprinting of heterogeneous human tissue will revolutionise our approach to screening, moving away from a reductionist approach to a more sophisticated phenotypic approach, linked back to informatics from clinical data sets. Testing of printed organs on chips will allow earlier assessment of drug efficacy and safety, thus further reducing the use of animal models.

- **Next-generation chemistry:** New synthetic chemistry methodology which is quickly industrialized is needed in order to quickly make molecules to test in the clinic. Encoded Translation of these chemistries to develop platforms such as DNA-encoded libraries and fragment-based screening methods will gradually enable reduction or even elimination of high-throughput screening. Targeting to diseased tissues enabled by molecular and special recognition methods will improve therapeutic indices. 'Chemical vaccination' via advanced long-term drug delivery systems and in-situ synthesis will improve compliance and offer alternatives to oral administration. Even incremental advances in advanced polymer engineering, structured nanotechnology and molecular imprinting will enable the development of tools and therapeutic options for novel interventions. Longer-term the medicines of the future will increasingly incorporate new modalities – bifunctional molecules, antibody-drug-conjugates, oligonucleotides, enzymes, genes etc – all of which will require chemistry methods to optimise them as cost effective medicines. Beyond chemistry, development of bio-electronics medicines to achieve therapeutic modulation of the sensitive electrical signals in human nerves will be used to regulate chronic diseases such as diverse as diabetes, pain and immunoinflammation. Increasing use of advanced robotics will be enable new ways of working in the discovery stage, ranging from rapidly creating chemical diversity to more sophisticated whole cell or 3-D tissue 'phenotypic screening'.

- **Next-generation analysis:** High-resolution molecular imaging (e.g. nano-NMR, nano-SIMS) and advances in non-invasive mass-spectrometry will enable quantitative measurement of drug distribution at the cellular level and across the body. The reverse engineering of the molecule selection process will result in biological sensors for the therapeutic entity-single molecule transistors. Detection of metabolites within a tissue will become even more highly resolved such that metabolism and parent concentration within a cell type in a tissue will be possible. Importantly, we will be able to study the concentration of drug at the site of action or the site of unwanted effect. These technologies will change our assessment of dose-response relationships and thereby impact efficacy and safety determination.

Testing the medicine

Clinical development of medicines will continue to require significant investment and substantial clinical insight. Likely advances in this area in the EPS include better monitoring and recording of patients' data through innovative diagnostic devices (emanating from the drug discovery technologies) and complex data informatics. Coupled with changes to target validation approaches, the selection of the precise patient population and the likely phenotypic effects of the medicine will become much more intimately linked from day one of the process of discovery. Trends in three main areas provide a focus for innovation in this space.

- **Clinical proof-of-concept trials:** New technologies which can allow rapid translation from pre-clinical models or 3-D human tissue models to humans with the disease condition will reduce the timelines in medicines development. This is linked to the notion of selecting targets from human biology rather than from animal studies; these same processes will define the target populations for initial testing. Simple point-of-care biomarker measurement in the doctor's surgery, in the home and increasingly, through smart bio-sensors worn or implanted in the body, will allow trial centres to be virtualised with physicians enrolling patients due to their sensor 'score' – 'teletrials'. Much greater detail will be gained about the patient's condition and their response to medicines allowing a better assessment of quality of life indices.

- **Real-world data:** The improved safety of molecules in the clinic will result in conditional approvals of medicines with positive proof-of-concept data to reduce the need for conventional phase III trials, especially in therapeutic areas awaiting transformational drugs (e.g. oncology, rare diseases). Real-world treatment and observational information from large population evidence will dramatically reduce the cost of development and provide a much more real-world assessment of the performance of medicines. At the same time, improving technology and analytics that will establish new clinical measures of what matters to patients in real-time: e.g. mobility, cognition. Modelling of these data will open up avenues in social medicine allowing predictive diagnosis, innovative clinical trial design and preventative treatments before the patient becomes ill. This, in turn, will pave the way for the future healthcare infrastructure to facilitate wellness and proactive intervention.

- **Patient adherence/compliance:** Around 50 per cent of medicine prescriptions are not adhered to by patients correctly resulting in poor health outcomes and a much greater burden of disease for the healthcare system. Improved drug delivery devices which allow more convenient dosage forms of medicines, alongside simple sensor technologies which can detect drug levels in patients will dramatically reduce this phenomenon.

Fostering creative and forward-looking collaborations between engineering, the physical sciences and clinicians through focussed research funding in these three areas will be essential to realise these advances in clinical settings for the benefit of the future patient.

Case study – Alzheimer's Disease (AD)

Alzheimer's Disease is the most common form of dementia and is a chronic, neurodegenerative disease characterised by cognitive impairment. A startling statistic is that one per cent of the world's GDP is spent every year due to the effects of the disease – all would agree that this justifies significant effort to treat and prevent AD for future generations. Like many 'diseases' including cancer, AD is not a homogenous disease and has a long pre-clinical phase where symptoms do not appear to the patient. This provides significant challenges in terms of defining patient populations for clinical trials but also offers huge opportunities for potential preventative treatments in the future. However, currently many billions have been spent on Alzheimer's research across all the big pharmaceutical companies with barely any success and in the past five years a number of promising mechanistic medicines have failed to demonstrate efficacy in large/expensive Phase III studies after many years of development. Targets such as amyloid-beta, beta/gamma-secretase, tau protein are all in current clinical trials but unfortunately there are still no good biomarkers of the disease which can be used to predict future progression or assess the success of treatment. This is one area of medicine which dearly needs collaborative work between the EPS and HLS – advances in diagnostics capability to earlier predict the disease, in simulating computational/mathematical models of the disease, in developing medicines which can enter the brain safely, in developing human tissue models of the disease and in quickly progressing medicines to human clinical testing. Other approaches such as surgical implants delivering electrical impulses to the brain tissue or stem cell therapies regenerating the brain cells will be investigated alongside. We would predict in 20 years we will see a much greater understanding of the disease with the potential for clinical successes not far behind.

Making the medicine

Making the medicinal product reproducibly, safely and at suitable scale, while limiting effects on the environment is key to the future discovery and development process, and essential if we are to provide access to medicines across the globe. We see a trend to increasing access to medicines in developing and emerging markets which will require industrialised technologies which significantly reduce the cost and flexibility of manufacture. Advances in flow chemistry, catalysis and the continuous processing of drug substances, utilising engineering advances to produce plant-scale quantities in a shipping container-sized rooms, will revolutionise drug manufacturing. Synthetic biology, which modifies natural enzymes to make new medicines safely and in an environmentally friendly way, will evolve in tandem to increase the complexity and reduce the environmental impact of manufacture. Longer-term there is a possibility that some drugs will be synthesised directly in the target tissue using the human body as a factory, triggering synthesis using the turn-on of molecular switches. These advances will require focussed investments in collaboration across the physical and biological sciences.

UK engineering and physical sciences - innovation and training

Basic research in the UK, across the engineering and physical sciences and particularly at the interface with the health and life sciences (HLS), is well regarded and our best universities are world-class in many areas. Translation of this innovative research into treatments for patients is where more focus should be applied and requires the building of a more vibrant investment community, willing to share the risk and reward of drug discovery. Around the world, where engineers, physical scientists, biologists and chemists have come together in academic and research institutes we see real prospects for advances relevant to our industry, and real opportunities for high quality training. Establishing such centres in the UK would be a world-leading step. Such skills training should not be the duty of academia alone and certainly should not be parochial in terms of student intake or global links. Technologies and advances will come from collaborative proposals at the interface between disciplines and research investment in areas such as tissue engineering, synthetic biology, high-resolution clinical imaging and nanotechnology are all great examples of this in action. Further initiatives focussed on the developing the different skill sets required in the shift away from traditional small molecule medicines will be needed to keep the UK at the forefront of the global industry.

The biggest issues in drug discovery and development – environmental production of pharmaceuticals; development of medicines and vaccines for the developing world; the spread of anti-biotic resistance – need big thinkers and there will be an increasing demand for well trained, creative, multidisciplinary scientists and engineers to tackle these challenges fearlessly. Scientists and engineers with a broad skill set of the interlinking disciplines involved in drug discovery, aware of the wider clinical issues and business challenges are required to help drive this change to a healthcare system that addresses the needs of all stakeholders.

Healthcare of the future: medical devices and surgery

Professor The Lord Darzi of Denham, Professor of Surgery, Imperial College, London

Introduction

Since the start of the 20th Century, advances in healthcare have transformed human health – life expectancy has doubled in this time. This remarkable progress has happened through improvements in public health, sanitation and pharmaceuticals, including the transformative discovery of antimicrobials. Amongst medical practices, developments in surgery and innovative medical devices have also made major contributions to this progress.

In the field of surgery the advances have been motivated by the aim of reducing the physiological and psychological trauma of going under the knife. This has led doctors on a journey towards surgery that is *minimal access* – striving to reduce the scar or size of the point of entry into the body; and *minimally invasive* – reducing the amount of damage and trauma to body tissues. Achieving this has required co-evolution and a figurative 'arms-race' of technology and clinical translation, with each pushing the boundary of the other.

Innovative developments in engineering and physical sciences have enabled crucial surgical advances. An excellent example is the work of Harold Hopkins, a British physicist, whose work revolutionised the field of medical optics, enabling the creation of high quality lenses, coherent fibre optics and the development of the fibre optic rod in collaboration with Karl Storz in the late 1950's. Subsequent work took these technological advances through the development and manufacture of the first laparoscopes for visualizing the human body, thereby creating an entire new field of medicine and surgical intervention. This has led to advances in both minimal access and minimally invasive procedures including laparoscopic, or 'keyhole surgery', a technique that shaped the foundations of the cutting-edge robotic surgery that we see today.

Looking forward – the next ten years

We face significant healthcare challenges in the coming decades such as the global threat of non-communicable disease and growing and universal necessity of economic accountability and cost-effective, efficient and value-adding healthcare expenditure.

The trend towards integrating technology into our every-day lives, including smartphones and greater access to the internet, is a driver and opportunity for advancing innovation in medical devices, surgery and technologies to promote health. The translation of these technologies into surgical and medical devices is a challenge, but will create new and disruptive treatments and diagnostics that are both a) sympathetic to humans and their physiology; and b) intelligent, by using information that is specific and relevant to the patient and their environment.

These goals require the parallel advancement of cutting edge robotics, micro-processing, computer technology, miniaturisation and sensing technology, with the goal of creating bio-compatible technologies and devices for integration with humans. These advances are being led by the engineering and physical sciences to address a major clinical need. Two examples of such technological advances being developed at Imperial College London (ICL) are:

- The **iKnife** from Professor Jeremy Nicholson and Dr Zoltan Takats uses big data and rapid evaporative ionization mass spectrometry (REIMS) as an emerging technique to allow near-real-time characterisation of human tissue by analysing the particles in the air released during electrosurgical dissection. This intelligent device can identify cancerous tissue and support surgical decision making during an operation in real time. This instant information normally takes up to half an hour to reveal using laboratory tests.

- **Body sensor networks** from Professor Yang's team at the Hamlyn Centre, within the Institute of Global Health Innovation. The aim is to integrate sensor technologies into man to monitor physiological parameters. The challenge ahead will be further integration and the development of implantable sensors to feed into data repositories. Analysing the wealth of information and data sets derived from these sensor technologies will assist patient and clinical decision-making, diagnostics and treatments.

The relationship between engineering and physical sciences and surgical advances

Britain has a historic strength in leading engineering and healthcare advances across academic institutions and industry. Surgery is always advancing and improving in parallel with technology; the intersection between the fields is blurring as clinicians, industry and academia see benefits of both super-specialisation in niche fields of R&D and the need for multidisciplinary collaboration to create worthwhile innovations that will benefit patients and their care.

In the field of surgery and in the research and development of medical devices we are seeing considerable focus and advances across cutting edge robotic surgery, for example using master and slave devices. One home grown technology, the **iSnake**, aims to advance keyhole surgery further, enabling surgeons to carry out more complex surgical tasks that were previously only possible using invasive surgical approaches. Using fully articulated joints powered by special motors, with multiple sensing mechanisms and imaging tools at its 'head', it will have the potential to allow surgeons greater flexibility to navigate difficult and restrictive regions of the body.

The intersection between the clinical translation of engineering and physical sciences can only be advanced through collaboration and strong relationships across academia, clinical partnerships and industry. These relationships must be multidisciplinary with engineers, industrial designers, clinicians, healthcare support workers and basic scientists working together to advance the leading edge of research and development. Specialised academic institutions and multidisciplinary centres are required to foster innovation with a mix of skills and resources in order to develop.

Communication and diffusion is vital – as cutting edge devices and technology become more mainstream in clinical environments, and as they are shown through clinical trials and rigorous testing to be effective and improve outcomes, there needs to be channels and means of disseminating and diffusing technologies to benefit the widest possible population. There is also a clear role for maintaining relationships between the academic research base and industry to support commercialization in order to incentivise research and development and contribute to the economy.

Opportunities for the UK

The UK can play a pivotal role in the future of surgical device development. Currently, academic institutions have a history of slow technology transfer, which must be addressed. There is a need to develop more partnerships between academia and industry to gain from the expertise that exists for rapid and effective commercialization of products and devices. There also needs to be other levers to improve technology transfer, such as funding opportunities from research bodies, government and industrial organisations to aid in the research and development within the academic arena. Diffusing technology across clinical sites and national and international healthcare systems will is a significant challenge. Utilising Academic Health Science Networks in the United Kingdom will be one approach to access and expand the population for the trialing and implementation of new healthcare innovations and medical devices.

Realising the vision

Low-technology solutions can frequently be as effective and arguably more innovative and disruptive than high-cost high-tech solutions, particularly in lower income economies. A positive move therefore is the impetus towards **frugal innovation** and towards reverse engineering many of the complex healthcare solutions and medical devices present in high-income health care practices. This will aim to improve provision and access to health care in developing and lower-income economies. Examples of successful frugal innovations:

- **GE Healthcare V-Scan low cost ultrasound machine or ECG machine:** Initially designed as a low-cost solution for the developing world, this technology has disrupted the UK and other western economies by a) providing cheaper and more local access to diagnostics; and b) helping shift patient assessment from the hospital to the primary care setting.

- **Jaipur foot:** The development of low-cost, low-technology prosthetic limbs is improving the lives of people in India who did not previously have access to life improving aids. Over 1.3 million people have benefitted from Jaipur Foot prostheses, calipers, and aids and appliances, mostly in India and also in 26 countries across Asia, Africa and Latin America.

Precision medicine will also become increasingly important in the future, providing tailored healthcare solutions to patients and clinical decision makers. Understanding the complex interactions of our genetic make-up and the products of those genes has opened up the field of personalized and precision medicine. The collection and analysis of vast amounts of person-specific information, from an individual's genome and even the unique composition of the bacteria and organisms that sit within their digestion system, is revealing previously unimagined potential for precision diagnostics and treatments. Technology will play a pivotal role in advances across this field, such as the power of sensors, smartphone technologies and big data computing analysis. Computer scientists will be vital in unlocking the information and key findings from the huge amounts of data generated by this emerging and exciting field of healthcare.

Conclusion

There is a complex range of healthcare challenges facing us in the 21st Century. Delivering a high quality health service alongside surgical advancement will require continuing innovation and partnership across the physical sciences and engineering sectors and the health and life science industry, along with a focused emphasis on strengthening the relationships between academia, industry, clinicians and policymakers.

Big data, genomics and the healthcare revolution

Professor Sir John Bell, Regius Professor of Medicine, University of Oxford

Introduction

The UK has an outstanding opportunity to revolutionise the quality and the costs of health care and meet the major health challenges associated with an ageing population. We have major competitive advantages to capitalise in the global healthcare market and radically improve the efficiency, effectiveness and affordability of the National Health Service (NHS).

Big data

The NHS has some of the richest health data available in the world, and we need to utilise this immensely powerful asset. This is a real game changer in the next 20 years – until now we have been very 'data rich' and relatively knowledge-poor in medicine. Medical sciences has struggled somewhat to do research at scale as studies and clinical trials were limited to the number of patients signed up to participate – a study involving 1000 patients was considered very large. But even the largest clinical trials are unable to take into account each person's thousands of genetic variables which influence their health. Often this data sits in hospitals and medical centres in isolated spread sheets, databases and medical journals.

Big data in health is the way forward – it is exponentially the largest set of clinical trials and research and diagnostic tools available. Big data will bring together millions of complex health care data and cross-reference – 'mosaic' – them, piecing together pictures of people, diseases and treatments in such incredible detail never before possible. Over the next ten years, medical research and health care delivery will be very different than today and completely different in 20 years.

Using the power of advanced data analysis, medical researchers will be able to predict the trends and patterns across genetics, clinical trial results and even lifestyle and environmental factors. As a result, doctors will be more able to prescribe with precision the best health treatments and preventative care available. This 'stratified medicine' will also lead potentially to personalised health care – prescriptive care bespoke to an individual's unique genetics and circumstances.

Complementing the NHS is the UK's superb academic research system. UK universities are extremely strong in both life sciences and the physical sciences and our academic research base is supported by a track record in healthcare technologies commercialisation that is second only to Silicon Valley.

The application of genomics

Genome sequencing and a systems approach to analysis is helping researchers improve diagnostics and our understanding of many diseases. Genomics is a powerful tool for helping to decipher cancers, inflammatory diseases such as arthritis, as well as Alzheimer's and vascular disease. The UK is also poised to benefit from the 100K Genome Project, sequencing the genomes of 100,000 patients.

Having the most comprehensive knowledge can help doctors determine the proper treatment at the critically right time, especially when it can make the vital, life-saving difference. In the middle stages of breast cancer, for example, when there are many treatment options and many uncertainties about the rate and direction at which the cancer is progressing, genomics can shed light on best treatment options.

For patients with multiple medical conditions for which they are taking several medications and treatments, big data can cut through the complications caused by so many factors and enable doctors to determine what will work best, eliminating wasteful medical care by using the data of millions of others to determine the most effective treatment for the patient.

An added benefit is the rapidly decreasing cost and time needed for genome sequencing: sequencing now costs less than £1000 per genome and will continue to fall.

The crucial role of engineering and physical sciences to medical advances

Genomics research has always been interdisciplinary and highly interdependent: DNA origins were in the physical sciences and all of the advances in genome sequencing have been discovered in the UK, mostly through engineering-based technological advances. Platform technologies have been essential to genomics in inflammatory diseases and immunology. With genome sequencing with single-nucleotide polymorphism (SNP) detection, it was the statisticians who led the way.

At every key step of technological discoveries in all life sciences, engineering and the physical sciences has played a crucial role. There is a cadre of engineering and physical sciences that supports life sciences, including chemistry, high tech manufacturing and structural biologists. Many life scientists are engineers, chemists, statisticians, physicists, mathematicians and computer scientists. They design and engineer medical devices, develop chemical diagnostic tests and new pharmaceuticals and analyse health data.

New medical advances will require new advances in engineering and physical sciences. At Oxford, 30 per cent of researchers are physical scientists and many of them are working in medical sciences. We have recognised how important engineering and the physical sciences are to medical science and as a result, have taken an interdisciplinary approach to the Oxford Old Road campus that removes department 'silos'.

Mobile health

With the help of engineering and physical sciences, 'mobile health' can be delivered to a whole new level by increasing the efficiency and effectiveness of health care. Patients can manage their own medical conditions every day and be – and feel – empowered to give the best care for themselves. Being able to administer their own health care exactly when they need it most can hugely improve their quality of life at home and speed their recovery. Doctors and nurses can monitor and interpret patients' health remotely but with more frequency and accuracy, avoiding costly GP appointments and home health visits when they are unnecessary.

Even with the best of efforts, today's medicine can be hugely inefficient as a GP is only able to get a single snapshot in time of a patient's health during a surgery visit – for example, a blood test. It can be difficult to tell from small samples if the patient is coping well and receiving the right health care. For example, postural position can be vitally important for patients with acute vascular disease as it can cause stress with blood flow. By wearing an intelligent 'patch' that communicates with a handheld tablet computer, patients are able to self-monitor in real time or at regular intervals – respiration, temperature, heart, movement, even medication compliance – and know when they need to sit up or lie down or adjust their medications to relieve the potentially damaging stress. These technologies and data can shorten hospital stays, enable patients with the best rehabilitation at home, and improve patients' health.

The way forward

Other countries are recognising the need for investment in life sciences and are increasing engineering and physical sciences funding as well as life sciences funding. All of the largest challenges to health care, such as ageing and infectious diseases, require experts throughout the life sciences and physical sciences to work together. However, there is a natural tendency amongst researchers to shy away from challenge-based, interdisciplinary research as it is difficult to evaluate in traditional academic peer review. Because it is easier to fund the known problem in medicine directly than the tools or techniques, very important engineering and physical sciences research used in life sciences goes without the imperative funding. We need to change that.

For the biggest challenges facing healthcare in the next 20 years, the UK must continue an interdisciplinary and collaborative approach in health research, policy and delivery. British universities are finding more ways to collaborate with each other. There is such a thing as good, friendly competition that motivates excellence in research, but for real health care advancements, the focus of competition must be truly global. Universities must continue to collaborate not only across institutions, but also across disciplines as well.

As big data, genomics and new technology reshapes how we can do research and deliver health care, there will need to be new policies and funding strategies in place. Government funding and policy bodies across government and charities will need to build even stronger bilateral relationships. MRC, EPSRC, Wellcome Trust and others currently work closely together for the benefit of medical science. EPSRC's funding support in bioengineering and medical imaging has been very successful.

Together, the NHS, Department of Health, life scientists and physical scientists will need to determine the best means to maximise our data assets. The huge volume of health data means that continued forward planning is necessary to prepare the right tools to be in place. For capturing new data, there will need to be standards for collecting the right information in usable format. For historic health data, existing in multiple databases, spreadsheets and other sources, retrofitting plans are needed.

We will need more data scientists, often from computer science, working with health experts to determine how to analyse data and to interpret analysis outcomes. Captured health data alone is useless without the ability to cross-reference against other data.

On the front line of patient care, doctors will be able to better diagnose using medical data, but, again, will need the quantitative knowledge to utilise this information. Medical schools will need to shift their teaching and prepare doctors and researchers in training with appropriate quantitative skills in addition to patient relationship management and communication skills. Oxford is preparing our medical school graduates with these quantitative skills so as doctors or medical researchers they will be readied to work with medical data in new ways.

Conclusion

There is an opportunity now like no time before to deliver better health care at lowest cost in the NHS. The UK has global competitive advantage in medical sciences with the commercialisation of new medications and breakthrough personalised health monitoring technologies and other health services developed from health diagnostics done at scale. With strong investment and policies in data, life sciences, engineering and physical sciences and skills, we are ready to make it happen.

Appendices

Appendix A: Review group membership and terms of reference

Professor Patrick Maxwell (Chair)	Regius Professor of Physic, University of Cambridge
Professor Sir Mike Brady	Professor of Oncological Imaging, Department of Oncology, University of Oxford, formerly Professor of Information Engineering, Department of Engineering Science
Professor Peter Donnelly	Director, Wellcome Trust Centre for Human Genetics, University of Oxford
Professor Carole Goble	School of Computer Science, University of Manchester
Professor Jim Naismith	Director of Biomedical Sciences Research Complex, School of Chemistry, University of St Andrews
Dr David Rees	Senior Vice-President of Medicinal Chemistry, Astex Pharmaceuticals
Ian Shott	Shott Consulting, President of AMRI Europe
Professor Peter Wells	School of Engineering, University of Cardiff

Terms of reference

The terms of reference for the review group are to:

1. Consider the interactions between engineering and physical sciences (EPS) and health and life sciences (HLS) in order to identify the variety, extent and impact of these relationships.

2. Provide expert advice and strategic direction for the project, agreeing the overall priorities and timeframes for delivery.

3. Identify any gaps in the analyses and propose areas of work to strengthen the evidence base.

4. Identify key areas and individuals to write short forward looking 'think pieces' which would outline future opportunities in key HLS areas and indicate how they will draw on EPS capabilities.

5. Develop conclusions and recommendations and identify target organisations for these recommendations.

Appendix B: Publications highlighting the engineering and physical sciences/health and life sciences interface

Recent literature highlights two aspects of the relationship between EPS and HLS. Firstly, that many areas of HLS have developed, or have drawn upon, fundamental EPS research. Secondly, that the increasing interdisciplinary requirements of health and life sciences research, drawing upon engineers, mathematicians, chemists and physicists working with biologists and physicians, is developing to the point that the boundaries of these disciplines are increasingly blurred.

The second point is highlighted by the **MIT** report published in 2011, T*he Third Revolution: The Convergence of the Life Sciences*[9], which provides an introduction to convergence, bringing together engineering and the physical and life sciences. It discusses how this convergence will help address the health care challenges of the 21st Century, by providing a new knowledge base as well as a new generation of diagnostics and therapeutics. The report argues that the combination of two previous revolutions (molecular and cellular biology with genomics) with engineering and physical sciences is producing a third great revolution in life sciences and biomedical research. One such example is the advanced DNA sequencers that have helped significantly to reduce the cost of full genome sequencing. Other examples where interdisciplinary research teams have led to novel outcomes include:

- Computational biology for immune response
- Imaging technologies to prevent blindness
- Nanotechnology for targeted chemotherapy
- Brain grafts for treating brain disorders and injury
- Detecting cancer metastases using microchips

The report also argues the economic case for supporting this convergence of research disciplines.

The **US National Academy of Science** report published in 2009, *A New Biology for the 21st Century*[10], discusses the view that a crucial aspect of biology in the future is the integration into biology of physicists, chemists, computer scientists, engineers, and mathematicians to create a research community with the capacity to tackle a broad range of scientific and societal problems. The report identifies health as a major challenge, to make it possible to monitor each individual's health and treat any malfunction in a manner that is tailored to that individual: the goal is to provide individually predictive surveillance and care.

A recent **European Science Foundation** report *Personalised Medicine for the European Citizen*[11], brought together experts from a wide range of disciplines to identify the most pressing issues affecting the development and implementation of personalised medicine across Europe. Personalised medicine, a strategy based on moving away from the long established 'one-size-fits-all' approach, identifies elements that predict individuals' responses to treatment and their predisposition to disease. This healthcare model places heavy emphasis on the maintenance and investment of these cohorts providing a healthcare system with a modern, prospective approach; an essential strategy for the analysis and understanding of disease over time in well characterised populations. Relevant recommendations include the need for comprehensive, accessible and interoperable datasets, improved models and decision-making processes and interdisciplinarity, participation and translational research.

[9] http://dc.mit.edu/sites/dc.mit.edu/files/MIT%20White%20Paper%20on%20Convergence.pdf

[10] http://www.nap.edu/catalog.php?record_id=12764

[11] http://www.esf.org/index.php?eID=tx_nawsecuredl&u=0&file=fileadmin/be_user/CEO_Unit/Forward_Look/iPM/FL_2012_iPM.pdf&t=1365075780&hash=64af85c8e8f96b8e9145eeea2fe600fac6e423cc

The contribution of engineering and physical sciences to health and life sciences

In addition to the increasing importance of interdisciplinary research, there is also a significant amount of evidence demonstrating the impact of individual EPS disciplines (including physics, chemistry, mathematics and statistics, ICT and engineering and materials) to HLS. Examples of this evidence are highlighted below.

Physics research has made a major contribution to medical imaging, the structure of DNA, the use of lasers and optical fibre technology in medicine, and cancer diagnosis and treatment[12]. A summary of the contribution of physics to medicine was published in 2012 in a special series of five short papers in The Lancet *Physics and Medicine*[13]. These papers outline the historical connections between physics and medicine, as well as providing overviews of specific contributions.

Advances in chemistry are in areas as diverse as personalised medicine, raising agricultural productivity and crop protection and even the development of new methods for water treatment and reuse, highlighting the importance of clean water supplies for public health. The development of new drugs has also been heavily reliant on the knowledge and skills of chemists developing novel compounds.

Mathematics and statistics have played an important role in health and life sciences[14]. Examples include: modelling the action of drugs in the biotechnology industry; searching genomes for genes relevant to human disease or relevant to bioengineered organisms; designing targeted radiation therapies; computational anatomy to enable remote surgery; the use of statistical techniques in the development and subsequent adoption of randomized clinical trials; better understanding of viral structures; and modelling of blood flow to better understand flow patterns in the body and contribute towards reducing heart disease. Mathematics has also played a crucial role in signal processing in medical imaging such as magnetoencephalography (MEG), single photon emission computed tomography (SPECT) and positron emission tomography (PET).

Joint replacement, regenerative medicine, simulation and medical training and surgical innovation have all have major contributions from engineering and advanced materials. Modern medicine and healthcare rely heavily on engineering to deliver improved prevention, diagnosis, monitoring and treatment of disease, including medical imaging, surgery, cardiac implants, neural engineering, mobile health, healthcare IT and independent living[15, 16].

[12] http://www.iop.org/publications/iop/2013/file_60314.pdf

[13] http://www.lancet.com/series/physics-and-medicine

[14] http://www.ima.org.uk/i_love_maths/mathematics_matters.cfm

[15] http://www.raeng.org.uk/societygov/policy/current_issues/biomedical_engineering/pdf/About_Us.pdf

[16] http://www.raeng.org.uk/societygov/policy/current_issues/biomedical_engineering/publications.htm

Appendix C: Structural relationships between engineering and physical sciences and health and life sciences

Summary

This study focused on identifying and then analysing multidisciplinary centres or their equivalents within the 32 most research intensive UK universities and comparing those with internationally prominent health/life sciences research institutes. The purpose of this analysis was to identify: strategic interdisciplinary EPS/HLS collaboration, the main success features and any remaining barriers to interdisciplinary working.

A number of coherent messages were derived from examination of all types of activity. Namely:

1. the need to focus activity around a key problem or grand challenge and bring to bear the most relevant skills, regardless of discipline 'label';
2. the importance of organisational culture; and
3. access to flexible funding to underpin dynamism.

By focusing on a grand challenge researchers were able to interact more effectively and see how to apply their own skills and knowledge, with a clear and agreed end goal. It facilitated decision-making, allowed clearer focus on the end result, thus facilitating agreement of the relevant skills for each underpinning project and allowed researchers from different disciplines or training to talk more easily together.

The culture of a particular grouping of people or in a place was also viewed as hugely important and relied heavily on the way in which the leader or senior team approached the challenge and actively demonstrated their appreciation of complementary skills brought by others. Interviewees from the international prominent institutes were unanimous in the reflection that the vast majority of cutting edge biology/health sciences results to have emerged from their labs have only been made possible by preceding advances in physics, chemistry, computing, mathematics, materials or engineering. For example Professor Sir Hugh Pelham, director of MRC's Laboratory for Molecular Biology said that "in order to conduct efficient DNA sequencing one first required chemists to put in place the key step of being able to synthesise dideoxynucleotides and that thanks to new computing techniques it is now possible to see the side chains of alpha helices in electron microscopes. These techniques and others provide new tools and techniques to biology and act as catalysts, opening up huge swathes of previously inaccessible new biological discoveries".

The third consistent message to emerge from all interviews was the availability of flexible funding to enable the leaders of small or large activities to dynamically refocus activity as results emerged allowing activities to be moved on. For some this meant being able to change research direction whilst for others this meant being able to flexibly move from fundamental discovery right through to translation and real-world application. In all cases it was the ability to be the master of one's own destiny and the flexibility of funding to enable that which made swift success possible.

There was clear division when it came to views of whether one should set up as a bricks and mortar institution, housing all relevant researchers together or whether one should operate a networked model. In all cases each interviewee felt their model worked most effectively, i.e. the internationally prominent institutes saying that bricks and mortar and differently trained/skilled researchers working as a research group, formed around a particular challenge was more effective than setting up as discipline based departments. However, they did report difficulties in hiring those skilled in engineering/physical science disciplines as there was a perception that these skills would simply be used as a service to biologist/medical colleagues and that such researchers would not advance their careers in their 'home' discipline as quickly. The opposite view was held by centres within universities where interviewees were clear that forming around a grand challenge gave focus, but that they needed to remain in a 'home' department to enable their subject area expertise to grow and contribute to advances in the 'core' of their discipline. These interviewees were concerned that co-locating all researchers into a single facility would just create a different type of silo.

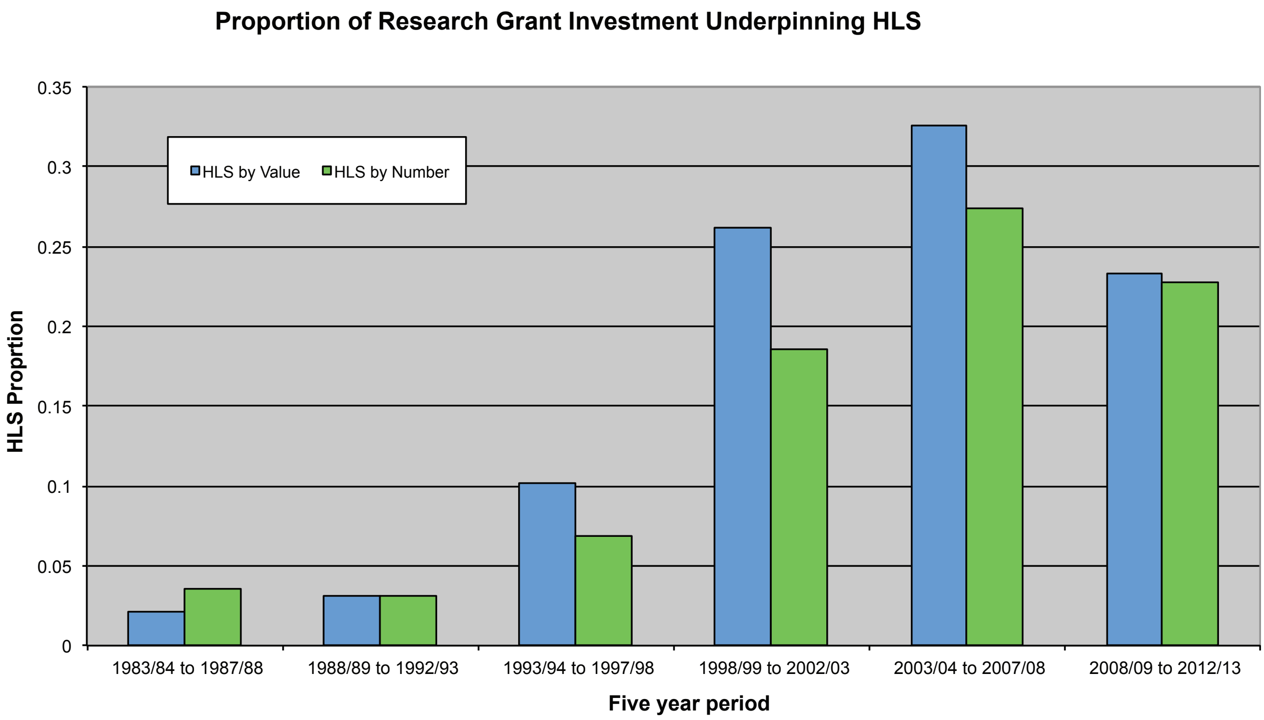
Appendix D: EPSRC funded research underpinning health and life sciences

Summary

Analysis of the Science and Engineering Research Council (SERC) (pre-1994) and EPSRC investments (post-1994) in grants has been carried out to determine the value of such investments and their contribution to health and life sciences in research, technology and clinical developments.

Value of investment

Over £2 billion or around 25 per cent of EPSRC investment in research grants over the last 20 years can be considered as underpinning the health and life sciences. The figure for the proportion of underpinning research is higher for investment in fellowships at around £220 million or 36 per cent and lower for training grants (£230 million or 13 per cent) although the nature of Doctoral Training Grants makes it difficult to determine individual student research areas at the award stage so this figure is likely to be an underestimate..



The HLS investment is concentrated in a number of key organisations. Four universities, Imperial College London, University of Cambridge, University College London, and the University of Oxford have each received investment of over £100 million in research underpinning the health and life sciences in the last 20 years.

Areas of research

EPSRC has classified its portfolio into research areas since 2005. Although much of the underpinning research is at the life sciences interface, there have been substantial contributions from more traditional physical sciences and engineering research areas. The research areas classified as having the greatest direct relevance to HLS by value to 2012/13 are:

Research area	HLS value (£million)
Medical imaging (including medical image and vision computing)	67.6
Clinical technologies (excluding imaging)	53.6
Biomaterials and tissue engineering	53.2
Sensors and instrumentation	43.9
Chemical biology and biological chemistry	43.0
Analytical science	38.3
Biophysics and soft matter physics	33.8
Process systems: Components and integration	33.6
Synthetic organic chemistry	30.8
Optical devices and subsystems	28.2

Other important areas include polymer materials, assistive technology, human-computer interaction, chemical reaction dynamics and manufacturing technologies.

Highlights

Medical imaging (MRI, ultrasound and PET) has revolutionised medical sciences over the last 20 or 30 years. The initial development by physicists is often taken up by chemists before being extended and adapted for use by life and medical scientists.

Other highlights include **chemical synthesis and analysis** which underpin pharmaceutical research; **materials characterisation; tools and techniques for manipulating biological materials**; and **physics of soft solids**. **Mathematical science** underpins much of medical imaging and provides support for clinical trials and **biomedical statistics**. Mathematics is also vital in **manipulating the large data sets found in biological systems, in complexity and bioinformatics as well as ecology, epidemiology and population studies. Process engineering, fluid flow, powder technology and reactor design** have all contributed to new and improved drug production. Research in the **built environment** has improved the design of hospitals to reduce infection and **information technology** underpins a range of assistive technologies in healthcare. New research avenues in **synthetic biology and regenerative medicine** have been made possible by **underpinning chemistry and work on biomaterials**.

Research community

A total of 7400 distinct investigators have been supported on HLS-relevant grants since 1984/85. Over 4,000 research students have been trained in the life sciences or related areas from 2000/01 to 2012/13.

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