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European Medical Research Councils (EMRC)
White Paper II

A Stronger Biomedical Research for a Better European Future

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Acknowledgements

Foreword

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Biomedical research has had a major impact on European citizens and society.

Over the past 40 years, infant mortality in Europe has dramatically dropped through the implementation of social and public health advances such as childhood immunisation for polio and diphtheria. For adults, efficient drugs have revolutionised the treatment of heart attacks and high blood pressure and enabled many people with schizophrenia to emerge from mental hospitals to live at home. More recently AIDS patients have likewise experienced a dramatic change of life through drug treatment breakthroughs. While cancer is still a major cause of death, it should not be forgotten that leukaemia for example was once a fatal disease and many now live with a variety of cancers.

Technical advancements have also brought significant benefits. With ultrasound, computed tomography, and magnetic resonance imaging, medical imaging can now ensure that people are accurately diagnosed and receive the right treatment. Major improvements have also been brought to surgical and anaesthetic techniques. Finally, artificial joints such as knee and hip replacements and organ transplants have become commonplace.

The importance of biomedical research is also reflected in its output. It generates today about half of all of Europe's scientific publications and these European publications represent the largest world share, ahead of the United States.

Economically the return on investment in biomedical research cannot be better illustrated than by a recent UK report. "Medical research: what's it worth?" shows that for each pound invested by the taxpayer or charity donor in cardiovascular disease and mental health research, a stream of benefits is produced equivalent to earning 39 pence and 37 pence respectively each year 'in perpetuity'.

For the future, biomedical research holds more promises. As proven in the past it can lead to better health, welfare and economic prosperity for Europe if the right political and strategic choices are made.

In 2007, the publication of the first EMRC White Paper drew a lot of praise and numerous EMRC science policy publications followed. They were well received and have had a big impact on European legislation, research policy and funding. EMRC's policy advice has even gone beyond Europe as it played a key role with the German and Spanish governments in triggering an OECD Global Science Forum on international clinical research.

As we celebrate EMRC's 40th anniversary this year, its maturity and reputation placed the organisation in the position to undertake a long awaited update of the first white paper. At a strategic core group meeting held in Madrid on 3 and 4 February 2011, the authors had extensive discussions based on renewed analysis of medical research input and output in Europe and globally. This edition still focuses on Europe and North America but special attention is also given to emerging nations and the pharmaceutical industry. An overview of the European landscape was added to contextualise the findings. Finally a SWOT analysis introduces five major recommendations whose implementation we hope will ensure a stronger biomedical research for a better European future.

We would like to finish by warmly thanking all the participants of the white paper group and we are very grateful to the EMRC core group and unit, all dedicated and passionate people without whom this white paper could not have been published and who have made what EMRC is today.

Professor Liselotte Højgaard, *EMRC Chair*

Professor Marja Makarow, *ESF Chief Executive*

Executive summary

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Medicine is advancing at a rapid pace. Genome sequencing is becoming routine, and the prospect of medical treatment tailored to individual patients on the basis of a genetic profile is now realistic. Stem cell technology is progressing at a fast rate, with new possibilities for replacing damaged cells and tissues. Innovations in information technology are producing powerful new imaging and diagnostic techniques.

These technological advances are not happening in a social, cultural or economic vacuum. In the West we are on average living much longer and healthier lives than just a few generations previously. However, society is changing both within Europe and globally. In Europe we are facing a number of great challenges: an ageing population, obesity and metabolic syndrome, mental health disorders, allergy and chronic diseases – and cancer and cardiac diseases as the big 'killers'. Healthcare expenditure is rising as we can do more and populations expect more. Globally, the geopolitical landscape is being reshaped, with powerful new economies emerging, such as China, India and Brazil.

It is against this backdrop that the European Medical Research Councils (EMRC) have produced this new White Paper, "*A Stronger Biomedical Research for a Better European Future*". It complements and updates the previous White Paper, published four years ago, "*Present Status and Future Strategy for Medical Research in Europe*".

This white paper presents a thorough examination of the present status of biomedical research in Europe and the rest of the world with a special attention to the North-American situation. Through a detailed analysis of funding and of data relating to research publications, the relative strength of

The white paper makes five key recommendations which should underlie future policy and strategy for biomedical research in Europe:

1. Citizens and patients should be closely engaged with biomedical research
2. The results of biomedical research should be rapidly and efficiently brought to the patient
3. Biomedical research should be conducted with high quality in an open, honest and transparent way
4. European biomedical research should be conducted within a global context
5. Investment should be increased to create the right world-class biomedical research

biomedical research in Europe compared with its international collaborators is assessed.

Europe spends substantially less per person on biomedical research than does the US. Despite this, the share of worldwide biomedical research publications produced by EU countries has remained stable over recent years while that of the US has fallen: in 2009 Europe had a higher share of world publications, at 38%, than the US at 33%. While US biomedical research tends to be published in journals with greater influence than research from the EU, as measured by citation rates, the gap is closing.

In spite of the significant difference in funding, Europe is punching above its weight in terms of biomedical research when compared with the US. Emerging economies such as China, India and

Brazil are catching up. Globalisation presents issues of greater competition, but it also gives rise to new opportunities for international collaboration, which should be fully exploited. The white paper provides a detailed description of how biomedical research activity is distributed across regions within Europe, and also provides, for purposes of comparison, a description of how research is organised in the US and Canada.

In the future global collaboration and cohesion will be needed more than ever to overcome the grand challenges of tomorrow. Investment in medical research has been shown to yield a return of 39% per year perpetually, so appropriate funding and best practice for medical research are not only essential to secure health and welfare in Europe and the rest of the world, but also make sound economic sense.

1.
Introduction

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This new EMRC White Paper, "*A Stronger Biomedical Research for a Better European Future*" follows the well-received first white paper published four years ago, "*Present Status and Future Strategy for Medical Research in Europe*". The new white paper presents an updated and more detailed analysis of the current state of biomedical research in Europe and identifies a number of recommendations on how biomedical research can be further strengthened to provide a better future for Europe, its citizens and industry as well as better global healthcare and improved human welfare generally.

Biomedical Research – the science of the 21st century

The ultimate aim of biomedical research is to answer medical questions leading to the discovery of treatment, prevention and diagnosis of diseases that cause illness and death. It is a vast field of science that includes parts of life, physical and social sciences. It is commonly divided into **basic research**, which broadly investigates the underlying processes of living organisms to help understand how they function; and **clinical research**, which applies basic research discoveries to human subjects to determine the effectiveness and safety of drugs, methods and devices used to diagnose, support and maintain individuals during and after treatment for diseases. **Translational research** has recently emerged as a new discipline to emphasise the importance of translating basic research 'from the laboratory bench to the bedside'.

Molecular medicine

A consequence of the human genome project, completed more than a decade ago, was the development of advanced genome sequencing technologies that can now produce an individual's genome sequence in an afternoon. Many thousands of genetic variations have now been found that are associated with an increased risk of diseases such as heart disease, stroke, diabetes, dementia and cancer. High throughput sequencing is just one of the new technologies that pose enormous challenges to modern biomedical research and to clinical practice.

Large data sets need large data repositories and the capacity to manipulate and analyse the information. Storage of biological data was until recently being measured in terabytes (a million million bytes) but is now already in the tens of petabytes (a petabyte is a thousand terabytes) and will increase a further million-fold by 2020. Making good use of this technology for patient care means coupling the capacity of genomics to large epidemiological cohorts and biological specimen collections in national and international biobanks[1].

Understanding the biological consequences of genetic variation requires an integration of other '-omics' approaches at the protein, RNA and metabolite level. Putting this together, with a lot of mathematical modelling, structural biology and epigenomic analysis will lead to an integrated systems approach to medicine and towards an increasing individualisation of treatment and healthcare, away from the more generalised treatment and prevention that we are used to. Such personalised medicine will place much greater burdens on our health systems to

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1. ESF Position Paper 'European Biobanks and sample repositories – relevance to Personalised Medicine', 2011, ISBN: 978-2-918428-41-1.
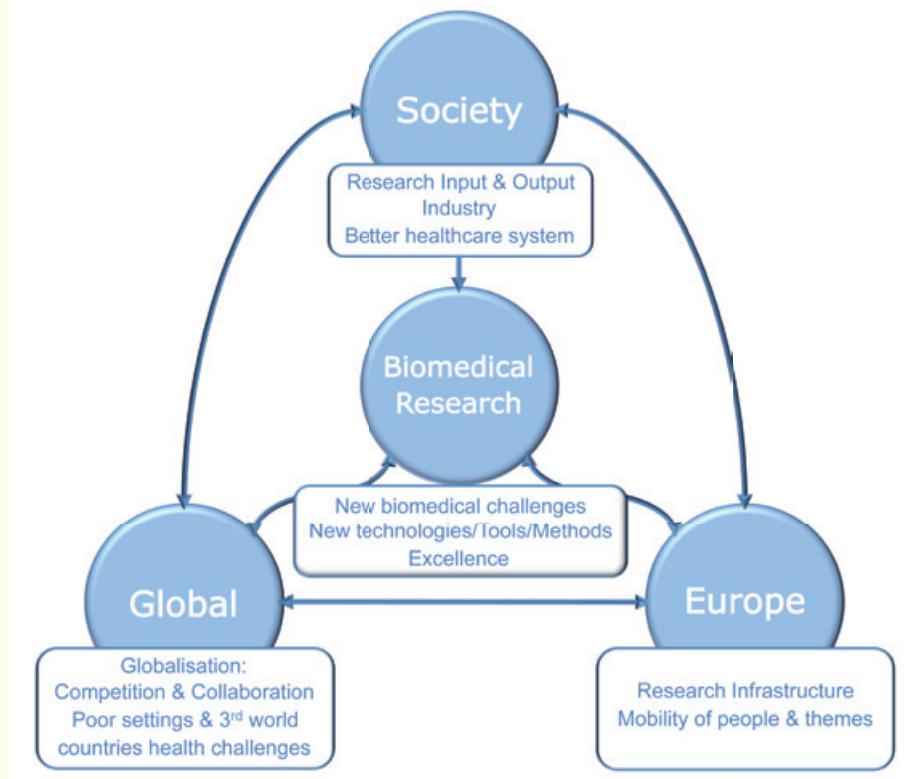
Figure 1.
Biomedical research interacts with three key contextual areas.

diagnose and treat individuals using the best available technology.

Other technologies

This molecular approach to medicine is taking place alongside advances in other areas such as medical imaging[2], regenerative medicine[3] (e.g. through the use of stem cells), nanomedicine, electronic implants and proton therapy. While new technologies open possibilities for improving medical care, they can also present new risks and require more monitoring and follow-up. MRI and ultrasound imaging for example may reveal pathologies that are incidental to the condition being evaluated. Small modifications to diagnostic technologies or treatment modalities can therefore have significant knock-on effects for health services and for the patient's perception of health and wellbeing.

Social factors

Research on the factors influencing health is revealing the importance of health inequalities in determining the outcomes and distribution of health burden. Social, economic and environmental determinants of health have a significant impact

and key behavioural risk factors may be as important as genetic or other biological factors. Lifestyles that include poor diet, exposure to tobacco smoke or alcohol and lack of physical exercise carry high levels of risk and may be coupled to educational status or income. Understanding the social and environmental determinants of health is complex and requires different research strategies and methodologies. Ameliorating the environmental determinants of health will require the engagement of many sectors of society outside the health services. In Europe around 18% of deaths (1.7 million *per annum*) are directly attributable to environmental factors and account for a third of the total burden of disease for children and adolescents under 19. Health systems may need to develop differential capabilities to handle the geographic variation in environmental impact. This suggests a need for increased research in health systems, social sciences and health economics alongside biomedical and clinical research.

Because of its impact on society, biomedical research in particular is poised to become the predominant science of the 21st century. However, this will happen only if it interacts successfully with three key areas shown in Figure 1: society, in which it is anchored and for whom it can help solve 'grand challenges'; Europe, as its nurturing ground of scientific excellence; and the world, which will offer both competition and collaboration.

2. ESF Science Policy Briefing 'Medical imaging for improved patient care', 2007.
3. ESF Science Policy Briefing 'Human stem cell research and regenerative medicine – A European perspective on scientific, ethical and legal issues', 2010; ISBN: 978-2-918428-12-1.

Society – the big challenges for the 21st century

Improvements in sanitation, living standards and healthcare in Europe have seen our population living longer and enjoying overall healthier lives. Many of the fatal diseases of a century ago are no longer life-threatening thanks to discoveries and advances in medicine. But the changing demographics have resulted in a shift towards an increasing prevalence of chronic diseases and acute diseases becoming chronic, ranging from cardiovascular disease, diabetes and cancer through cataracts and incontinence. As stated in a report published in 2010 by the ESF Standing Committee for the Social Sciences (SCSS) and EMRC, the ageing of populations is one of the main economic and social developments shaping the 21st century[4]. In Europe the number of people over 50 is expected to more than triple by 2050. In the population overall death rates per 100,000 from cardiovascular disease and cancer are falling but together these diseases account for around 75% of all deaths in the over 65s, and those in the lower socio-economic groups have a 30-65% higher risk of developing a chronic disease than those in the higher. Ageing brings with it different physiological problems: frailty, late-life depression and dementia. Often these diseases can occur together presenting a more complex clinical picture. Beside the strain on society resulting from a combined reduced working age workforce and a higher retired population, an ageing population will also lead to an expansion of age-related disorders such as degenerative diseases. If the aim of leading an independent life in general good health in old age is becoming more realistic, new medicines, treatments and diagnostic tools will be needed[5].

Europe is also facing a serious public health issue associated with poor dietary habits and lack of physical activity. Obesity is a major problem: about half of the EU population is now considered overweight or obese[6]. Another epidemiological challenge is the emergence or re-emergence of infectious diseases in Europe and the world. Diseases like malaria, HIV/AIDS and tuberculosis affect around 300 million people worldwide. As the H1N1 influenza pandemic demonstrated, and as was discussed at an ESF Colloquium in April 2010 on the management of medical risk in European society, health will become increasingly influenced by the process of globalisation. The rate and scale of global change on demographics, mobility dynamics, agriculture and trade among many other complex factors are yet to be fully understood to respond to emerging infectious diseases like H1N1 or Severe Acute Respiratory Syndrome (SARS). Climate change will also need to be taken into account as we are already seeing shifts in the geographical distribution of diseases such as Lyme disease or malaria. Furthermore, climate and globalisation will raise new challenges in the health needs of migrants. Finally, the role of the environment on diseases and more generally the role of lifestyle and environmental factors is increasingly recognised for their major impact on health[7]. The increasing incidence of chronic inflammatory disease observed in industrialised countries is clearly linked to environmental and lifestyle factors. Nevertheless, there is evidence of familial inheritance in a number of diseases. Consequently, diseases such as asthma, allergy, and inflammatory bowel disease (IBD) are widely considered to be due to a combination of environmental and individual risk factors[8].

Europe – the biomedical research environment in the 21st century

To address these challenges, biomedical research in the 21st century needs to be well prepared and well organised. Breakthroughs in life and health sci-

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4. ESF Forward Look report 'Ageing, Health and Pensions in Europe: An Economic Perspective', 2010, ISBN 978-2-918428-16-9; ESF Science Policy Briefing 'Ageing, Health and Pensions in Europe: An Economic Perspective', 2010, ISBN 978-2-918428-22-0.
5. Huber and colleagues recently proposed a new definition of health as 'the ability to adapt and self manage' in the face of social, physical, and emotional challenges because the World Health Organization (WHO) definition as complete wellbeing is no longer fit for purpose given the rise of chronic disease. Huber M *et al.* How should we define health? BMJ, 2011, 343: 235-237.
6. Eurostat yearbook 2010 (Product code: KS-CD-10-220; ISBN: 978-92-79-14884-2 ; ISSN: 1681-4789; DOI: 10.2785/40830), available online at http://epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KS-CD-10-220.

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7. This was recently addressed for male reproductive health disorders in an EMRC Science Policy Briefing, the first such policy document in Europe (ESF Science Policy Briefing 'Male Reproductive Health – Its impacts in relation to general wellbeing and low European fertility rates', 2010, ISBN: 978-2-918428-23-7). It raised awareness on an area that received little attention so far but where impaired male fertility is resulting in lower birth rates especially in industrialised countries. This is actually only one of many emerging research areas in biomedicine studying the impact of lifestyle and more generally the environment.
8. This will require significant and integrated investment in research, without which the effectiveness of European healthcare will be weakened. To maximise the potential of future healthcare strategies, insights will be required from a number of different fields, including epidemiology, genetics, cell biology, immunology, and bioinformatics, all feeding ultimately into effective clinical research. This is currently being investigated in an EMRC Forward Look for which more information can be found in a review by the Forward Look Scientific Committee: Renz *et al.*, Gene-environment interactions in chronic inflammatory disease, *Nat Immunol*, 2011, 12:273-7.

ences cannot be planned but for the most creative researchers to express themselves and for innovative fields to emerge, it is vital to create the most favourable scientific environment and research infrastructure. The construction of a real European Research Area (ERA), based on research excellence, is a key factor for European competitiveness.

European cooperation schemes, student and researcher mobility and bilateral partnerships need to form the backbone of research in the ERA. Research teams must be motivated and supported to participate in such initiatives. However, this alone will not be sufficient to allow the ERA to reach its full potential: the sum of coordinated or integrated research programmes for example only accounts for about 15% of the total budget for public research in Europe. ERA will only reach its full potential when there is also a 'mobility of themes' where research inventories, priorities, and decisions are no longer based on national considerations but take into account complementary European skills and high critical mass. Investment in major facilities such as CERN for Europe or ITER[9] in an international context, show that this approach is possible, even if it takes decades of continuous and convergent actions.

Biomedical research in Europe will need to be resourced at an appropriate level. As will be made evident by this white paper's chapters on scientific publications and funding in biomedical research, despite recent progress more needs to be done. EMRC recommended in 2007 a doubling of public funding for biomedical research but today we remain well behind the US, our biggest competitor, where about 50% of public funding goes to biomedical research, with the comparable figure for Europe being only 30%. While the number of publications is greater in Europe than in the US, European publications have less impact.

A further challenge for biomedical research in Europe is its diversity. As reflected later in this report, the majority of funding and productivity is concentrated in only a few countries. These major performers of health research and development (R&D) receive more than 84% of the public spend on biomedical research, producing as a consequence some 80% of all European scientific papers.

That said, progress is being made in Europe. For example the weight of funding towards health directly – besides a large share for the non-research area and specific cross-sectional funding – has increased in the successive Framework Programmes (FP) for Research and Technological Development

from about 10% in the early 1990s to 15% in the current programme[10]. There is also encouraging progress for research infrastructure in Europe where the European Strategy Forum on Research Infrastructures (ESFRI) is leading advances towards unity and international impact in the field of biomedical research infrastructures. ESFRI now has thirteen initiatives in the field of medical and biological sciences.

A new integrated way of building collaboration between European countries is illustrated by the Joint Programming Initiative (JPI), the first of these being in the field of biomedical research with the Joint Programming on Neurodegenerative Disorders (JPND). In the more recently approved initiatives, new health-related topics have also been selected with 'A healthy diet for a healthy life' of importance in the context of the obesity crisis, 'More years, better life' focusing on the potentials and challenges of demographic changes, and 'Antimicrobial resistance'. The JPI will extend the ERA by mobilising national and European resources toward common scientific goals. The opportunities offered by the Innovative Medicines Initiative (IMI) joint undertaking for closer interaction between academic teams and small and large drug manufacturers, particularly through competitiveness clusters, must also be fully exploited.

Another important initiative is the European Research Council (ERC), which has seen its budget increase since its creation in 2002. The ERC has so far granted €3.5 billion for project grants, involving 1,600 top level researchers. Participation in ERC programmes will increasingly become an indicator of excellence for researchers and of the environment provided by European research institutions. There remains however a lack of medical expertise at the ERC and clinical research is consequently underfunded. Only one third of the funds are allocated to project grants in the broad field of life sciences. Focus must be placed on the presence and visibility of biomedical research in this major European research institution.

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9. CERN, European Organization for Nuclear Research; ITER, International Thermonuclear Experimental Reactor.

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10. In the third programme FP3, running from 1990 to 1994 and with a total budget of €5700 million, there were allocated nearly €630 million directly to the life sciences, while in the currently running FP7 (2007 to 2013) with a funding amount of over €54 billion in total the funding directly allocated to biomedical research increased to €8035 million (cf. analyses of the EU Office of the Federal Ministry for Education and Research in Germany 2011).

The world – globalisation in the 21ˢᵗ century

As well as the historical competition from North America and Japan, Europe is witnessing the emergence of more international competition as well as collaboration opportunities from countries that are emerging as important players in biomedical research. Some of these countries such as India and Brazil have made a clear choice to specialise in life and medical sciences. Asian countries are also rapidly accelerating their scientific activities, gaining momentum through a combination of high-quality training, investment and resources. These upcoming scientific nations have forged close interactions between research, innovation and the creation of economic output. Because many of the scientists in these countries train in the US, this contributes to the creation of strong research links between the US and Asia.

As described later in this white paper, the US has maintained its global dominance in health and life science research, unmatched by the rest of the world generally and not only by individual European countries. One consequence of this is that the US remains an attractive destination for researchers, resulting in a 'brain drain' from Europe which is especially acute in the field of biomedical research[11].

However, globalisation does not only result in competition, it also presents opportunities for important and synergistic international cooperation. For Europe it will be important to strengthen the internationalisation of health research through the establishment of joint large infrastructures and the development of international research networks.

Europe must aim to participate actively in international health research both in terms of policy-making and implementation. A particular focus should be placed on the study of neglected and poverty-related diseases in cooperation with the developing countries.

It is in the light of these four overarching themes of **biomedical research** having an impact on **society** within the **European** and **global** contexts that this white paper and more importantly the recommendations it puts forward should be read. Only if Europe manages to position biomedical research in its rightful place will it be able to be strong enough to provide a better future for European citizens.

11. Dente K. Scientists on the move. *Cell*, 2007, 129:15-17.

2.
Biomedical research in Europe
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a. The impact on society of biomedical research

The success of modern medicine

Modern medicine has been hugely successful. Infant mortality in the EU has, for example, decreased from 28.6 deaths per 1,000 lives in 1965 to 4.7 in 2006. Death rates in the EU have fallen for all main causes of death but one for both men and women between 2000 and 2008 as shown in Figure 2.a.1[12].

The development of effective drugs has revolutionised the treatment of heart attacks and high blood pressure and enabled many people with schizophrenia to emerge from mental hospitals to live at home. In the treatment and prevention of cardiovascular diseases, a third of the gains can be attributed to high-tech invasive treatments such as coronary bypass surgery, another third to medications that treat conditions such as hypertension, and a final third to behavioural changes achieved through clinical trials revealing evidence for education on smoking, diet and exercise[13].

Modern imaging techniques have also brought significant benefits. Ultrasound, computed tomography (CT), and MRI have helped to ensure that people are accurately diagnosed and receive the right treatment. Surgical and anaesthetic techniques, too, have been greatly improved. Artificial joints such as knee and hip replacements have helped countless people, and organ transplants have become commonplace. Throughout this white paper, examples from across Europe are given to illustrate the impact of biomedical research on society.

Economic benefits of health research

There is now also overwhelming evidence that investment in biomedical research yields economic returns both through improved health gains (a healthy workforce) and through commercial exploitation of research outputs[14]. In 2008 a UK study demonstrated that the health and Gross Domestic Product (GDP) gains derived from the country's public and charitable investments in biomedical research are equivalent to an annual rate of return of about 39% for cardiovascular diseases and 37% for mental health research. This combined an annual rate of return of 30% in GDP gains and of 9% and 7% in health gains from new preventive and therapeutic interventions. The study crucially also showed that the time lag between research funding and health return is approximately 17 years. A similar study performed in the US found that every US\$1 spent by the National Institutes of Health (NIH) typically generates US\$2.21 in additional economic output within 12 months[15].

Another recent study has for example shown that 143 drugs approved by the Food and Drug Administration (FDA) in the last 40 years were discovered by public-sector research institutions (PSRI), leading to a rate of PSRI discovery compared to all FDA approvals of 9.3%[16].
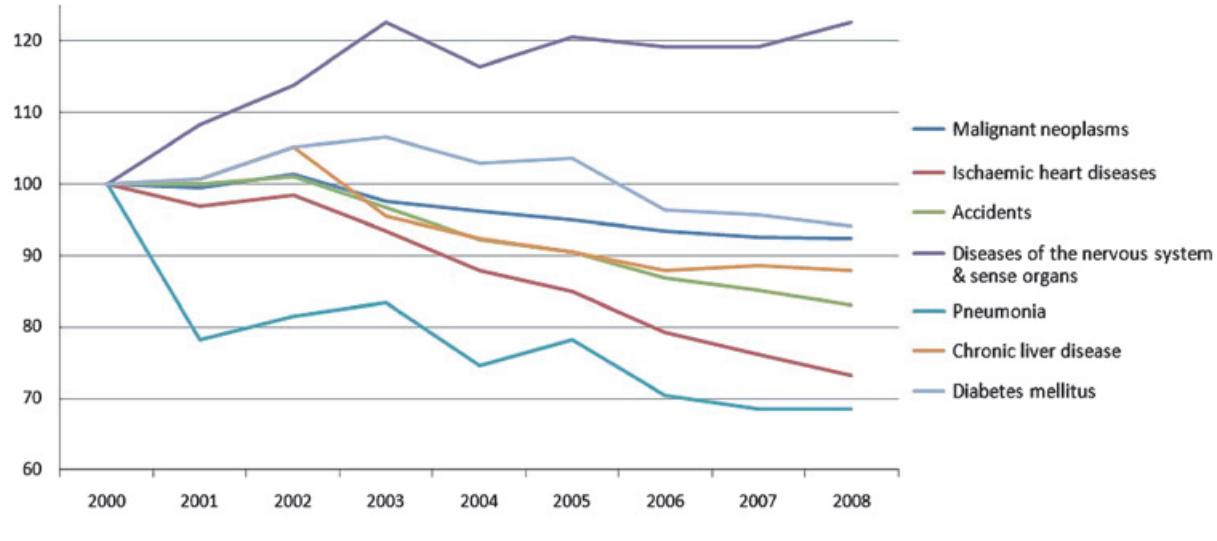
12. Eurostat yearbook 2010 (Product code: KS-CD-10-220; ISBN: 978-92-79-14884-2 ; ISSN: 1681-4789), available online at http://epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KS-CD-10-220
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15. Macilwain C. What science is really worth. *Nature*, 2010, 465: 682-4.
16. Stevens AJ *et al*. The role of public-sector research in the discovery of drugs and vaccines. NEJM, 2011, 364: 535-41.

b. The current research landscape

Europe versus the rest of the world

The EU has decided to respond to society's challenges, such as the demographic shift and increased globalisation, through innovation[17]. The 'Innovation Union' aims to address key issues such as under-investment in knowledge, through an aligned EU, national and regional strategic approach. The first proposed actions of this plan are relevant to this white paper as they intend to deliver the ERA and excellence in education and skills. Europe has unique strengths in its values, creativity and diversity and it offers excellent opportunities with motivated world-leading researchers, higher education institutions and governmental research organisations[18]. Nevertheless, as this report demonstrates, despite significant efforts of Member States and the European Commission (EC), research output in Europe though improving still lags behind the US, a region of comparable population size and total wealth. Increased competition can also confidently be expected to arise from China and India.

When it comes to health, Europe has a number of unique characteristics. While the organisation and delivery of healthcare is a competence of Member States, the EU complements national policies through actions which impact on cross-border health or patient mobility. As for public funding of biomedical research, a majority still originates from national funding organisations, with the larger play-

Figure 2.a.1.
Causes of death – standardised death rate per 100,000 inhabitants, males, EU27 (provisional; 2000=100) (Source: Eurostat, http://ec.europa.eu/eurostat/product?code=hlth_cd_asdr&mode=view)

ers accounting for approximately 85% of the total. The remaining 15% is handled today by the EU through instruments such as the FP or the ERC. A risk-averse culture in Europe seems to be influencing its public funding for biomedical research. While private funding in the area is similar between the US and Europe, public funding, as shown later in this white paper, is much lower.

Organisation of research in Member States

Fragmentation of research strategies across Europe remains, both in a positive and negative manner, one of the main issues for research in Europe where national strategies still prevail. The distribution of biomedical research funding throughout the now completed FP6 nicely illustrates this diversity.

There are significant differences in the relative shares of funds allocated to the different R&D performing sectors between the European states. While in the UK, the largest share of the funds went to the university sector, in France, for example, governmental research organisations like Inserm (Institut national de la santé et de la recherche médicale) or CNRS (Centre National de la Recherche Scientifique) can be identified as key players in the national research landscape. It should be noted that this situation is evolving with a recent French law giving universities both autonomy and a greater role in performing research. This is leading to a new organisation of laboratories' operations and strong partnerships between universities and national research organisations. In Germany, the governmental sector, with institutions like Fraunhofer

17. Europe 2020 Flagship Initiative – Innovation Union (COM(2010) 546 final; Oct 2010).
18. Green Paper: From challenges to opportunities: towards a common strategic Framework for EU research and innovation funding (COM(2011) 48; Feb 2011); EU27 R&D intensity in 2009 was 2.01% GDP, US 2.77% (2008), Japan 3.44% (2007).

How biomedical research has an impact on society
Examples from around Europe

UK Research and Development that could lead to significant new clinical applications within the next five years

The United Kingdom Multicentre Aneurysm Screening Study (MASS) has shown that screening men aged 65 to 74 once is cost-effective and halves the number of deaths from abdominal aortic aneurysms[1] (AAAs) over 10 years. This research provided evidence for screening programmes now in place in England (nationwide by 2013), Scotland (starting in 2011) and the US.

Medical Research Council (MRC) research undertaken in India by a team led by Dr Caroline Fall (University of Southampton), investigated whether adult diabetes[2] is preventable by measures that optimise foetal, infant and childhood nutrition. Dr Fall's team found a link between a mother's diet and her child's susceptibility to diabetes, and an increased risk of diabetes if the child has a low birth weight, does not grow well during the first year and grows rapidly after the age of two even without being obese.

Up to 10% of HIV-infected African people are affected by a fungal condition called cryptococcal disease[3] and about half of them die from it. A trial carried out by scientists from the MRC unit in Uganda and the Liverpool School of Tropical Medicine revealed that African people with HIV are less likely to get the deadly cryptococcal disease if they take a regular dose of the drug fluconazole.

Cardiac resynchronisation therapy (CRT) improves the heart's pumping efficiency by re-synchronising the pumping action of the chambers, which is decreased with heart failure. The total annual cost of heart failures to the UK's National Health Service is estimated to be £716 million per year (nearly 800 million euros). Approximately 70% of this total is due to hospitalisation costs. Most people who receive the CRT device present fewer symptoms and are hospitalised less often. CRT therapy reduces mortality by almost 30% and hospital admissions by about 50%, and pro-

vides a substantial improvement in quality of life[4]. Hospital admissions due to heart disease are projected to rise by 50% over the next 25 years largely due to the ageing population but the CRT implantation is proven to reduce hospitalisation of heart failure patients[5].

'The MRC pipeline'[6], published in 2010, describes how 24 new products and interventions based on MRC research were launched onto the market between 2006 and 2009. MRC research has been cited in over 70 international clinical guidelines since 2006, including 15 guidelines issued by the National Institute for Health and Clinical Excellence (NICE) in the UK. MRC Technology (MRCT) has contributed to the development of over 10% of the worldwide pipeline of therapeutic antibodies. In addition, the Cambridge MRC Laboratory of Molecular Biology (LMB) has hosted 12 Nobel Prize winners since DNA structure discovery, and more than 12 companies have been started up by LMB scientists.

False-colour transmission electron micrograph (TEM) of Cryptococcus neoformans, showing a single, circular encapsulated yeast.
© CNRI / Science Photo Library

1. www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC007263
2. 'Research changes lives', MRC strategic plan 2009-2014, May 2009.
3. Parkes-Ratanshi R., Wakeham K., Kamali A., Levin J., Coutinho A., Whitworth J., Grosskurth H. and Lalloo David G. Successful primary prevention of cryptococcal disease using fluconazole prophylaxis in HIV-infected Ugandan adults (CRYPTOPRO). HIV Medicine, 2009, 10 (Suppl 1): 8-9.

4. Freemantle N. *et al*. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction – a systematic review and meta-analysis. *Eur J Heart Fail.*, 2006, 8(4): 433-40.
5. Life Sciences in the UK – Economic analysis and evidence for 'Life Sciences 2010: Delivering the Blueprint'. January 2010; http://www.bis.gov.uk/assets/biscore/economics-and-statistics/docs/10-541-bis-economics-paper-02
6. 'The MRC pipeline'. Research and development by the MRC that could lead to significant new clinical applications within the next five years. September 2010; available at www.mrc.ac.uk/Newspublications/News/MRC006173
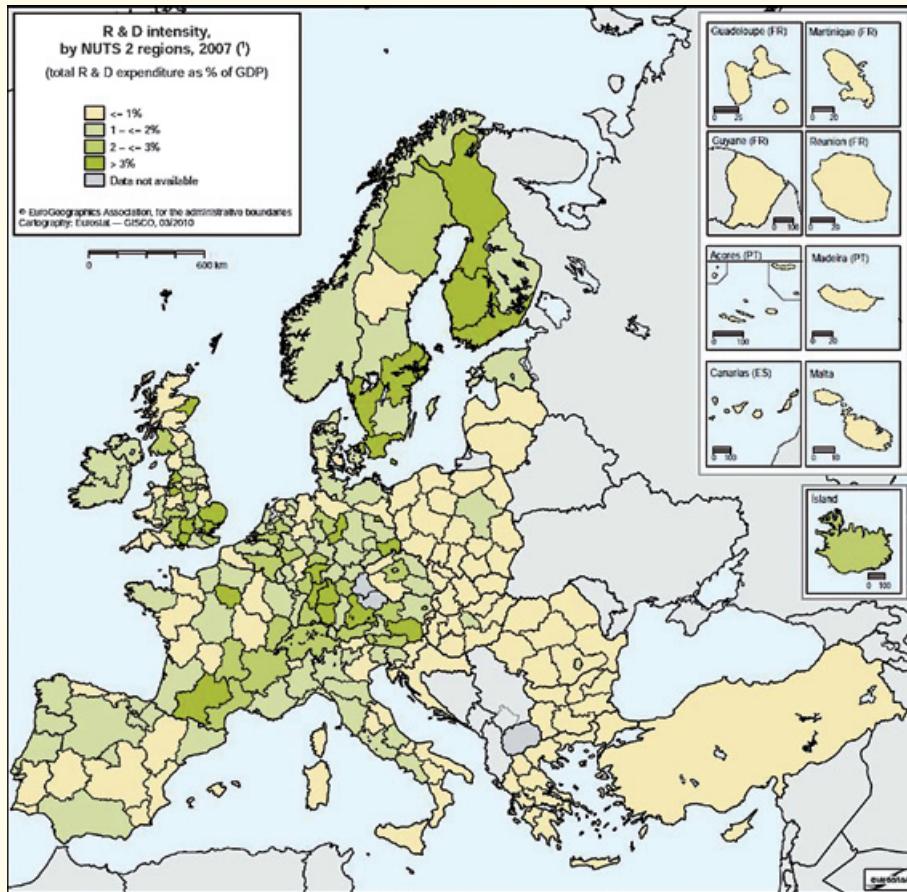
or the Max Planck Society, as well as the industry and university sectors were allocated roughly equal funding amounts.

Finally, as also shown later in this report, the majority of funding and productivity is concentrated in a few countries which provide more than 84% of biomedical research public funding in Europe and produce about 80% of all European scientific papers in this field.

This prompts two observations. First, research in Europe is sometimes described, or perceived, as heterogeneous or disparate. It would be more accurate to speak about 'diversity' and to examine how this diversity can constitute a mutual enrichment. Second, it is preferable, if the aim is to strengthen the cohesion and not competition between Member States, to focus on the level of regions.

Distribution of research activity across European regions

Figure 2.b.1., taken from the 2010 Eurostat regional yearbook[19], shows the 10% of European regions that reach the 'Europe 2020 strategy' target of spending 3% or more of their GDP on R&D. These regions are also the ones that consequently generate 40% of the EU's total R&D expenditure. This analysis also shows that Europe has a number of major scientific clusters that are strong, competitive, visible and attractive at the world level.

Twenty-five European regions account for more than 42% of the European publications in basic biology and in medical research. Six regions offer strong specialisation in medical research[20] with the London and Paris regions alone providing 2.2% and 1.67% of the world medical research publications respectively. The world share of publications has decreased for most of the European regions with only four regions not showing a reduction of their relative weight when all research fields are included. Biomedical research presents a more favourable situation with seven regions increasing their relative weight between 2003 and 2008[21].

In terms of technological production, the top 25

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19. Eurostat regional yearbook 2010 (Product code: KS-HA-10-001; ISBN: 978-92-79-14565-0; ISSN: 1830-9674), available online at http://epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KS-HA-10-001

20. Specialisation index for a region is the ratio of the proportion of world publications of this region in the medical research field to the proportion of world publications of this region: London (1.82), Amsterdam (1.78), Rotterdam (1.55), Lombardy (1.49), Athens (1.47), Copenhagen (1.36).
21. Amsterdam (+1%), Tuscany (+5%), Rotterdam (+6%), Catalonia (+7%), Rome (+9%), Warsaw (+27%), Athens (+54%).

European regions account for 53% of the European registration and 22.6 % of the world registration of European patents. Six regions each individually represent more than 1% of the world share of European patents in the pharma-biotech sector[22].

While the world share of European patents has decreased by 8% from 2003 to 2008 (-2% for pharma-biotech), many regions show an important increase in their world share of European patents, reflecting a positive evolution of their innovation capacities[23].

Barriers to research

Mobility of people and ideas across Europe is hampered by the complexity of national and European regulatory frameworks. Research and innovation are often impeded by a lack of harmonisation of policies that are outside the responsibility or influence of research agencies. Some of the specific barriers to transnational clinical research may arise through the differences in regulation between European countries following national legislation as well as the impact of EU legislation that is implemented in different ways by Member States. There may also be barriers due to gaps in regulation. For example in the UK there is a raft of different pieces of legislation that biomedical research may need to comply with[24] while in Finland there is one single act, the Medical Research Act no 488/1999, that covers nearly all aspects of medical research in a single piece of legislation. Sweden, Norway and Denmark have similar streamlined legislation with most aspects covered by just one or two acts. While this clearly facilitates research within each country, collaboration between these countries and the UK, for example, clearly needs to comply with the relevant legislation in all countries.

In addition to national legislation there are varying requirements to comply with international or European directives[25]. The European Clinical Trials Directive (EU 2001/20/EC) has for example, had a negative impact on investigator-driven clinical trials[26] despite its laudable aim to improve the safety and efficiency of clinical trials, and to provide the basis for improved European competitiveness. Regrettably, the implementation of the Directive by individual EU Member States has caused legislative differences between different Member States and obstacles to the conduct of clinical trials resulting in a reduction in the number of new clinical trials performed by academia. It has taken a decade for the EC to understand this failure and to accept to now revise the Clinical Trials Directive. Similar legal and bureaucratic dangers are also facing other biomedical fields with upcoming Directives. The new European Directive on the protection of animals used for scientific purposes (2010/63/EU) was voted by the European Parliament (EP) in September 2010 with again the best of intentions for animal welfare, the scientific community and Europe's competitiveness. Yet there are true risks reviewed in a recent EMRC position paper as we are entering the critical period when Member States enact national legislation on the basis of the Directive[27]. Legislation should continue to allow the responsible use of animals in research for maximum scientific and medical benefit carried out in conditions that optimise animal welfare.

The magnetic resonance research community might also be facing such an issue with the Directive on Electromagnetic Fields (2004/40/EC) currently being drafted by the EC[28]. Solid scientific grounds have convinced the EC to keep magnetic resonance exempt of any limit values but this could still change once the Directive is reviewed by the EP.

There are also critical legislative gaps at the European level, particularly in relation to the use of human biological material (tissue) that is a fundamental part of medical discovery but falls outside the Clinical Trials Directive. New legislation is needed to harmonise basic principles of privacy protection as well as dissemination of results and conflict of interest policies while at the same time retaining sufficient flexibility for innovative research.

22. Paris (3.2%), Copenhagen (1.62%), Darmstadt (1.36%), Düsseldorf (1.2%), Munich (1.2%), Lombardy (1.02%).
23. Arnsberg, Eindhoven, Emilie-Romagna, Fribourg, Piedmont, Lombardy, Nürnberg, Souabe, Tübingen, Venetia, Würzburg.
24. Medicines for Human Use Regulations (2004); Human Tissue Act (2004) and Human Tissue (Scotland) Act (2006); Data Protection Act (1998); Mental Capacity Act (2005); Health and Social Care Act (2001, 2008); Human Fertilisation and Embryology Act (1990); Human Rights Act (1998). The UK Academy of Medical Sciences recently published a report on this complex environment: *A new pathway for the regulation and governance of health research* (http://www.acmedsci.ac.uk/p99puid209.html).
25. OECD: Collaborative intellectual property handling; Biobanks; Pharmacogenomics; UN: Cloning; Bioethics declaration (UNESCO); Disability Convention; Council of Europe: Biomedicine convention; Protocols on research, biological materials, genetics; EU: Stem Cell Research (EU FP7); EC activities in genetic testing; Cells & Tissue Directive; Tissue Engineering Regulation; Clinical Trials Directive; EU Data protection directive (95/46/EU).
26. ESF Forward Look 'Investigator-Driven Clinical Trials', 2009, ISBN: 2-912049-95-4.
27. ESF Position Paper 'Position on the Directive on the Protection of Animals used for Scientific Purposes (2010/63/EU)', 2011, ISBN: 978-2-918428-33-6.
28. ESF Position Paper 'ESF-EMRC Position on the Implications of the EMF Directive 2004/40/EC for European Biomedical Magnetic Resonance Research', 2010, ISBN: 978-2-918428-13-8.

Research infrastructures

Large research infrastructures are another key to European competitiveness in the field of biomedical research. Infrastructure in this research field does not necessarily imply large central resources: access to series of skills and distributed services is also important.

Large research infrastructures are strategic instruments to increase scientific integration of Europe and to strengthen its international outreach and attractiveness. They can foster cooperation on a pan-European scale and provide a large research community with the required access to innovative methods and technologies. Research infrastructures can further strengthen the European position by encouraging mobility and by improving training and education. The competitive and open access to high-quality research infrastructure thus supports and benchmarks the quality of the activities of European scientists, and attracts the best researchers from around the world. National investments can be maximised by pan-European mobilisation, sharing and exchange of knowledge around research infrastructures. The European Molecular Biology Laboratory (EMBL) can be regarded as a successful example of such research infrastructure in the biomedical area.

ESFRI has called for the construction of thirteen pan-European research infrastructures. Several of these are strategically important for biomedical research: BBMRI for biobanking and biomolecular resources, ECRIN for clinical research, EATRIS for translational research, ERINHA for high safety level laboratory, Euro-bioimaging for biomedical imaging infrastructure, Openscreen for screening platforms for chemical biology, and ELIXIR which underpins all the biological information and data storage for biomedical research. Many of these are also now engaged in the legal framework for a European Research Infrastructure Consortium (ERIC) to facilitate the joint establishment and operation of research infrastructures of European interest.

Open access information

The first decade of the 21st century has seen a revolution in communication with internet potentially providing easy and low-cost technological answers to some of Europe's infrastructure challenges. Several initiatives to distribute freely educational and scientific information on the World Wide Web have for example grown recently. The aim of the open access initiative is to guarantee an unrestricted online access to articles published in scholarly journals. Open access could be provided through institutional repositories by the authors or by directly publishing in open access journals with publishing costs paid by author's institutions, their grants or philanthropic support. Open access has already changed the publishing world with the appearance of open access journals, some of which are highly successful and have high impact in the scientific community (e.g. PLoS journals, www.plos.org). The scientific community should now establish appropriate measures to maintain high standards, ensuring reliable quality, timely availability and transparency in data sharing. Several biomedical research funding bodies require that all investigators they funded submit to a central archive an electronic version of their final peer-reviewed manuscripts upon acceptance for publication.

Several funding agencies worldwide have put in place open access policies requiring electronic copies of research articles published in a peer-reviewed journal and supported in whole or in part by them to be made freely available within six to twelve months of publication[29]. More recently, the ERC mandated open access by requiring all peer-reviewed publications from ERC-funded research projects to be made publicly available within six months of publication. The ERC will also cover publication fees in open access journals[30].

Education and training

High quality biomedical research needs high quality biomedical education and training, producing well-educated medical researchers, especially medical doctors (MDs). Europe has large numbers of well-educated MDs[31]. The number of MDs embarking on a research career remains too low and efforts should be made to raise the numbers. In addition 50 to 60% of PhD and postdoctoral students leave for the US where research careers are better rewarded. Medical education as well as biomedical research education differ within Europe and are as fragmented as the European research landscape. Today a huge diver-

29. MRC: http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Openaccesspublishing/index.htm; Wellcome Trust: www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Open-access/index.htm; Swedish Research Council: http://www.vr.se/inenglish/aboutus/policies/openaccess.4.44482f6612355bb5ee780003075.html; NIH: http://publicaccess.nih.gov/FAQ.htm#753; Howard Hughes Institute: http://www.hhmi.org/about/research/QA_papp.pdf

30. ERC: erc.europa.eu/pdf/ScC_Guidelines_Open_Access_revised_Dec07_FINAL.pdf

31. An estimated 70,000 medical students graduate every year from about 440 medical schools for a European population of 770 million people (Frenk *et al.* Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. *The Lancet, 2010,* 376: 1923-58).

How biomedical research has an impact on society
Examples from around Europe

The best way to give oxygen to resuscitate newborn babies, improved coeliac diagnosis and better bladder cancer care
(Research Council of Norway – RCN)

Resuscitation is the most common procedure performed in neonatology[1]. For the last 200 years pure oxygen has been used in the standard procedure for resuscitation of newborn infants. Over the past 40 years Norwegian researchers at Oslo university hospital Rikshospitalet have systematically performed scientific studies to determine the optimal gas composition for resuscitation of term and preterm newborns. The results from their basal scientific experiments, mainly performed in newborn piglets as a model, challenged the traditional procedure in newborn resuscitation. First they showed that ambient air (21% oxygen) is "as good as" 100% oxygen in the resuscitation procedure. Later they were able to show that 100% oxygen is actually harmful and should not be used. Thus, in 1998 the WHO changed its guidelines for term and late preterm resuscitation from 100% to 21% oxygen, and in 2010 the International Liaison Committee on Resuscitation (ILCOR) decided to implement the results in their coming guidelines. These scientific results imply that resuscitation may be performed globally, and are estimated to save more than 100,000 newborn lives every year.

Other researchers at the same university hospital have developed a method that identifies gluten-specific T-cells[2]. The method can be used for facilitating the diagnosis of patients with coeliac disease, an inflammatory disease of the small intestine that leads to symptoms such as chronic diarrhoea, weight loss, osteoporosis and fatigue. The disease is caused by an autoimmune reaction of gliadin (gluten protein) and similar proteins found in wheat, rye and barley. People diagnosed with coeliac disease need to follow a strict diet, avoiding all foods containing gluten proteins. Coeliac disease has traditionally been difficult to diagnose after exclusion of gluten proteins from the patients' diet. The new diagnosis tool, which is based on specific binding between gluten-specific T-cells and molecules marked with

© iStockphoto

fluorescence, only requires a gluten-containing diet for three days. In comparison, the traditional diagnostic method required the patients to follow a gluten-containing diet for several months. The method is currently being tested on patients with an uncertain coeliac disease diagnosis.

Bladder cancer is the fourth most common malignancy among men in the Western world. Owing to long-term survival rates and life-long monitoring and treatment, it is the most expensive cancer to manage from diagnosis to death. Significant costs are attributable to treatment of recurrence and complications. Improved tumour detection and more complete resection is the best way to decrease tumour recurrence. A recently published study[3] suggests that photodynamic diagnosis using Hexvix® (Photocure, Norway) markedly improves initial resection of bladder cancer tumours. If the technology is used appropriately, it necessarily affects patient management and follow-up, with the benefits for both the patient and, ultimately, the healthcare economy.

1. Saugstad OD. Resuscitation of newborn infants: from oxygen to room air. *Lancet,* 2010, 376(9757): 1970-1.
2. Ráki M *et al.* Tetramer visualization of gut-homing gluten-specific T cells in the peripheral blood of celiac disease patients. *Proc Natl Acad Sci U S A*, 2007, 104(8): 2831-6.

3. O'Brien T and Thomas K. Bladder cancer: Photodynamic diagnosis can improve surgical outcome. *Nat Rev Urol*, 2010, 7(11): 598-9.

sity of PhD and/or DSc, PhD and parallel MD/PhD programmes exist within Europe. Comparable standards and structured multinational programmes should be implemented to make it possible for medical students and doctors to start and continue an international research career. These needs are clear priorities and opportunities for Europe as the number of students is drastically increasing, soon reaching 200 million worldwide[32]. While large growth is expected in emerging countries, Europe and the Americas are seeing a substantial increase in their student population concentrated in higher education and research. Importantly, these students have become more mobile with an increasing number studying outside of their home country. This is where Europe can also make a difference as four of the top 10 student hosting countries are already from within the EU[33].

There have been a number of initiatives to increase the potential for collaboration and joint working in Europe. More and more regional clusters of excellence are emerging triggered by initiatives such as the Excellence Initiative in Germany. Other national initiatives are leading the way to a new organisation and coordination of the biomedical research system such as France's creation of Aviesan[34] (Alliance nationale pour les sciences de la vie et de la santé, National alliance for life and health sciences) where nine major research actors are joining their efforts. At the European level too much diversity and fragmentation is being replaced by more harmonisation. The D-A-CH collaboration is, for example, spearheading the opening of mutual funding programmes to promote researchers' mobility and cross-border research between research organisations in Austria (FWF), Germany (DFG) and Switzerland (SNSF)[35]. For the Nordic countries a similar approach is being realised with Nordforsk since 2003 already[36].

Medical societies

The academies or learned scientific societies in Europe are member organisations for clinicians and researchers specialising in certain fields or disciplines. Often there is a scientific society for each speciality in each country (Danish Society of Cardiology, German Society of Cardiology). There are also European-wide scientific societies (European Society of Cardiology, European Society of Gastroenterology). Clinicians with a research interest are often members of both national and European societies. The scientific societies hold annual or biannual conferences where new knowledge is shared and continuous medical education is provided. The societies may have their own peer review journal published in their own languages. The European societies often have an English language peer review journal.

The societies also publish policy papers and advice for researchers and clinicians, hospitals, governments and other organisations. They have a certain political influence, and some of them collaborate with industry in as much as industry may participate in annual society exhibitions or sponsor congresses and award travel grants. Companies may also advertise in the societies' journals.

The health industry

The health industry faces a number of challenges: the evolution of biomedical research is producing a massive increase in the complexity and quantity of data; there is a move towards so-called 4P medicine (personalised, predictive, preventative and participatory) with the need for global health solutions; the number of market approvals is decreasing while R&D costs continue to increase, together with the emergence of generic medicines; there are moves towards enhanced anticipation and minimisation of risk within the industry.

This new landscape has resulted in new relationships between academics, biotechs, Small and Medium Enterprises (SMEs) and multinational companies: industry can no longer rely on in-house research alone.

Europe's pharmaceutical and biotech industry has for many years been the world's principal developer of new medicines. However, since the 1990s this position has been taken by the US. Between 1998 and 2007, around 12.6% of all new chemical and biological entities (NCE/NBE) receiving market approval comprised pharmaceuticals. The latest data available (2006-2010) for the pharmaceutical sector confirms the leading position of the US, the world's main inventor of NCE/NBE (Figure 2.b.2). The US accounted for 47.7% of the NCE/NBE between 2006 and 2010; the figure for Europe was 32.5%. Only 25 NCE/NBE reached the market for the first time in 2009, continuing the decreasing global trend since the 1990s. This decrease is thought to arise from a range of factors, such as the increasing cost and complexity of research and the fact that clinical trials require unprecedentedly large numbers of participants. A 2007 report esti-

32. Conference des Grandes Ecoles, Paris, October 2010 ; www.cge.asso.fr/presse/CGE_ActesCongresParis2010.pdf
33. US ranks first followed in Europe by the UK (2nd), France (3rd), Germany (5th) and Italy (10th).
34. www.aviesan.fr/
35. www.dfg.de/en/research_funding/programmes/international_cooperation/joint_proposal_submission_dach/index.html
36. www.nordforsk.org/en?set_language=en

How biomedical research has an impact on society
Examples from around Europe

Innovative new drugs for AIDS and other diseases: Czech Republic and Belgium

When Professor Antonín Holý (Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic) and Professor Erik De Clercq (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium) met in 1976 at a symposium in Germany they began an effective collaboration which has continued ever since. In 1978 they published their first joint paper in the prestigious journal *Science* on a new type of antiviral that was resistant to decomposition in the organism. Eight years later, their continued effort led to the discovery of undegradable nucleotide analogues which are now generally known as "acyclic nucleoside phosphonates". This cross-border discovery opened a new field of research in medicinal chemistry aimed at the development of antiviral drugs[1].

In collaboration with the American pharmaceutical company Gilead Sciences, their combined efforts resulted in the development of three important antiviral drugs. Cidofovir has been approved since 1996 for treatment of cytomegalovirus retinitis, a condition occurring in the late stage of AIDS. Cidofovir acts against essentially all DNA viruses, particularly all herpes viruses, pox-, adeno-, papillomaviruses, and others. It is also regarded to be the most active drug against variola (smallpox) and monkeypox. Adefovir as its oral prodrug is aimed at hepatitis

B, a dangerous disease which affects several hundred million people across the world. The third drug is essential for fighting human immunodeficiency virus (HIV), the virus causing AIDS. The oral prodrug of tenofovir is at present one of the most frequently used drugs for the successful treatment of AIDS patients. Its combination with another anti-AIDS drug, emtricitabine, gave rise to a novel drug formulation. A recently developed drug, *Atripla*™, a triple combination with another drug, Efavirenz, allows one-pill-a-day treatment of AIDS. Gilead Sciences provides this drug at a non-profit price to those developing countries with the highest incidence of AIDS. With the use of tenofovir soon to be extended to the treatment of hepatitis B virus (HBV) infections, tenofovir may be expected to save even more lives in the future.

The collaborative work on new classes of nucleosides brings unexpected results almost every year. Recently, a new compound was discovered, which was more than two orders of magnitude more potent against a broad spectrum of viruses including variola than existing treatments. The new class of drugs is not only active against viruses, but it also shows promise for the treatment of some cancers.

1. De Clercq E and Holý A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. *Nat Rev Drug Discov,* 2005, 4(11): 928-40.
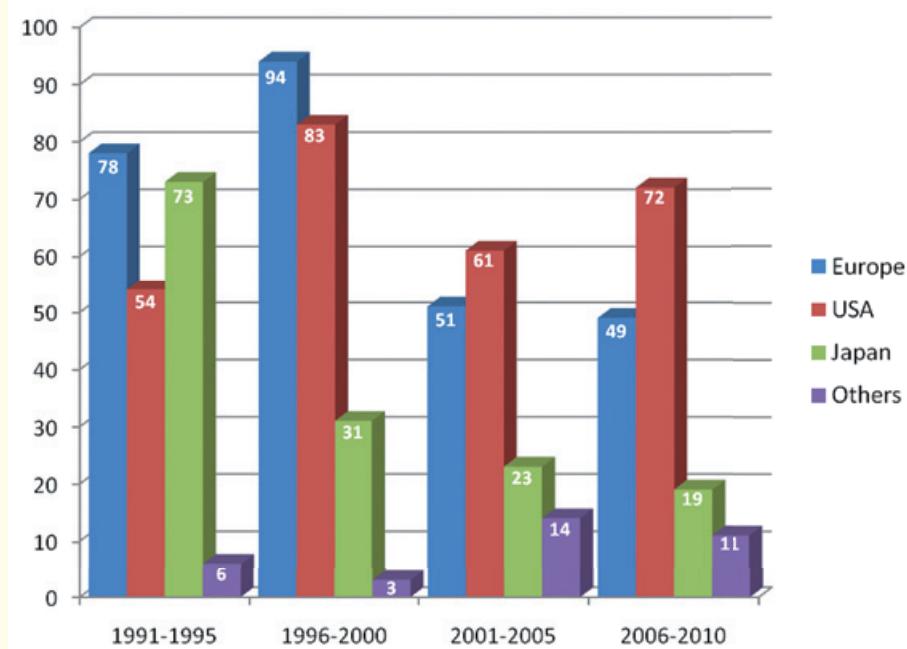
Figure 2.b.2.
Number of new chemical or biological entities (1990-2009). (Source: SCRIP-EFPIA calculations (according to nationality of mother company)).

mated the average R&D costs of NCE/NBE to be €1,059 million. During the next ten years biotechnology is anticipated to play a bigger role in the discovery, development and manufacture of almost all new medicines.

Likewise, biotech-based diagnostics (especially genetic testing), bioinformatics and pharmacogenetics will probably also increase.

Europe's pharmaceutical industry faces competition because of the rapid growth in both the market and the research environment of emerging economies such as Brazil, China and India. The markets of Brazil and China expanded by over 20% in 2010 and the pharmaceutical markets of these emerging economies are anticipated to grow at between 14 and 17% up until 2014, according to the 2010 IMS Health report. It is therefore important that support is maintained for innovation and R&D within Europe's pharmaceutical sector.

Emerging issues in bioethics

Rapid advances in technology surrounding the sequencing of the human genome have given rise to a number of important ethical considerations. For example if a study participant is at a high risk of breast cancer or cystic fibrosis, do we have a duty to let that person know? The unprecedented ability to test foetal DNA for abnormalities from samples of maternal blood also presents new ethical questions. Approximately 5-10% of the 'cell-free' DNA in pregnant women comes from the foetus. Cheap and sensitive sequencing techniques nowadays allow researchers to examine this DNA and to analyse the

foetal genome. Fears have been expressed that if this technology moves from detecting serious diseases to determining non-medical characteristics, the result could be a move towards eugenics. Advances in technologies based on stem cells must also be accompanied by robust ethical debate surrounding issues such as human cloning and potential problems of introducing genetic abnormalities into patients. The international Oviedo Convention on Human Rights and Biomedicine, signed by most of the European States of the Council of Europe, sets out the fundamental principles applicable in day-to-day medicine as well as those applicable to new technologies in human biology and medicine[37]. The legislative and philosophical approach to cloning and stem cell research, *in vitro* fertilisation and abortion is very different between European countries.

37. Oviedo Convention: http://www.coe.int/t/dg3/healthbioethic/ Activities/01_Oviedo%20Convention/default_en.asp
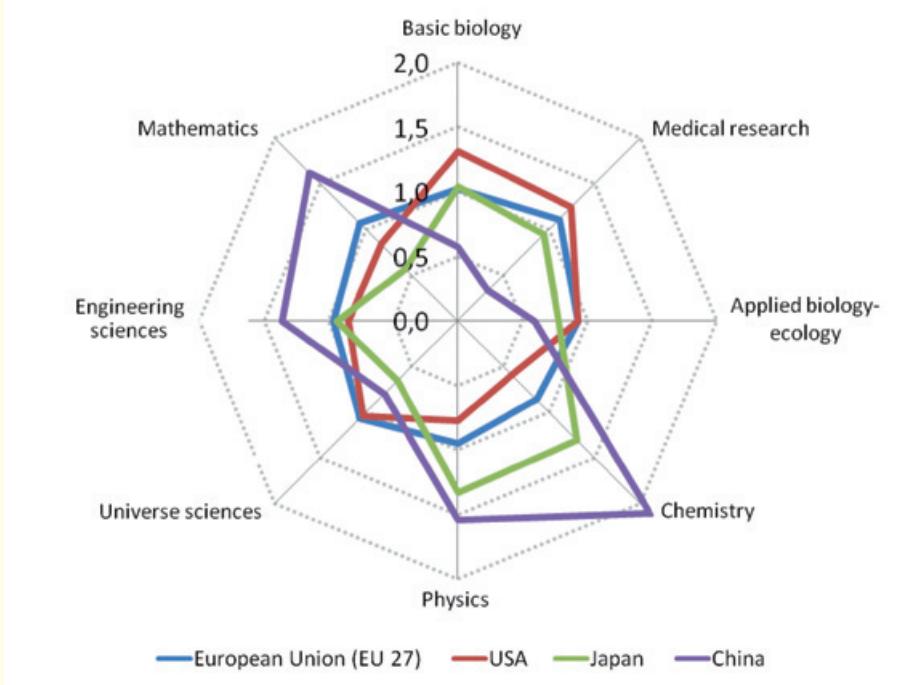
Figure 2.c.1.
Scientific specialisation index per discipline: EU27, US, Japan and China (2008 data from Thomson Reuters, analysis by OST).

c. Scientific output: how much and what is published in the world in biomedical research?

This section focuses on the bibliometric output of biomedical research in Europe and the rest of the world[38]. In its recently published report, the Observatoire des Sciences et des Techniques (OST: *Indicateurs de Sciences et de Technologies*) identifies the US, EU, Japan and China as the world's four most important producers of science when all scientific domains are taken into account. The EU was the only player for whom medical research was the dominant specialised scientific discipline based on 2008 publications, a clear indication of the EU's pre-eminence in this area internationally. Figure 2.c.1 shows how Europe is well balanced in terms of specialities, albeit with greatest strength in medical research. In Europe, eight out of the top ten sub-disciplines in which the EU produces 35-40% of the world publications are in biomedical research[39].

The NSF report *Science and Engineering Indicators 2010* published in January 2010 looks at the distribution of a country's research publications across different fields to broadly reflect its research priorities as changes in research portfolios often reveal government policy choices. In the EU27 in 2007 (Figure 2.c.2), the share of research articles in the medical field was 28.7% (including nursing, public health, psychology) and in the biological field it was 20.6%. This represents a total of 49.3% for biomedical research in comparison to all other research fields.
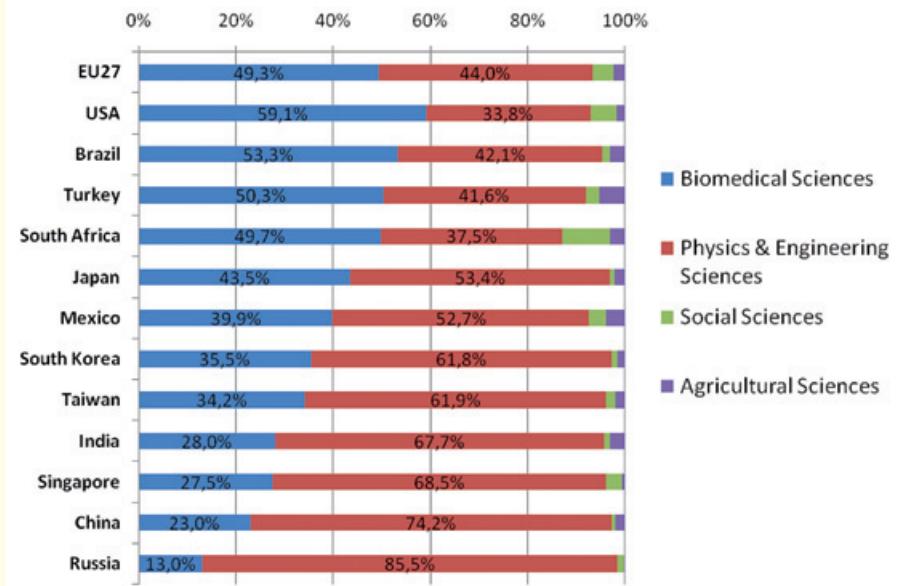
Europe and the US: a closing gap
The number of world publications or publication counts indexed by the Thomson Reuters Web of Knowledge (formerly referred to as ISI Web of Science) database has steadily increased from 1996 to 2009[40]. This is in line with the general growth of both the number of covered journals and the number of publications published by most journals. The bibliometric analysis of biomedical publications clearly demonstrates the dominant role of the US and EU15 (1996-2003) and EU25 (2004-2009) in biomedical research. Jointly they produced almost two-thirds of the world total in this field[41].

The share of European biomedical publications of

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38. The chapter is based on an analysis performed in collaboration with Dr Glänzel and Dr Thijs from the Department of Managerial Economics, Strategy and Innovation (MSI) at KU Leuven (Belgium); and complemented by three reports: *Indicateurs de Sciences et de Technologies 2010* published in December 2010 by the Observatoire des Sciences et des Techniques (OST, France); *Science and Engineering Indicators 2010* published in January 2010 by the National Science Foundation (NSF, US); and *International Comparative Performance of the UK Research Base* published in September 2009 by UK Evidence Ltd (United Kingdom).
39. cardiology/pneumology; endocrinology; oncology; surgery/gastroenterology/urology; reproduction/developmental biology; neurosciences/behavioural sciences; microbiology and virology/immunology; medical varia (e.g. internal medicine, ophthalmology, etc.).

40. The methodology used to perform this bibliometric study and a glossary are available in Annex 1. In summary, publications (counts and rates) and citations to publications (counts and rates, normalised or not) are the basis of this analysis focusing exclusively on biomedical literature.
41. See details in table A1 in Annex 1.

Figure 2.c.2.
Country/economy research priorities as shown by country/economy share of publications in various fields (2007). (Modified from NSF report *Science and Engineering Indicators 2010*; Biomedical Sciences include biological sciences, medical sciences, other life sciences (essentially nursing and public health) and psychology. Physics and Engineering Sciences include engineering, astronomy, chemistry, physics, geosciences, mathematics and computer sciences).

all worldwide biomedical publications has remained fairly stable over the last 14 years while the share of US biomedical publications has dropped over the last five years (Figure 2.c.3). However, the world share of both the US and Europe tends to decrease – a consequence of the growing output of emerging countries like China, India and Brazil. This decrease is much higher in the US than in Europe, with a decreased world share of publications of 4.6% for the US and only 0.6% for the EU between 1996 and 2009. Thus, the publication rate gap between the US and Europe has considerably narrowed in favour of Europe, which experienced a higher world share of publications than the US (38% vs. 33%, respectively) in 2009.

Citation counts measure the number of times scientific publications are cited in other publications. The counts for US publications in the field of biomedical research largely exceeded those for European publications during the period 1996-2007, although growth rates were higher for the EU, with a 64% growth in the US against 98% in the EU[42].

Citation rates. The share of world citations for biomedical publications remained about 50% for the US and 40% for European publications throughout the studied period (1996-2007)[43] (Figure 2.c.4).

However, it is important to highlight the decreasing gap in the crude citation rates between the US and Europe during the period 1996-2007, again in favour of the EU: the citation rate decreased by 5.2% for the US while it steadily increased to 3.5% for Europe (Figure 2.c.4). While American scientists publish on average in journals with distinctly higher impact than their European colleagues, jour-

nals published by European scientific societies in biomedical fields are also closing the gap in impact factor compared to those of American societies. When sampling 167 biomedical journals in four biomedical fields for the past decade, the European journals' impact factor rose by almost twice the percentage of their US counterparts[44].

In terms of **scientific specialisation** (Figure 2.c.1), the US's leading field of research specialisation is basic biological science research, followed by medical research and applied biology-ecology. In Europe it is first medical research followed by basic biological science research and applied biology-ecology. Eight out of the top ten specialisation sub-disciplines in Europe are in life sciences and medical sciences, which is close to the situation found in the US (nine out of ten). Additionally and confirming the data above, the report shows that Europe produced 35%-40% of the world's scientific publications in these 10 sub-disciplines, a higher number than the US (29-35%). On the other hand the impact of these publications after two years as expressed by the impact index[45] was superior by 20-40% in the US to the mean world impact index. Despite its dominance the US impact index decreased between 2003 and 2008 contrary to the European index that increased in the same period.

As mentioned in the context of Figure 2.c.2, medical research is Europe's strongest field of scientific publications for all research areas. The same figure shows that in the US, the medical sciences field share of research articles is of 34.1% (including

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42. See details in figure A1 in Annex 1 (Crude citation number).
43. See details in figure A2 in Annex 1 (Normalised citation rates).

44. Karageorgopoulos *et al.* Temporal trends in the impact factor of European versus US biomedical journals. *PLoS One*, 2011, 6(2): e16300.
45. See details in figure A3 in Annex 1 (Impact index at 2 years).

How biomedical research has an impact on society
Examples from around Europe

Gene therapy hope for devastating diseases
(Deutsche Forschungsgemeinschaft – DFG – Germany)

Professor Dr Christoph Klein is a paediatric haematologist at the Munich Medical School (LMU) in Germany. Professor Klein specialises in applying basic research in clinical practice and has pinpointed a number of genetic faults that result in defects of the immune system, several of which can be life-threatening. For example Professor Klein discovered that if an enzyme called glucose-6-phosphatase is faulty, this results in a catastrophic absence of a certain type of white blood cell, neutrophilic granulocytes, in newly born children. The disease is hereditary and children who inherit the condition are unlikely to survive. This discovery has opened the possibility of new treatments for the disease, particularly through gene therapy. For this work the DFG awarded Professor Klein the prestigious Gottfried Wilhelm Leibniz prize in 2010[1].

Other pioneering work by Klein's group included the first gene therapy trial for the rare and potentially fatal disease Wiskott-Aldrich syndrome, caused by a mutation in a gene called WAS. In 2006 two seven-year-old boys were successfully treated for the syndrome by gene therapy. Blood stem cells from the boys were removed and a healthy copy of the WAS gene inserted into the cells' DNA using a so-called retrovirus vector before the cells were transplanted back into the body. The treatment was successful[2] and today the boys are in good health.

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A further eight children from around the world subsequently joined the trial[3]. While most of the patients showed signs of improvement, such as increased platelets in the blood and the presence of new immune cells, some problems have arisen. It was difficult to harvest sufficient stem cells from one Lebanese boy, for example, and the cells did not 'take' well when they were re-implanted, requiring the boy to have a bone marrow transplant from his father. In 2010 another boy in the trial developed leukaemia. While this was successfully treated with chemotherapy and the patient is now in remission, it was decided to put the trial on hold. One key problem appears to be associated with 'enhancer elements' within the retroviral vectors. These are necessary to activate the healthy gene once it has been inserted into the stem cell genome. However, a side-effect is that nearby genes can inadvertently and detrimentally be switched on. The team is looking to develop new viral vectors that are less likely to activate genes other than those that specifically need to be targeted. These new vectors are being tested in animal models and human cells, and it is hoped that the trial can start up again in the coming months.

1. www.dfg.de/gefoerderte_projekte/wissenschaftliche_preise/leibniz-preis/2010/klein/index.html; the-scientist.com/2011/05/01/new-blood-for-gene-therapy/
2. Boztug K *et al.* Stem-cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med,* 2010, 363(20): 1918-27

3. Boztug K *et al.* Correction of Wiskott-Aldrich Syndrome by Hematopoietic Stem Cell Gene Therapy. American Society of Hematology meeting, December 4-7, 2010, Orlando (Florida), US; available at ash.confex.com/ash/2010/webprogram/Paper33064.html

nursing, public health, psychology) and 25.1% for the biological sciences research, reflecting a strong bio-medical research priority in the US as 59.1% of all US scientific publications are in biomedical research.

In conclusion, European countries published slightly more biomedical publications than the US over the last 14 years but the number of citations of US publications exceeded the number of citations of European publications. This suggests a quality difference in research visibility, reception and impact of the published results. However, all citation analyses using various indicators show that although the US still has higher citation counts and rates than Europe, the gap has decreased between 1996 and 2007. The European countries have progressed compared with the US as shown by the increase in the citation counts and rates for biomedical publications.

Figure 2.c.3.
World share of EU15 (1996-2003) or EU25 (2004-2009) and US in total biomedical ISI publications (1996-2009).
[Data sourced from Thomson Reuters Web of Knowledge (formerly referred to as ISI Web of Science)].

Europe and the rest of the world: the rise of the scientifically emerging countries
Japan

As shown in Figure 2.c.2. Japan has a total combined share for biomedical research of 43.5%. Only three out of Japan's top 10 specialisation sub-disciplines are found in medical research[46] in comparison to the 8 and 9 top 10 specialisation disciplines for Europe and the US respectively. Medical research specialisation is thus low when compared to Europe and the US. Japan's volume of publications in biological sciences is now similar to the UK, Germany, and China but its impact has improved slowly over the past decade (1999-2008).

In conclusion, Japan cannot be considered as a strong competitor to Europe in biomedical research as of 2008.

BRICSAM (Brazil, Russia, India, China, South Africa and Mexico)

Between 2003 and 2008 **China** showed an increase of 111% in its world share of publications. Despite this large increase, its world share of publications in the biomedical field is not significant, at only 2.9%. China's share of highly cited publications remains low at around 0.5% (Glänzel and Thijs, personal communication). Despite all indicators being currently low, China will still be a country on which to keep a close eye in the years to come given its fast rate of economic growth and its ability to implement a significant national scientific policy.

India is the only one of the emerging countries that experienced both an increase in specialisation

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46. pharmacology/toxicology; surgery/gastroenterology/urology; oncology.

in medical research (22% in 2003-2008) as well as an increase, of 34%, in the impact index of its publications. India still ranks low in terms of its national biomedical research share of research articles (Figure 2.c.2), but its impact is likely to increase in the coming years.

Brazil produced a large increase of 97% of its world share of publications between 2003 and 2008 as well as of its scientific specialisation with a 37% increase but these increases are yet to translate into higher impact of publications. As shown in figure 2.c.2, the share of research articles in 2007 for biomedical research was of 53.3%, ranking Brazil very high just behind the US (59.1%). This impact is likely to increase in the coming years.

South Africa is another BRICSAM country that will need to be carefully followed due to its sub-disciplines of specialisation (microbiology, virology, immunology) and more importantly its increase of 47% in scientific publication impact index in 2003-2008. In 2007, its share of research articles in biomedical research was also very high at 49.7%, ranking it slightly ahead of Europe (49.3%).

Russia increased its biomedical scientific specialisation (19%) but not its world share of publications in 2003-2008. The country is highly specialised in physics and under-specialised in biomedical research with a low specialisation index in 2008. Thus Russia is not likely to be a significant player in biomedical research in the coming years.

Mexico's world share of publications in medical research grew by 21% between 2003 and 2008, 14% in basic biology and 25% in applied biology-ecology. Medical research was still the research area with the lowest specialisation in 2008.

Between 1998 and 2008, **South Korea** saw

How biomedical research has an impact on society
Examples from around Europe

Keeping track of deadly influenza outbreaks for better strategic planning: The Networked Centre for Biomedical Research on Epidemiology and Public Health *(CIBERESP, Spain)*

The Networked Centre for Biomedical Research on Epidemiology and Public Health (Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública, CIBERESP[1]) is one of the nine existing CIBERs in Spain which are defined as National Biomedical Research Centres in a particular area of knowledge.

CIBERESP supported, for instance, the research programme on A/H1N1 influenza and drew the first conclusions on the 2009 pandemic. It will continue supporting epidemiological monitoring as well as the prevention and control of the pandemic and measuring its impact for the period 2010-2011, with final results expected by 2012. The 2009 results showed that the vaccination proved to be fully effective although its late implementation limited its potential impact in preventing some cases and hospitalisations. Also, the majority of school centres successfully adopted non-pharmacological prevention measures. Future recommendations include: improve information to the population and health professionals; introduce monitoring of serious hospitalised cases in order to assess the impact of seasonal flu and have historical references; make full use of existing databases in order to measure socio-economic and occupational costs; improve anti-influenza vaccination rates by better involving health staff in vaccination programmes. The final aim of this CIBERESP research programme is to measure the impact of A/H1N1 influenza on the Spanish health system.

In May 2010, the CIBERESP Strategic Research Action MCC-Spain (Multi-case control study on cancer in Spain) published a series of 10 original articles in *Annals of Oncology* (Volume 21, Supplement 3[2]) on the topic of cancer control in Spain and its assessment in a European context. This supplement represents the first joint attempt by all of Spain's population-based cancer registries to provide a systematic analysis of cancer incidence trends for all cancers combined (with the exception of non-melanoma skin cancer)

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and a review of changes in risk factors, mortality trends and screening activities nationwide for the period 1981-2006 with projections up to 2012. This project was a co-operative effort sponsored by Spain's official health research agency, the Carlos III Institute of Health (Instituto de Salud Carlos III), and the Ministry of Health Cancer Strategy Unit, which provided the necessary network funding. Estimates and projections of cancer incidence and mortality show divergent trends in Spain by sex and tumour type. This information is basic for planning and enhancing public health strategies and resources. The 17 autonomous regional health authorities and the Ministry of Health, which has a co-ordinating role, have decided to set up a common cancer strategy in the medium term.

1. www.ciberesp.es
2. Cancer Control in Spain: an assessment in a European context. *Ann Oncol,* 2010, 21(3): iii1-iii114; available at annonc.oxfordjournals.org/content/21/suppl_3.toc

biomedical research going from 17% of the country share of publications to 38%, and registering an increase of 69% in the world share of publications in the medical research field between 2003 and 2008. But the country showed low specialisation and impact indexes in this field of research in 2008. **Taiwan** and **Singapore** both increased their world share of publications in the medical research field (28% and 24%, respectively) and in biological research (37% and 71%, respectively) between 2003 and 2008, but their specialisation and impact indexes too remained below 1 in both fields. **Turkey,** an EMRC member country, posted both an increase in the world share of publications (+42% in 2003-2008) and a high specialisation index (1.62 in 2008) in the medical research field, but again with a low impact (0.30 in 2008).

Conclusion

Biomedical research in China is rapidly progressing and as for India it will only take a few more years for them to be considered as competitors in this field while already being major partners for Europe. Both these countries will need to be carefully monitored in the near future. Similarly the progression of Brazil and South Africa will need to be followed closely but over a longer term.
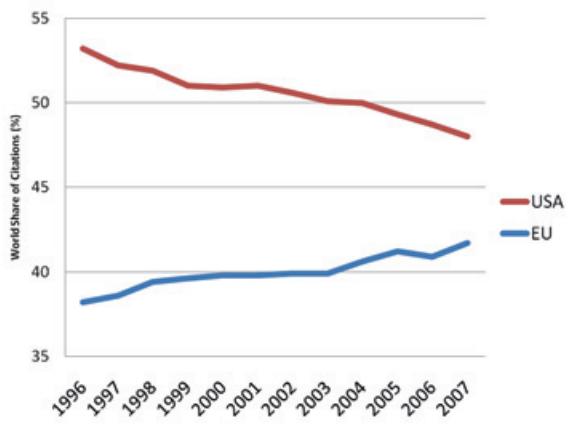

Figure 2.c.4.
Biomedical research output from US and EU15 or EU25 estimated from ISI citations to publications from 1996-2007: share of EU15 or EU25 and US citations (100% = citations to all worldwide biomedical publications).
[Data sourced from Thomson Reuters Web of Knowledge (formerly referred to as ISI Web of Science)].

d. Funding for biomedical research in Europe and globally

This section compares Europe's funding of biomedical research in the public sector and private industry with the two other main players among the world's most advanced industrialised countries, the US and Japan. Together, this triad still accounts for approximately 90 percent of the world's total, estimated to amount to around US$ 200 billion in 2009, although in recent years some smaller countries in Asia, such as South Korea and Singapore, as well as China have begun to allocate significant resources towards biomedical research, mainly in the public sector. Yet China's funding is still too low on a per capita basis and the other players in South East Asia are simply too small to compare with the triad. The Global Forum for Health Research (GFHR, 2008) estimates that the world spent US$ 160.3 billion on health-related R&D in 2005, of which 41% came from the **public** sector, 8% from the **private non-profit** sector and 51% from the **for-profit business** or industry sector.

High income countries, including the OECD countries, Israel and Singapore, accounted for US$ 155.2 billion or 97% of the 2005 total, for more than 95% of worldwide public sector spending and for virtually all spending of the world's private non-profit sector. Based on observations between 2001 and 2008, the group of low- and middle-income countries that includes China, Taiwan, Brazil, Chile, Cuba, the Philippines, Romania, the Russian Federation, South Africa and Venezuela accounted

for less than 5% of the world's public-sector and private non-profit spending on health R&D. See Annex 2 (Appendix A) for more detail.

Biomedical research in the public and private non-profit sectors

Within the triad, spending on health R&D in the public and private non-profit sectors, which are summarily known as the **non-market sectors** and include higher education and the government sector, has largely continued – albeit not in every year – to follow the divergent trends that emerged in the mid-1990s when the US began to race ahead, doubling its public funding for biomedical research within eight years until 2003. This massive boost of public funding increased the weight of health R&D not only in absolute terms, but also relative to other areas of research, such as science, engineering and the humanities. Through the American Recovery and Reinvestment Act (ARRA) of 2009, the new Obama administration has infused an additional unprecedented one-off spending boost of US$ 10 billion for health R&D and construction of new National Institutes of Health (NIH) facilities. European public funding for health R&D has continued to increase on a relatively stable growth path and indeed, in nominal terms, has outpaced Japan's throughout the 2000s. Yet, Europe has only begun to catch up with US spending increases during the mid-2000s, accentuated by a one-time one-off jump of almost 10% in Europe's nominal aggregate in 2006.

These conclusions are based on detailed analyses first of absolute spending differences between
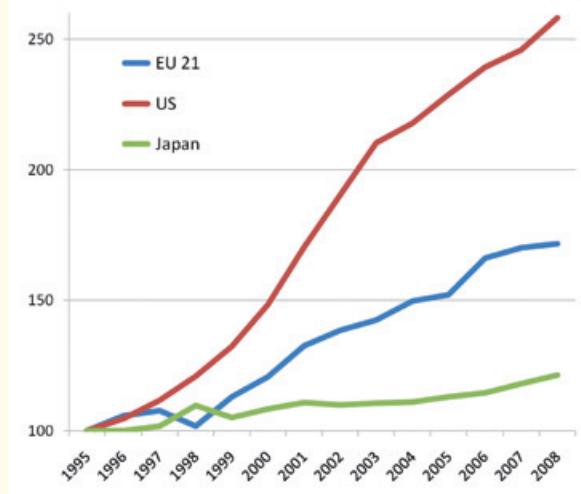
Figure 2.d.2.
Expenditure growth – time trends for nominal medical research expenditures performed in the non-market sectors relative to 1995 levels (=100) in national currencies (euro for all European countries) (See Annex 2 (Appendix B) for notes).

the triad countries in 2009, 2008 and 2007, the latest year for which a full set of reliable data on health R&D performed in the non-market sectors is available, and secondly of the time series for health R&D spending since 1995. The absolute spending differences are shown in Figure 2.d.1 for 2007, 2008 and 2009 and confirm the strong lead of the US over Europe. At € 14.0 billion or US$ 17.0 billion at purchasing power parity (PPP) in 2007, the combined total minimum spending in Europe's major performers of health R&D – Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and the UK, which are summarily labelled the EU9 countries – is only 53% of the standard minimum spending in the US, reported as US$ 32.0 billion by the OECD. At € 16.7 billion or PPP US$ 20.3 billion, the combined total of the EU21 – including Austria, Belgium, the Czech Republic, Greece, Hungary, Iceland, Ireland, the Netherlands, Poland, Portugal, Slovakia and Slovenia in addition to the EU9 – is still below two-thirds of the US standard minimum spending level, yet more than twice Japan's level, as reported by Japanese expert Tomohiro Ijichi (US$ 8.6 billion), and even more than three times Japan's OECD-reported standard minimum spending. The Ijichi-reported and the OECD-based spending levels are shown in two separate columns for Japan each year.

Note that Figure 2.d.1 also has two entries per year for the US total because the difficulty of finding reliable data for health R&D financed by state and local governments has led to estimates that can differ markedly and because the medical sciences budgets reported by the OECD (labeled 'US OECD'

in the graph) tend to underestimate US health-related R&D due to the structure and detail of the field of science classification that the US applies. In a careful attempt to correct these data deficiencies, Alison Young, the well-known international expert formerly at the OECD and now affiliated with the GFHR, has provided an upper estimate of all health R&D performed in the US non-market sectors that is also shown in Figure 2.d.1[47].

The underlying dataset has been compiled mostly from the results of the joint OECD/Eurostat R&D questionnaires among the organisations performing health R&D[48], using the methodology outlined in the Frascati Manual (2002) under the auspices of A. Young[49]. Where both are available, the higher figure is selected. Overall differences in price levels between countries are taken into account by using purchasing power parities (PPPs), as described in Annex 2 (Appendix B).

In Figure 2.d.2, the performer-reported data are used for a more detailed comparison of time trends in health R&D performed in countries' non-market sectors since 1995, setting all spending in 1995 equal to 100 and plotting the observed growth in nominal spending relative to that base level. For most of the time, the aggregate for 21 European countries shows steady growth that exceeds the slow growth of nominal health R&D in Japan, except for the years 1997-1998 and perhaps 2004-2005 when European spending seems to have stagnated. With an overall increase of 170% between 1995 and 2007 and 177% between 1995 and 2009, Europe's spending clearly fails to match the much stronger growth that the US aggregates show during the same period.

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47. An even more comprehensive approach has been taken by Research America, Inc., a private advocacy organisation, that estimates government funding and other funds flowing into the US non-market sectors performing health R&D in 2007 to exceed US$ 54 billion, or € 44 billion at purchasing power parity. This is more than two-and-a-half times the non-market health R&D performed in the EU21. International comparisons for 2008 and 2009 without the extra US spending triggered by the American Recovery and Reinvestment Act in 2009 are quite similar overall, but are less reliable as we use estimates for a number of countries and impute, for example, the 2008 upper estimate in the US (based on Young) as well as use an incomplete update of the US standard minimum (based on the OECD). The most comprehensive update for 2009 may well be Research America's report, which includes the US$ 10 billion spending boost for the NIH and puts the total spent on medical research performed in the US non-market sectors at US$ 64.6 billion.
48. The underlying definition of medical science comprises numerous subfields in basic medicine, clinical medicine and general health sciences, but does not follow the 2007 revisions in the Frascati Manual that recommend broadening the definition and including new fields, such as medical biotechnology.
49. To minimise the incidence of gaps in the data, funder reports of R&D for the health objective, such as official government budgets, are used as a substitute where performer-reported data are not available.

How biomedical research has an impact on society
Examples from around Europe

Pioneering research to tackle AIDS
(Institut National de la Santé et de la Recherche Médicale – Inserm, French National Agency for Research on Aids and Hepatitis – ANRS – France)
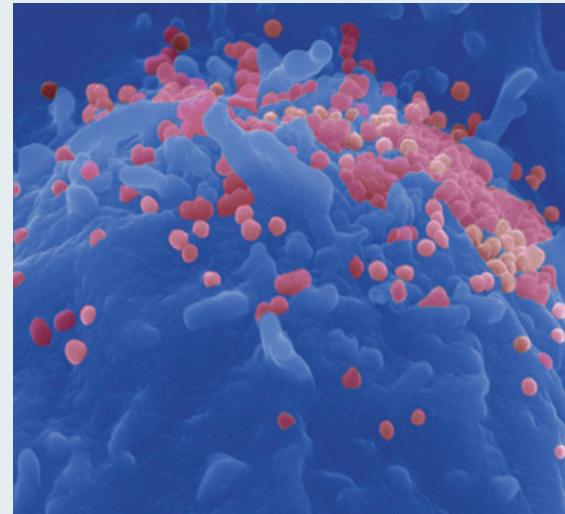
There has been remarkable progress in the treatment of HIV infection over the last 15 years. When AIDS was first discovered in 1981, it was a death sentence for most infected individuals, usually young homosexuals or people who injected drugs. Hospital wards were filled with these young men and women dying of opportunistic infections with severe diarrhoea, neurological diseases, or pneumonia. Patients were usually hospitalised in internal medicine, infectious disease or haematology departments but soon AIDS wards had to be created to provide a specialised management for these dying patients.

The human immunodeficiency virus (HIV, the causative agent of AIDS), was discovered in 1983 by Professor Françoise Barré-Sinoussi and Professor Luc Montagnier of the Pasteur Institute in Paris for which they received the Nobel Prize in 2008. This discovery opened the way to understanding the virus life cycle and to identifying drug targets. Soon the HIV enzyme 'reverse transcriptase' was identified as an interesting drug target and shortly followed by the development of zidovudine or AZT, the first ever drug approved to treat AIDS. Unfortunately, the virus was able to rapidly develop resistance to AZT so the drug only had a short-term effect. Patients were therefore still dying and the epidemic went on growing.

It was not until 1996 when patients were able to receive a triple drug combination (AZT with reverse transcriptase inhibitors and protease inhibitors) that a real impact on the disease was achieved. Indeed, within a few years a dramatic drop in the rates of AIDS-related deaths and AIDS-related opportunistic infections occurred. This benefit of anti-HIV therapy was seen in all countries where these drugs were available. New drugs against various other HIV targets (including integrase, chemokine receptors, proteins of entry, and others) have since been discovered in the last 10 years. Patients who previously had to be off work for years can now leave hospital and resume their professional activity. Today in Europe and in the US very few patients with HIV still need hospitalisation.

The cost-effectiveness of this treatment strategy is one of the best examples in medicine of

© Institut Pasteur / PFMU-Imagopole – Unité Virus et immunité – Colours by Jean-Marc Panaud.

how a potent treatment can almost cure a deadly disease. Indeed, although patients with HIV infection still harbour the virus, they are usually asymptomatic, and can live an almost normal life where they can have a job, children and present a very small risk for their partner in terms of HIV transmission. They are also believed to have a normal life expectancy.

The impact of anti-HIV drugs on the healthcare system has been dramatic, turning a deadly disease affecting mostly young individuals requiring frequent hospital admissions, into a chronic asymptomatic infection in patients now managed as outpatients, leading to significant healthcare savings.
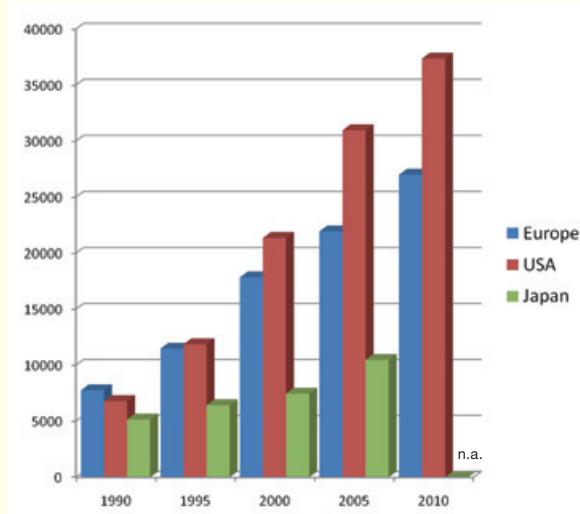
Figure 2.d.3.
Pharmaceutical R&D expenditure in Europe, US and Japan, 1990-2010 (Europe: € million; US: US$ million; Japan: ¥ million x 100; e: estimate; n.a.: not available). Source: EFPIA member associations, PhRMA, JPMA

According to both the standard minimum provided by the OECD and the upper estimate provided by A. Young, nominal spending on health R&D performed in the US non-market sectors has grown by around 250% from the respective base values in 1995[50]. In Japan, nominal expenditure on health R&D in the non-market sectors has grown by a mere 20% between 1995 and 2007, appearing almost flat compared with Europe and the US. However, it must be noted that Japan has been in a deflationary environment since the mid-1990s and the Japanese yen has strongly appreciated against the euro and the US$. Had the Japanese series been converted into euros or US$ using PPPs, it would have turned out almost as steep as the index we present for the EU21.

In the EU in 2006, 0.054% of GDP was committed to public funding of health research while similar 2008 figures in the US demonstrate a public funding of health research at 0.222% of GDP[51]. The US and EU GDPs being comparable (approximately US$15000 billion in 2008[52]), it shows how the US dedicate about 4 times as much public funding for health research as the EU.

Biomedical research in the for-profit business sector

With respect to health R&D funding by the industry sector the following focuses mainly on the recently published 2011 summary report from the European Federation of Pharmaceutical Industries and Associations (EFPIA)[53], which provides general data on the pharmaceutical but also the biotech industry's activities. Most of the information is directly supplied by EFPIA's member associations. In selective cases these data are supplemented using various other sources, such as the OECD or Eurostat[54,55].

The health industry has seen its relative economic impact increase in recent years. In Germany for example the economic weight has shifted from the automobile industry towards the health industry. The pharmaceutical and biotechnology sector accounts for around 17 per cent of business research and development expenditure in the EU, making it one of the leading high-technology industrial sectors in Europe. In 2010 the sector contributed about 3.5 per cent of the EU's total manufacturing added value[56], and on most standard indicators the pharmaceutical industry performs well[57]. Investment in R&D from private sources increased from € 7.8 billion in 1990 to € 27 billion in 2010 (Figure 2.d.3). The sector employs some 640,000 across Europe, of whom some 117,000 work in facilities dedicated to R&D.

The role of biotechnology is becoming more prominent. The development of new vaccines, diagnostics and therapeutics increasingly relies on biotechnology and it is likely that by 2030 almost all value added in the pharmaceutical sector will at least partially depend on biotechnology. Investment in biotechnology R&D from the European private sector in 2008 amounted to € 3.5 billion, compared with € 17.2 billion in the US. Europe accounts for

50. According to Research America, US spending tripled until 2007 and between 2007 and 2009 made another upward leap in excess of 50% of the 1995 base value implied by the assumption of a constant non-market share of 44% in all US health R&D spending over time. The spending boost between 2007 and 2009 reflects above all the US$ 10 billion earmarked for health R&D in the 2009 American Recovery and Reinvestment Act.
51. OECD Science, Technology and Industry Scoreboard 2009, ISBN: 978-92-64-06371-6
52. CIA World Fact Book, https://www.cia.gov/library/publications/the-world-factbook/

53. European Federation of Pharmaceutical Industries and Associations (EFPIA) report: The pharmaceutical industry in figures. 2011 Edition; available at http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=11586
54. Human Health Biotechnologies to 2015. Anthony Arundel, David Sawaya, Ioana Valeanu, OECD Journal: General Papers – Volume 2009/3, OECD 2009. Data sources: OECD, US FDA, EMA, published literature, Pharmaprojects, Pharmapredict (proprietary data sources).
55. Study on the competitiveness of the European biotechnology industry: The financing of biopharmaceutical product development in Europe. The Framework Contract of Sectoral Competitiveness Studies – ENTR/06/054. Final report. European Commission, Enterprise and Industry, 2009. NB-31-09-224-EN-C. ISBN 978-92-79-14055-6. Data sources: Ernst & Young, Eurostat.
56. European Federation of Pharmaceutical Industries and Associations (EFPIA) report: The pharmaceutical industry in figures. 2010 Edition; available at http://www.efpia.eu/content/default.asp?PageID=559&DocID=9158
57. Data relate to EU27, Croatia, Iceland, Norway and Switzerland since 2005 (EU15, Norway and Switzerland before 2005).
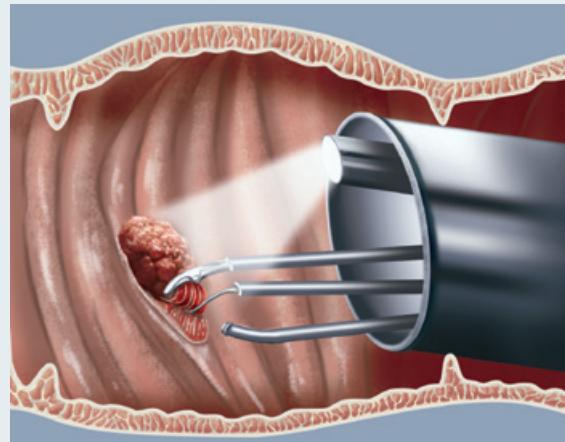
How biomedical research has an impact on society
Examples from around Europe

Ground-breaking microsurgery and better diagnosis of heart disease
(Federal Ministry for Education and Research – BMBF – Germany)

The German Federal Ministry for Education and Research (BMBF) has supported research programmes for new technologies such as minimally invasive surgery since 1983, leading to the development, for example, of transanal endoscopic microsurgery (TEM). Nowadays, TEM is used routinely to remove rectal or colonic polyps as well as early intestinal carcinomas. With TEM, the risk of infections and important surgical complications including those that can be life-threatening has considerably decreased.[1]

The BMBF-supported German researcher Professor Hugo Katus (now at University Clinics in Heidelberg) developed in the early 1980s the troponin test that has since become a mainstay of cardiology with support of Boehringer Mannheim. Katus's team isolated and purified proteins from heart muscle. Troponin was found to be systematically detected in patients' blood following damage to the heart muscle cells. The researchers also developed the first lab test that allowed the detection of cardiac troponin and thus the early diagnosis of myocardial infarct. Today, the number of diagnosed infarcts has almost doubled compared to the "pre-troponin"

© BMBF

era but the mortality of infarcted patients has dropped to around one third because people with micro-infarcts can nowadays be adequately handled. Since then, the newest generation of highly sensitive troponin tests has been developed. In 1995 the heart infarct quick detection test developed together with Boehringer Mannheim received the prestigious Innovation Prize of German Science (Innovationspreis der deutschen Wirtschaft).[2]

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1. Bundesministerium für Bildung und Forschung (BMBF) report. *Erfolge der Gesundheitsforschung.* Berlin, 2008. Available in German at http://www.gesundheitsforschung-bmbf.de/de/2436.php (accessed June-15, 2011).

2. Bundesministerium für Bildung und Forschung (BMBF) report. *Erfolge der Gesundheitsforschung.* Berlin, 2008. Available in German at http://www.gesundheitsforschung-bmbf.de/de/2436.php (accessed June-15, 2011).

just over 16 per cent of biotech R&D expendi-
ture – dwarfed by the US at almost 80 per cent
(Figure 2.d.4). The European biotech sector con-
tinues to expand rapidly, but not as quickly as in
the US.

A strong and sustainable industrial biotechnol-
ogy base in Europe must be built upon competitive
and innovative research.
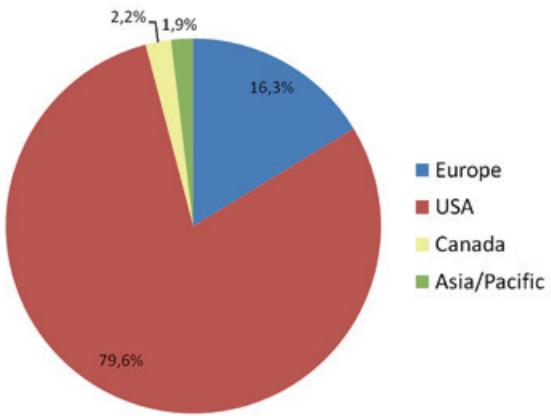
Figure 2.d.4.
Share of global biotechnology R&D expenses, public companies
(2008). Data source: EFPIA report, 2010 Edition.
Source: Ernst & Young, 'Beyond Borders, Global Biotechnology
Report 2009' (data relate only to publicly traded companies).

3.
Biomedical research in North America

● ● ●

a. United States – National Institutes of Health (NIH) funding trends and priorities

Susan B. Shurin, MD, Acting Director, NHLBI, NIH

"NIH's mission is to seek fundamental knowledge about the nature and behaviour of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability.

The goals of the agency are to:
- foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health;
- develop, maintain, and renew scientific human and physical resources that will ensure the nation's capability to prevent disease;
- expand the knowledge base in medical and associated sciences in order to enhance the nation's economic well-being and ensure a continued high return on the public investment in research; and
- exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science."

History

The NIH has grown dramatically in the period since the Second World War, but has an evolutionary history extending back to 1798, when the Marine Hospital Service (MHS) was established to provide for the medical care of merchant seamen. A key driver of the enhanced public investment in science after World War II was the perception that superior technological skills and knowledge (including the development of penicillin and the atomic bomb) contributed to the Allied victory. The emphasis
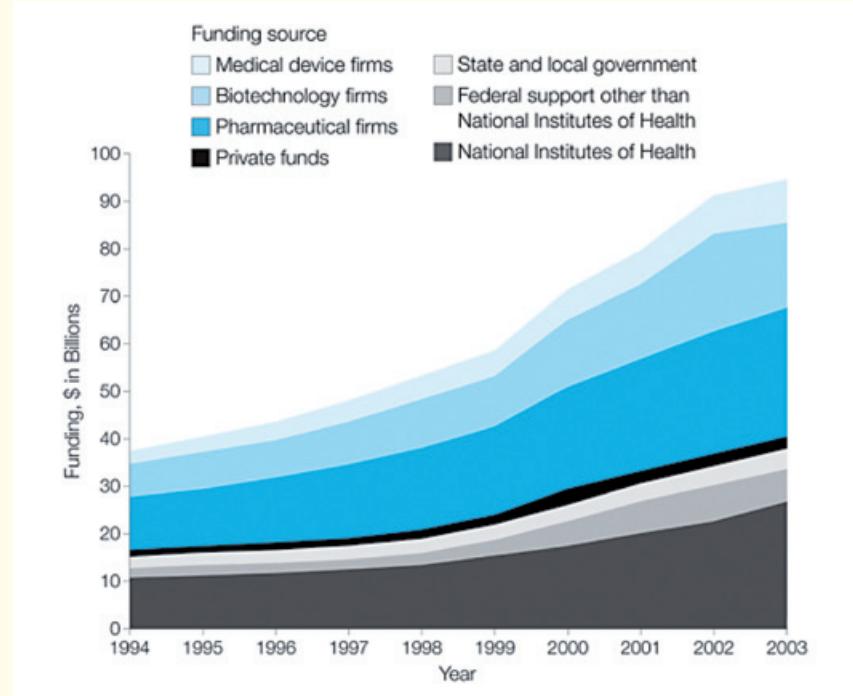
lessened early in the Cold War, but was re-ignited by the Soviet launch of Sputnik. Emphasis on scientific investment continues to vary with the political climate. Advances in technology can be perceived as contributing to both costs and value; such discussions continue as part of public dialogue.

In 1946 the extramural grants programme of the National Cancer Institute (NCI) was expanded to the entire NIH. From just over US$4 million in 1947, the programme grew to more than US$100 million in 1957, US$1 billion in 1974, and its present US$32 billion.

Organisational structure

The NIH is an agency within what is now called the Department of Health and Human Services (HHS) in the Executive Branch of the US government, reporting directly to the President. HHS includes other agencies with missions relevant to biomedical activities, including the Centers for Disease Control and Prevention (CDC), with a public health mandate; the Food and Drug Administration (FDA), which oversees drugs and biologics, as well as components of food safety; the Health Resources and Services Administration (HRSA), which addresses access to care for the underserved; the Center for Medicaid and Medicare Services (CMS), which supports delivery of healthcare which is publicly funded; and the Agency for Healthcare Research and Quality (AHRQ), which addresses health services research and issues of quality in healthcare delivery. HHS is responsible for about 25% of the annual expenditures of the US government.

Since World War II, the NIH has grown to include 27 Institutes and Centers ('ICs'). The 'categorical ICs' focus on disease- or organ-specific research and usually have intramural programmes

Figure 3.a.1.
Funding for biomedical research
by source, 1994-2003*.

* Source: Moses H III., Dorsey ER,
Matheson DH, Thier SO. Financial
anatomy of biomedical research.
JAMA, 2005, 294(11):1333–1342.

which conduct research on the NIH campus, while
the Centers – including the National Library of
Medicine, the Fogarty International Center and
the Center for Scientific Review – have trans-NIH
missions which are not disease-specific or organ-
specific. Each has its own budget, mission, advocacy
groups in the public and scientific community, and
leadership. The Director of the NIH is appointed
directly by the President, with confirmation of the
appointment by the Senate required. The Director
of the NCI is also a Presidential appointment, but
Senate confirmation is not required. Appointments
of other IC Directors are made by the NIH Director
in consultation with the Secretary of HHS.

The National Science Foundation (NSF) supports
fundamental science and engineering except for the
medical sciences. Its annual budget was US$6.9 bil-
lion in 2009. While NSF and NIH both support
research universities and institutes, the research
areas supported are different.

Each year, the president proposes a budget to
Congress, with specific allocations to the NIH
and individual ICs. Commitments are not made
beyond one year, although projects must be funded
for longer periods, usually four to five years. Both
houses of Congress must pass the budget, and any
differences between the House of Representatives
and the Senate versions be resolved. Congressional
authorisation is required for all parts of the govern-
ment, including the NIH, to expend. A major role
of the NIH leadership is communicating the impor-
tance of biomedical research to Representatives and
Senators.

In 2002, towards the end of the doubling of the
NIH budget, the Institute of Medicine convened a
working group to address structural issues at the
NIH. This report[58] made 14 recommendations to
enhance administrative efficiency, improve stra-
tegic planning and functioning, and optimise the
alignment of structure and function of the insti-
tute. A few of these recommendations have been
implemented, some are under consideration, and
still others have yet to be fully addressed. The
importance of periodic strategic review of large
bureaucratic institutions such as the NIH is well
appreciated by the Agency and by its constituent
communities.

Sources of support for biomedical research
The NIH is the primary source of funds for basic
biomedical research, and for the components of
biomedical research which are driven primarily
by public health needs. When biomedical research
is likely to result in commercialisable prod-
ucts, research tends to be supported by industry.
Foundations and private philanthropy support
research in areas of specific relevance to their mis-
sions. The combination of private and public funds
with the mission-driven investment of philanthropy,
plus contributions from state and local governments,
provides multiple avenues for setting priorities and
making research investments on the basis of a vari-

58. Shapiro HT *et al.* Enhancing the Vitality of the National
Institutes of Health: Organizational Change to Meet New
Challenges. 2003. National Academy of Sciences Press (accessed
online at http://www.nap.edu/catalog/10779.html).
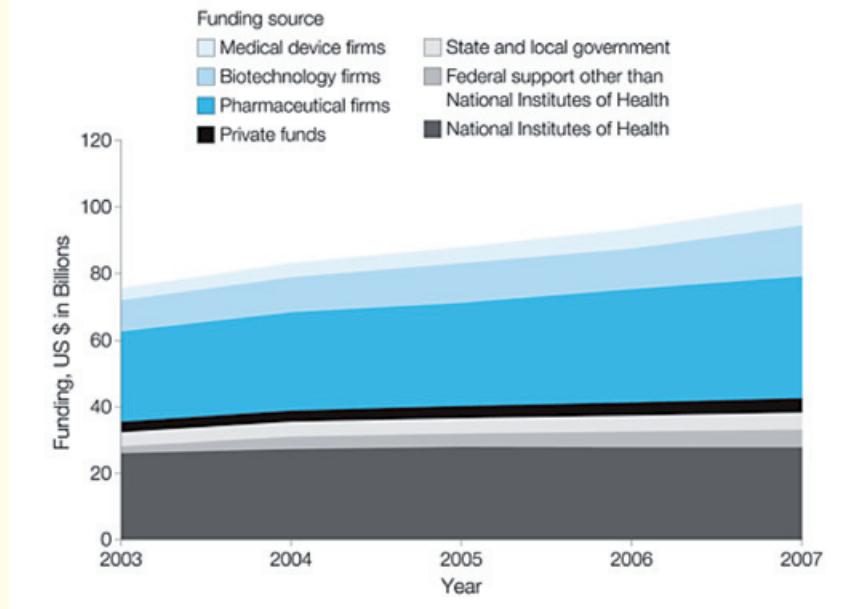
Figure 3.a.2.
Funding for biomedical research
by source, 2003-2007*.

* Source: Dorsey E.R. *et al.* Funding
of US Biomedical Research, 2003-
2008. *JAMA*, 2010, 303(2):137-143.

ety of motivations: public health benefit, benefit to specific patient groups, and meeting the needs of the market.

These multiple approaches are flexible and provide opportunities to complement each other, but are not efficient, consistent, coordinated, data-driven; or approaches to setting priorities, since each entity and sector sets its own priorities.

The NIH provides financial support in the form of grants, cooperative agreements and contracts to support research-related activities, including fellowship and training, career development, scientific conferences, resource and construction. Projects are funded on the basis of high scientific calibre as determined by peer review, and assigned to NIH ICs on the basis of their missions. Unsolicited research and training applications originate from investigators' research ideas or training from the majority of projects funded by the NIH.

NIH-funded research covers the full spectrum of basic science, early and later stage translational science, epidemiology, comparative effectiveness research and the training and building components needed to conduct research. Funding priorities overlap with other sectors, especially pharmaceutical and device manufacturers in translational research, but there is very little overlap in basic research.
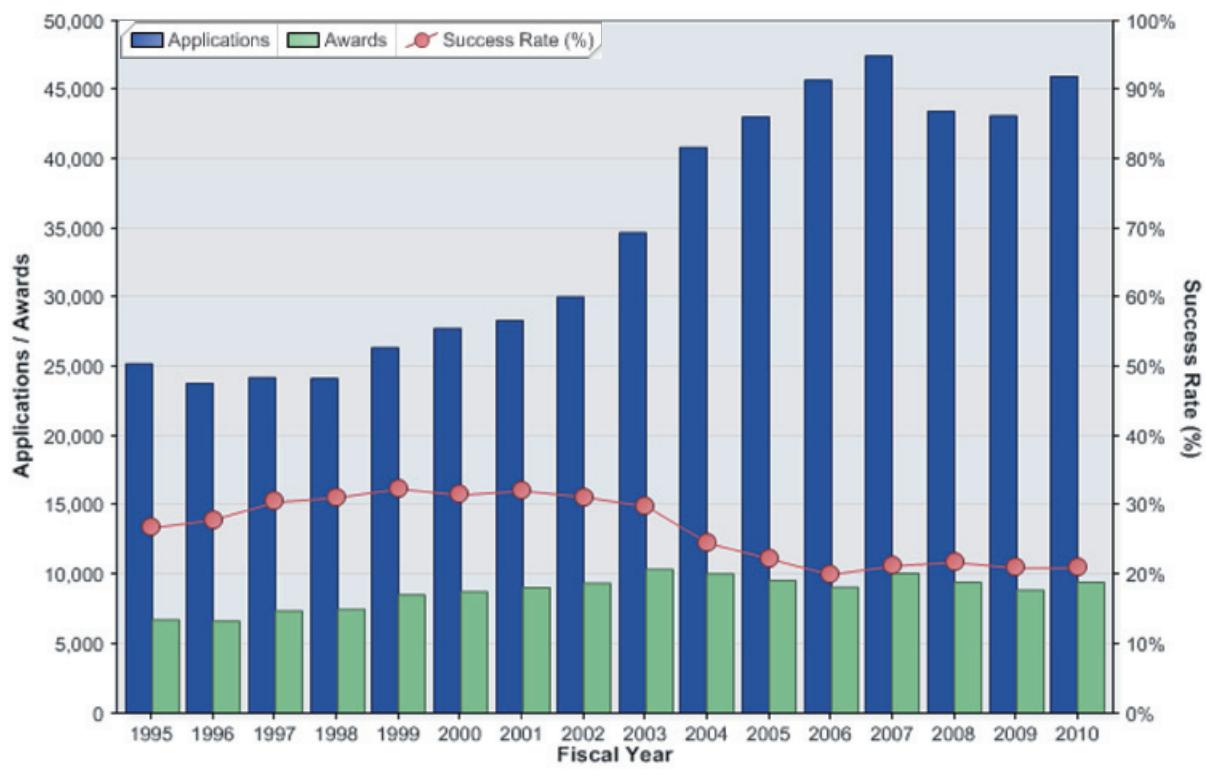
Funding patterns have varied with economic and political climates over the past several decades (Figures 3.a.1 and 3.a.2). Biomedical research funding increased from US$37.1 billion in 1994 to US$94.3 billion in 2003, and doubled when adjusted for inflation. In 2003, industry supported 57% and the NIH 28% of US biomedical research. Industry sponsorship of clinical trials increased from US$4.0

to US$14.2 billion in real dollars, while federal proportions devoted to basic and applied research were unchanged. In contrast, in the period from 2003 to 2007, both public and industry investments in research have not changed significantly. A decrease in the numbers of FDA approvals of new molecular entities and biologics in the past decade has decreased the industry profit margins. The length and cost of the drug development process have increased the caution of industry leaders for making investments in R&D. Many biomedical research advances are translated into medical improvements outside the realm of commercial product development.

Academic medical centres and the economics of healthcare

Along with the flattening of investment in biomedical research over the past seven years have come major changes in the financing of academic medical centres[59]. Of the 126 medical schools in the US, those which are research intensive rely heavily upon NIH funding for operating dollars, as well as for the funds to support research projects and faculty. NIH dollars bring indirect costs to the grantees which support many of the costs associated with doing research, as well as paying faculty salaries. However, the costs of doing research are considerable, and are usually not fully covered despite the very high indirect cost rates negotiated with the Office of Management and Budget. Hospital profit

59. Mallon W.T. and Vernon D.J. The Handbook of Academic Medicine: How Medical Schools and Teaching Hospitals Work. 2nd ed. Washington, DC: Association of American Medical Colleges; 2008.

Figure 3.a.3.
Success rates for scientists applying for NIH research project grants have dipped to an estimated 19%, down from 21% in 2009 and far lower than the 32% of 2000*.
* Source: Wadman M. and Collins F. One year at the helm. *Nature*, 2010, 466: 808-810.

margins have fallen as the cost of providing care has increased along with the numbers of charity patients in the face of declining reimbursement. The crisis in delivery of medical care in the US creates great strains on the institutions where clinically oriented research takes place.

Faculty sizes have grown; increasing percentage of overall income comes from faculty practice plans, which increasingly are owned by the institutions. All these changes in financial revenues substantially impact the pressures on faculty as to how they spend time, for the activities valued and rewarded at their institutions, and most incentivise organisational leaders to value participation of faculty members in clinical care and service more than in research. Medical school has become increasingly expensive, with many graduating physicians carrying US$150,000-200,000 in debt as they begin their careers, a profound disincentive to entering the prolonged training needed for academic subspecialties. Promotion and tenure are based on individual accomplishment rather than participation in team science. All of these factors have made the pursuit of careers in academic medicine, especially in translational research, more difficult.

Funding trends

After a relatively flat period of NIH funding, Congress authorised a doubling of the NIH budget, which took place between 1998 and 2003. Substantial construction and additional training programmes were established during this time period. Since the end of the doubling, there have been significant increases in the numbers of applicants and numbers of applications submitted per applicant. The budget, however, has failed to keep up with inflation, much less with the Biomedical Research and Development Price Index (BRDPI), and the rate of successful applications has fallen significantly from the mid-30% level in 2000 to below 19% in 2010 (Figure 3.a.3). Improvements in NIH funding are not anticipated in the near future. In 2009, the Congress appropriated US$10 billion to NIH under the American Recovery and Reinvestment Act (ARRA). These funds had to be spent in 18 months, and could support projects at institutions over one subsequent year; a major incentive was creation of jobs, which is highlighted in NIH reporting on the use of ARRA funds. The lag time between funds allocation and required expenditure was very short. Most ICs had strategic plans in place which enabled them to make intentional and targeted investments of funds in high priority projects.

The funding situation expected in the next five years or more requires that the NIH carefully examines all its programmes, achieves a high degree of

accountability, and ensures attention to the return on its investments in biomedical research. Each IC is examining its portfolio and establishing its priorities based upon scientific opportunities and public health needs.

As the volume of applications has increased, the peer review system has become overburdened. Over the past four years, the NIH has refined several aspects of peer review. The NIH receives nearly 80,000 applications a year and engages over 21,000 external experts to review them in study sections which meet three times during the year. For nearly 60 years, this peer review system has enabled NIH to fund cutting-edge research. Changes implemented include shortening the applications and the review process; revision of the review criteria to enhance transparency and clarity; train and support reviewers to improve the uniformity of review; and revise the review process for clinical research to ensure clarity of the scientific questions and process of conduct of clinical research.

Initiatives in translational medicine and therapeutics

Extensive discussions are taking place about how best to enhance the efficacy and efficiency of NIH support of translational research. Major reasons for this discussion include the high costs of drug development; the extreme inefficiency of the current system with above 95% failure of drugs which undergo early tests in humans; the long duration of drug development; the unprecedented promise of basic science discoveries in the genomic era; and an emerging shortage of translational physician scientists. This discussion is focusing on identifying the attributes, activities, and functional capabilities of an effective translational medicine programme for advancing therapeutics development; and broadly NIH landscape for extent programs, networks, and centres for inclusion in this programme and recommending their optimal organisation. Several of the ICs have translational programmes with substantial infrastructure investments, but these vary in effectiveness, and many of the smaller ICs do not have such programmes.

In 2006, the Clinical Translational Science Awards were initiated at NIH, creating a consortium of academic institutions across the country with capacity to support and perform translational research. This was undertaken in response to widespread concern that better translational infrastructure was needed. Within the past two years, several trans-NIH initiatives have begun to facilitate early stage translational work, including the Molecular Libraries Screening Center Network,

Therapeutics for Rare and Neglected Diseases (TRND), and Rapid Access to Interventional Development (RAID), an extension of a programme at the NCI.

Integration of these programmes into a common Center is planned to enable the various initiatives to work smoothly together to facilitate translation of basic discoveries into preclinical testing, early stage translation and full scale clinical trials. Key components of this discussion include the need to synergise with, and avoid competition with, resources in the private sector, and identification of metrics and methodologies for evaluating the impact of changes in the organisation and management of the therapeutic development programme.

b. Canada – perspective of the Canadian Institutes of Health Research (CIHR)

Alain Beaudet, President, CIHR
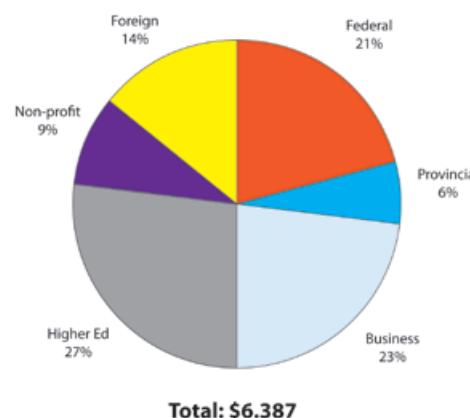
In Canada, the provision of publicly funded health research is under joint federal and provincial control. The provinces are mainly responsible for the salaries of investigators and the servicing of their workplace, by virtue of their constitutional jurisdiction over higher education. Indeed, as in the US, virtually all publicly funded health researchers in Canada hold a university appointment. By contrast, the federal government is the main funder of research operations and infrastructure, although some provinces also invest in research operations either directly or through their own provincial research organisations.

As can be seen in Figure 3.b.1, provincial (including the higher education sector) and federal health research funding jointly accounted for 54% of total health research expenditures, estimated at 6.4 billion Canadian dollars (hereafter C$) in 2009 (or 21.5% of Canada's gross domestic expenditures on R&D). The addition of investments from foreign sources (such as the NIH, the Gates Foundation, etc.) and from the not-for-profit sector brings the percentage of public investments in health research to 77% of the total over the same period. By contrast, the relative value of research performed by the business enterprise is low (23% of total): on this indicator, Canada ranks 15th among OECD nations, well below the average.

Unlike health research, healthcare is primarily a matter of provincial/territorial jurisdiction, with the federal government contributing to provincial/territorial health spending through transfer payments while also providing healthcare to Aboriginal peoples, the military and prisoners.

Provinces/territories receive federal transfer payments (currently at C$38.5 billion per year) if they abide by the five principles of the Canada Health Act (i.e. universality, comprehensiveness, portability, accessibility, and public administration), which is the piece of legislation that governs Medicare, Canada's universal health insurance programme for physician and hospital services. Thus, Canada could be viewed as a patchwork of more than 13 healthcare systems, which poses unique challenges to issues of knowledge transfer and integration of research and care.

Figure 3.b.1.
Total research expenditures (Source: CIHR)

The federal health research system

The bulk of federal health research funding is provided by CIHR, one of three federal granting agencies (Figure 3.b.2), known as the 'tri-agencies'; the other two are responsible for the funding of academic research in the natural sciences and engineering (NSERC), and in the humanities and social sciences (SSHRC), respectively. In addition to bilateral partnerships in specific interface areas (e.g. biomedical engineering, medical isotopes, etc.), CIHR, NSERC and SSHRC cooperate in the management of funding programmes that span the entire range of research disciplines, such as the Networks of Centres of Excellence (NCE), the Centres of Excellence for Commercialization of Research (CECR), the Canada Research Chairs (CRC), and the Banting and Vanier studentships. They also cooperate in matters of ethics and research integrity through the Interagency Advisory Panel on Research Ethics, which is placed under their joint authority.

In addition, CIHR collaborates closely with four other federally funded independent foundations that are also important supporters of health research (Figure 3.b.2): (i) Genome Canada (established in 2000) supports large-scale genomics and proteomics research projects and regional research platforms; (ii) Canada Foundation for Innovation (CFI) (1997) provides equipment and infrastructure (for both foundations, approximately half of their investments flow to health research); (iii) Canadian Health Services Research Foundation (1997), which pioneered the science and practice of knowledge translation (KT) and exchange in health research in Canada; and (iv) International Development Research Centre (1970), which helps developing countries use science and technology to find solu-

Figure 3.b.2.
The federal research and
innovation system
(Source: CIHR)

tions to their social, economic, and environmental problems, and is key to CIHR's global health activities.

Whereas CIHR reports to Parliament through the Minister of Health (Figure 3.b.2), the other granting agencies report through the Minister of Industry. Federal science policy is the responsibility of the Minister of State (Science and Technology), a junior Cabinet minister within the Industry Portfolio.

By virtue of its integration into the Health Portfolio (Figure 3.b.2), CIHR also interacts closely with the other two major agencies reporting to the Minister of Health: (i) Health Canada, which protects Canadians against risks from the environment, ensures the safety of consumer and health products, and is responsible for the approval of new drugs. It is also responsible for delivery of healthcare to First Nations people on reserves and to Inuit communities in the north; (ii) the Public Health Agency of Canada, which focuses on health promotion and prevention of chronic disease, health and disease surveillance, and is responsible for infectious disease control and the response to public health emergencies. It works with provincial, territorial and municipal governments, which share the responsibility for protecting public health.

The Canadian Institutes of Health Research: creation of a new model

The Canadian Institutes of Health Research were created ten years ago, replacing the Medical Research Council of Canada (MRC). In contrast to the MRC, which solely supported biomedical and clinical research, CIHR was tasked with supporting the whole spectrum of health research, including health services and public health research.

Consequently, CIHR's mandate calls for balanced support of the four themes of health research, defined in the CIHR Act as "bio-medical research (theme 1), clinical research (theme 2), research respecting health systems and health services (theme 3), the health of populations, societal and cultural dimensions of health and environmental influences on health (theme 4)". It also calls for equilibrium between 'open' (or investigator driven) funding *versus* 'strategic' (or targeted) funding. An early consensus of its governing body was to move gradually to a 70/30 split between open and strategic investments, and indeed the strategic funding proportion increased from 10% in 2000-2001 to 33% in 2009-2010.

In addition to this broadened mandate, CIHR was given the mission "to excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge", but also to ensure translation of this knowledge "into improved health for Canadians, more effective
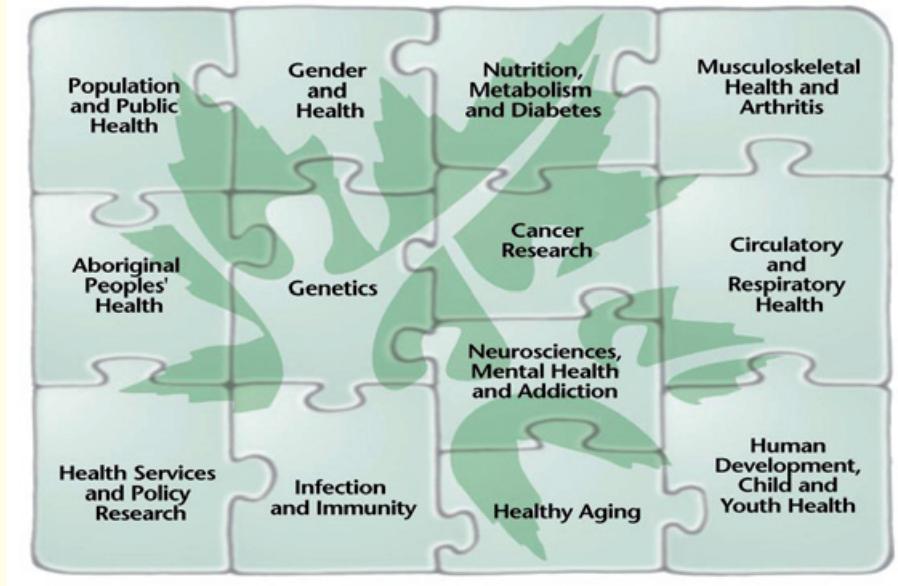
health services and products and a strengthened Canadian healthcare system". The second part of this mandate, dealing with Knowledge Translation (KT), was novel for a Canadian research agency, and unknown territory for most researchers.

CIHR's structure is fundamentally different from that of its predecessor and of other federal Granting Councils, in that it comprises 13 'virtual' thematic Institutes. In contrast to the US NIH, CIHR Institutes are not legislated entities, nor bricks-and-mortar organisations with intramural research programmes. They are delocalised networking entities, based in the institutions (university or hospital) with which their Scientific Director is affiliated.

The 13 Institutes (Figure 3.b.3) form the constitutive core of CIHR and are its distinctive and fundamental organisational feature.

CIHR: structure and governance

CIHR is governed by an independent Governing Council (GC) of 18 members, including the President, who are appointed by the Governor-General of Canada on advice from the Federal Cabinet. The President, who also acts as CEO of the organisation, chairs the GC.

GC is responsible for setting the overall strategic directions for CIHR and approving its budget. Members of GC include distinguished health researchers as well as a broad range of Canadians with an interest in health research, such as health system managers, health institution managers, senior administrators from academia, representatives of industry, governance and ethics experts and health policy-makers. The Deputy Minister of

the Department of Health (a civil servant) is an *ex-officio* non-voting member. GC usually meets three times a year, plus an annual strategic retreat.

A major role of GC is to appoint, on the President's recommendation, Scientific Directors (SDs). SDs are recognised leaders of their cognate research community, who normally devote 50% of their time to leading the Institute and 50% of their time to research, though many devote a greater proportion of their time to Institute responsibilities.

Each Institute has an approximately 15-member volunteer Institute Advisory Board (IAB) primarily composed of researchers, but including some members from the public, private and non-profit sectors, including health practitioners and healthcare system decision and policy-makers. The IABs help the SD draft the Institutes' own strategic plans, consistent with the over-arching CIHR plan, set and evaluate the Institutes' research priorities and allocate their research budgets accordingly.

The Institutes also add value to CIHR by providing specialist scientific acumen and the viewpoints of their research communities and relevant stakeholders in health research. Collectively, they form CIHR's Scientific Council, which is the highest-level decision-making forum for science strategy and management. Scientific Council provides scientific leadership and advice to GC on health research and KT priorities and strategies, in accordance with the overall directions determined by GC.

CIHR: budget and expenditures

CIHR receives its budget from funds voted annually by Parliament. The money must be spent on grants and awards by the end of the fiscal year
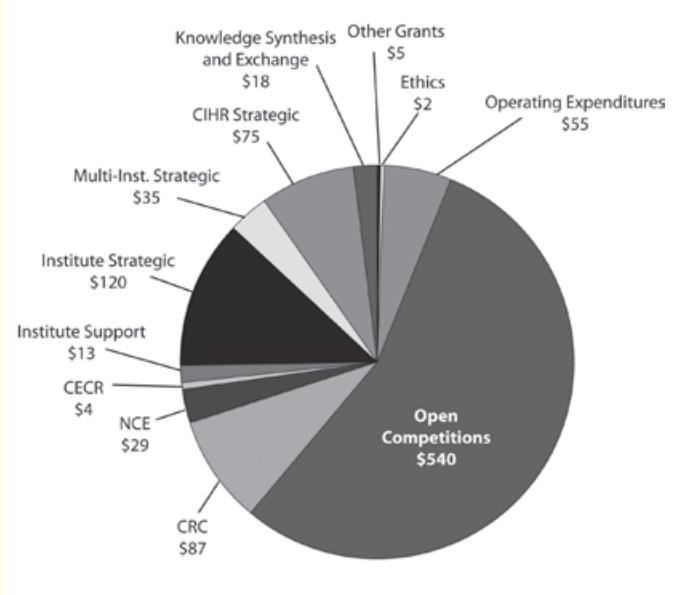
and CIHR cannot incur a deficit. There are three budget components: (i) operational budget, covering administrative costs and salaries of CIHR employees; (ii) the 'base' budget, whose allocation is under the control of GC; and (iii) funding earmarked by the Federal Government for specific programmes such as for HIV-AIDS research, radioisotope imaging and smaller mandated programmes. This also includes CIHR's share of tri-agency programmes such as the NCE, the CECR, the CRC, and the Banting and Vanier studentships programmes.

CIHR's overall budget has increased more than threefold since its inception and amounted to C$984 million in 2009-2010 (Figure 3.b.4). By comparison with the budget increases over the decade for agencies in other leading health research nations, CIHR has done well (Figure 3.b.5).
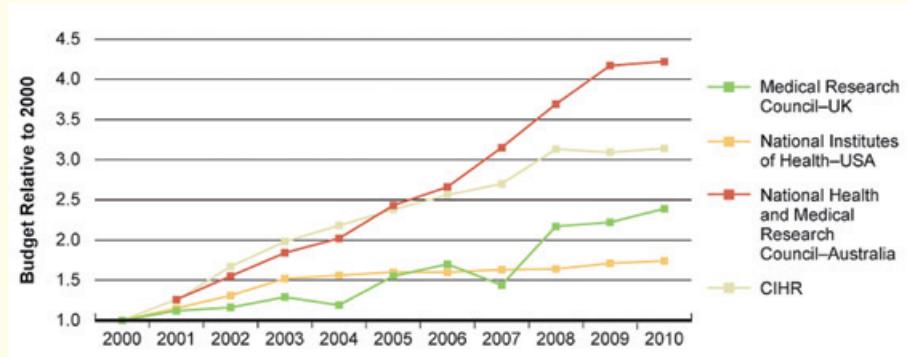
Open competition accounts for the largest share of CIHR expenditure. Included in this category are training and salary awards and open operating grants.

The open operating grants programme represented a C$403 million investment in 2009-2010, supporting 3,791 grants. These grants are awarded for periods of three to five years and their current median value is C$107,000 *per annum*. Although these grants may appear small in comparison with NIH grants, they exclude investigator salaries and institutional overhead. A separate tri-agency Indirect Costs Grant programme provides C$325 million a year in overhead to research institutions, based on the grants they receive from the tri-agencies, using a sliding scale that ranges from 80% to 20% of direct costs, with smaller institutions receiving the higher rates.

Approximately C$275 million of CIHR's budget was invested in strategic initiatives in 2009-2010. These strategic initiatives are implemented through open requests for applications and all applications are peer-reviewed. The topics are selected in conformity with individual Institutes' and overall CIHR's strategic plans.

As seen in Figure 3.b.4, Institutes' investments account for the bulk of strategic initiatives. Thus, even though each Institute has a relatively small research budget (currently C$8.5 million per year; total: C$110.5 million), the strategic use of these research budgets, individually, or in collaboration with a variety of external public or private partners, other Institutes and corporate portfolios have allowed them to invest significantly in neglected or emerging areas of health research (Figure 3.b.4). These investments, in turn, have contributed to generating new knowledge, building research capacity, and developing competence, so that investigators working in targeted areas can go on to secure continuing support from CIHR's open funding competitions.

CIHR-supported researchers (including trainees with studentships or fellowships) have increased from 5,370 in 2000-2001 to 13,695 in 2009-2010. Support for themes 3 and 4 (Health Services and Policy Research and Population and Public Health) has particularly increased. For example, the number of students with CIHR awards working in these two theme areas increased from 56 in 2000-2001, or 6.5% of the total, to 485 in 2009-2010, or 25% of the total. In 2009-2010, CIHR supported health researchers and trainees at 332 research institutions in every province of Canada.

Figure 3.b.5.
Increase in budget since 2000 (=1) for National Health Research Funding Agencies. (Source: CIHR).

Several Institutes have elected to fund or partially fund out of their dedicated budget additional operating grants that are close to the pay line through the mechanism of Priority Announcements (PAs). These are published well in advance of the competition deadline and describe areas of enquiry, or types of grants, which an Institute wishes to encourage. In 2009-2010, a total of 262 grants were funded through various PAs, in addition to the 772 new grants awarded through the open operating grants competition.

CIHR's positioning in the Canadian health research landscape

CIHR's success depends on its partnerships with other participants in Canadian health research. First and foremost are the universities, hospitals, and research institutes where health research is performed. CIHR maintains close relations with the Association of Canadian Academic Healthcare Organizations (ACAHO), the national organisation of teaching hospitals, academic regional health authorities, and their research institutes.

Second are health research funding agencies in most provinces, the largest being in Québec (Fonds de la recherche en santé du Québec, FRSQ, with a budget of ~$100 million in 2008-2009), Alberta (Alberta Innovates – Health Solutions), and British Columbia (Michael Smith Foundation for Health Research). Ontario has no comprehensive health research funding agency, but through its Ministry of Research and Innovation supports a number of organisations and programmes. In 2003, the provincial agencies formed the National Alliance of Provincial Health Research Organizations (NAPHRO) as a forum for discussion of common issues.

The 27 largest health research charities are members of the Health Charities Coalition of Canada, and CIHR, through its Institutes, has partnered with most of its members. There are significant mutual advantages to such partnering, includ-

ing: pooling resources for joint research priorities; reducing duplication; increasing opportunities for KT; showing CIHR and health researchers how to be responsive to citizen health concerns; engaging those affected by health issues in developing the research agenda; and assisting charities with their fundraising for research. CIHR, the members of NAPHRO, and the Health Charities Coalition meet twice annually at the Forum of health research funders to ensure coherence in the Canadian health research funding landscape.

CIHR's KT mandate includes commercialisation. Strong and ethical relations with the private sector are essential, and CIHR has regular discussions with BIOTECanada, representing the biotechnology industry, and Rx&D, the umbrella organisation for the research-based pharmaceutical industry. The relationship with Rx&D is formalised in a joint funding agreement through which, since 2000, the two organisations have jointly invested about C$360 million in research conducted in universities and hospitals.

A key evolution has been the rise of the academic health sciences centres and associated hospital-based research institutes. Although each is affiliated with a university, these institutions are often independently-governed with respect to research organisation, structure and priorities. The ACAHO noted that in 2006, member institutions received almost 80% of the public funding for health research.

There has also been a shift of CIHR-funded research into community-based organisations that exist entirely outside the academic sphere, including those that serve aboriginal peoples and those that provide care and education services to defined patient groups, in particular to HIV-AIDS community organisations. Further investment in aboriginal peoples' health and a greater emphasis on primary healthcare research will accelerate this trend.

4.
How to strengthen biomedical research in Europe
● ● ●

a. Strengths and opportunities for biomedical research in Europe

What follows is a SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis of European biomedical research in light of the present situation described in previous sections both within the European context and globally.

Strengths

One of the strengths of biomedical research in Europe, as shown in the SWOT analysis in Table 4, is its ability to foster an innovative environment. Europe has a well-established reputation for its excellence in basic research, and a strong and growing reputation in clinical research. Individual European investigators are highly motivated and recognised globally for their excellence. European students have access to a high-quality higher education system, and there are opportunities for mobility of researchers. Europe also has strong institutions and networks.

Europe's biomedical research system has become much more efficient in recent years and Europe produces more scientific publications than the US, with the quality of papers steadily improving.

Europe has had historically a large pharmaceutical industry but it now offers a wider range in health industry and services with important players in various fields such as medical devices and diagnostics, IT solutions or insurance.

Europe has a well-organised healthcare system that provides clinical research with an incomparable access to patients for clinical studies. Paired with excellent university hospitals delivering a high level of healthcare and full coverage of patient protection and access to innovation through our

social security system, this offers Europe a leading advantage.

Finally, Europe has a strong capacity to face complex challenges, both at the scientific and organisational levels, as demonstrated by the successful examples of CERN, EMBO and Arianespace or Airbus projects.

Weaknesses

One of the weaknesses in Europe is that people are still not placed at the very centre of the research on their health. Patients as well as citizens as a whole could and should become active allies of biomedical research. Society needs to be provided with good information on ongoing research and efforts should be made to make it easier for citizens to become involved in biomedical research, for example through patient organisations.

Another intrinsic weakness is Europe's heterogeneity which can hinder biomedical research. First, European regulations such as the Clinical Trials Directive, can drastically and negatively impact biomedical research, despite the best of intentions. Secondly, there is too little common European-wide strategic planning despite laudable but not yet fruitful efforts such as the Joint Programming or the EC Framework Programme. Thirdly, there is a lack of operational harmonisation on key medical research topics such as approvals, evaluation, assessment and European education and training. Key biomedical research bodies such as National Competent Authorities and Ethical Review Boards, for example, would also benefit from enhanced operational harmonisation. Finally, common European criteria and methods for the evaluation of research input, output and outcomes would also benefit research as a whole.

While researchers are highly motivated, career opportunities can be lacking because of the absence of structured career tracks. Poor working conditions such as low salaries and unattractive pension schemes are deterring people from research or from performing their research in Europe. There is a lack of opportunities for mobility for researchers' projects and more importantly for their funding. Finally, there is a need in Europe for a commitment and mutual recognition of MD/PhD programmes to offer better research possibilities within the medical curriculum.

Infrastructure and funding are also affected by low investment. As made clear by this white paper,

Europe's public funding for biomedical research is around half of that in the US. It is additionally fragmented, a situation that our biggest competitor does not have to face. The relatively low investment also drastically impacts upon the private sector, which still has too few growing SMEs in the pharmaceutical and biotechnology fields.

Opportunities

These weaknesses can all be overcome. Indeed, they could all become unique opportunities for European science. Biomedical research occupies a special place because of its crucial role in the health and well-

Strengths	Weaknesses
• A more innovative European environment fostered by biomedical research: European talent is *"excellence in science"* • A more efficient European biomedical research system • Strong and large European health industry including services • A more favourable European healthcare system • Europe's capacity to face high-level challenges and solve complexity	• Human beings are not at the centre of health research • European heterogeneity (differences among European countries) • Motivation and incentives • Infrastructures – *fragmented capacities* • Funding – *poor innovation investments*
Opportunities	**Threats**
• Crucial role of medical research on humankind's health and wellbeing • New health challenges are the most complex questions of the century • Increased engagement of scientific community and research institutions to address societal grand challenges • Change in the economic model of health industry • European diversity – *take advantage of regional differences* • Existing international collaborations in important disease areas	• Ever-increasing scientific progress of emerging countries • No key role of Europe in the global biomedical research landscape • Loss of attractiveness, investment capacity, leadership because of investment in US and rapidly emerging scientific countries (but partnership opportunities) • Lack of transparency in the setting of European research agenda • Poor political engagement on biomedical research and its possible impacts • No strong single European voice for the scientific community • Further increase in European heterogeneity • Increased healthcare costs with lack of proportionate increase of funding for biomedical research

Table 4.
SWOT analysis of European biomedical research

being of humankind. Research communities and organisations need to educate European citizens and governments about the high return on investment offered by biomedical research.

The new health-related challenges that Europe and the world face today are exceptional issues that affect society at large and could be the most complex questions to be addressed in the 21st century. New paradigm shifts such as personalised medicine or innovative solutions to research issues such as the translational research gap will be needed to rapidly bring research results to patients. The increased engagement of the scientific community and of research organisations in addressing these grand challenges could also lead to increased visibility but more importantly to improved reactivity and efficiency.

The health industry has seen a radical change of its economic model in the past decades that will increasingly call upon long-term public-private partnerships. We are starting to see the first large scale initiatives with associations between public institutions, academia and industry. These partnerships are now perceived as crucial opportunities to create synergies, reduce the costs and produce high value output within the new R&D model.

Outside Europe opportunities lie through existing international collaborations in important disease areas such as AIDS, the World Health Organization (WHO) leading infectious diseases programmes[60] or the International Cancer Genome Consortium[61].

Threats

Some of the threats to European biomedical research lie outside Europe. Emerging countries like China and India are currently investing in the development of their research capacities. This puts them in the position to elaborate science policy at national and global levels like the US. Europe could end up with no key role in the global biomedical research landscape because of its low involvement in the global biomedical research agenda setting and infrastructure. European research might produce good science but to no useful effect. Lack of investment could lead to a loss of attractiveness and of leadership which would remain with the US and shift towards emerging countries. If dealt with in a timely and efficient manner, Europe could transform these threats into opportunities where biomedical research partnerships could be forged with these countries and where Europe could be a

key player in setting the research agenda.

But Europe needs first to address certain internal threats, such as the current lack of transparency in setting its own research agenda. A situation most probably linked to the poor political engagement on biomedical research and its possible impacts that has led to mostly reacting to crises. The responsibility not only lies within the hands of politicians, but also the biomedical scientific community, which has not spoken with one strong single voice in Europe.

Another danger for Europe's biomedical field would be a further increase in heterogeneity. This could happen through the appearance of more legal discrepancies in national interpretations of EU regulations; through different levels of commitment of EU Member States; or because of the current heterogeneous expertise and experience in clinical research between European regions.

Finally, an external threat could come from increasing costs in healthcare as this increase could take place without a proportionate increase of funding for biomedical research. Lower research funding could of course be linked with the increasing costs of drugs but it could also come from lower hospital equipment budgets leading to lower innovation in medical devices and diagnostics. An increase in short-term planning in hospitals could lead to a lack of long-term planning in research.

Interestingly, all the threats identified above point to a realistic risk of a Europe that has no future capacity to produce a coherent science policy. Nations acting individually will never be able to compete with the US or the scientifically emerging countries. The key message from this white paper is that only through the development of a common European science policy will we be able to influence global healthcare to improve human welfare and provide a better future for Europe, its citizens and its industry. It is against this background that a series of recommendations were identified to conclude this white paper's analysis of the state of biomedical research in Europe.

60. www.who.int/topics/infectious_diseases/en/
61. ICGC: www.icgc.org

b. Recommendations

1. Citizens and patients should be closely engaged with biomedical research
2. The results of biomedical research should be rapidly and efficiently brought to the patient
3. Biomedical research should be conducted with high quality in an open, honest and transparent way
4. European biomedical research should be conducted within a global context
5. Investment should be increased to create the right world-class biomedical research

1. Citizens and patients should be closely engaged with biomedical research

Research is for the whole of society and for this reason patients and the wider public should be closely engaged with the research process.

Ways need to be developed to better engage with citizens about biomedical research, including on issues of prioritisations, funding, planning, conduct and reporting. The biomedical research community should develop participatory partnerships with wider society and seek to improve interactions between scientists, the healthcare system (including health insurance) professionals, policy-makers, decision-makers and the public. Patients and the public should be actively involved with the research process, through patient organisations for example, and training programmes should be developed to improve mutual understanding between the public and scientists. Patient associations should be encouraged to participate in European research and training projects and activities, and partnerships between researchers and charities should be facilitated to generate research programmes that respond to mutual aims and aspirations.

2. The results of biomedical research should be rapidly and efficiently brought to the patient

It is a moral and ethical duty to bring new knowledge generated by biomedical research as rapidly as possible to patients in the form of new drugs, procedures and technologies.

The gap between biomedical research and medical practice should be closed[62]. When evaluating new drugs and other technologies, there needs to be evidence and transparency of their comparative effectiveness and added value before they are given approval. Rigorous reporting of all clinical studies is crucial. Patient-oriented, translational research should be promoted to transform more rapidly new knowledge produced by biomedical research into medical practice and health products: this will require appropriate support for translational research infrastructure. Collaboration, coordination and funding of systematic reviews of existing evidence, comparative effectiveness research, health technology assessments and clinical practice guidelines should be strengthened and methodologically sound. High-quality clinical research inspired by gaps and uncertainties identified in systematic reviews that answers the needs of patients, health professionals and society should be supported and facilitated.

3. Biomedical research should be conducted with high quality in an open, honest and transparent way

Biomedical research is for the good of society, and so the results of research paid for from the public purse should be made open, accessible and widely communicated.

Researchers, public and private research organisations, universities and funding organisations must observe and promote the principles of integrity in biomedical research as described in the ESF-ALL European Academies (ALLEA) 'European Code of Conduct for Research Integrity'[63]. A common European policy should be developed to ensure open access to publicly funded biomedical research. Coherence, common principles and effectiveness in the peer review process (taking into account the recently published ESF 'European Peer Review Guide'[64]) should be promoted: common guidelines for evaluation of researchers are necessary to facilitate the mobility of scientists; common principles and criteria for evaluation of projects are a pre-

62. ESF Forward Look report 'Implementation of medical research in clinical practice', 2011, ISBN 978-2-918428-36-7.

63. ESF-ALLEA (ALL European Academies; European Federation of National Academies of Sciences and Humanities) 'The European Code of Conduct for Research Integrity', 2011, ISBN: 978-2-918428-37-4.

64. ESF Member Organisation Forum 'European Peer Review Guide – Integrating Policies and Practices into Coherent Procedures', 2011, ISBN: 978-2-918428-34-3.

requisite for the implementation of transnational research programmes. The EMRC statement on equal opportunities for performing research should be endorsed: "The EMRC advocates equal opportunities in all aspects of medical research – regardless of age, gender, origin, profession, race, religion or sexual orientation".

4. European biomedical research should be conducted within a global context

Biomedical research is a global pursuit providing opportunities for healthy competition as well as for fruitful collaborations.
Common strategic planning between European countries should be promoted in the field of biomedical research to identify priorities and allocate resources to strengthen biomedical research. The mobility of themes across Europe should be encouraged and facilitated, and biomedical research inventories and mapping, priority consideration and decisions should no longer be based only on national context but take into account complementary skills in Europe. Research institutions should be encouraged to establish, plan and manage shared strategies. The development of the European biotechnology and pharmaceutical industries including increased public-private partnerships should be stimulated. There should be enhanced collaboration and sharing of research and results via EMRC, its Member Organisations, EUROHORCs, EC, ERC, COST, scientific societies, medical journals, universities and academic medical centres. Europe should actively participate in international collaborations on major medical challenges (HIV/AIDS, demographic changes, etc.) through funding and excellent research. Europe should aim to play a leading role in global health research policy-making and implementation, defining the research agenda not only for Europe but globally.

5. Investment should be increased to create the right world-class biomedical research

Excellence requires an increased level of investment to provide the sort of environment in which the finest minds will flourish and bright young scientists will feel valued.
To remain competitive in the global context and to answer the future health needs of European citizens, public investment in life and health sciences in Europe needs to be at a minimum level of 0.25% of GDP with the necessity of a sustained steady growth above inflation. European and national funding profiles should be well-aligned with commonly established biomedical research priorities. Major pan-European infrastructure projects should be completed including construction of the European research infrastructures identified in ESFRI. Cross-border and innovative biomedical research should be promoted through transnational collaborative funding schemes on the model of a European Grant Union for biomedical research. A concerted effort should be made to attract the best brains to Europe and common training and career opportunities should be offered, together with opportunities for enhanced and easier mobility between Member States.

Overall the goals set in the first white paper in 2007 for strong basic, clinical and translational research are still highly relevant[65]. The tools offered four years ago to reach these goals seem today as pertinent for "best practice"[66].

65. ESF-EMRC White Paper 'Present Status and Future Strategy for Medical Research in Europe', 2007.
66. See Tool Box from EMRC White Paper (2007) in Annex 3.

5.
Conclusion
● ● ●

Biomedical research is of great benefit for patients, citizens and society in Europe and in the rest of the world. Science is global and the global society benefits from high-quality research results no matter where they are produced.

The revenue of investments in medical research are 40% *pro anno* perpetually, so the area is important both for patients and for societal economy.

The European Medical Research Councils have produced this White Paper II to assess the present status of biomedical research in Europe in a global context. Our main conclusions are that European biomedical research is doing well compared to the relatively small funding available. With more funding we could do even better.

We have previously observed a gap between the higher number of citations from the US publications compared to the European publications, but this gap is narrowing and the European quality is increasing.

Outside Europe and the US biomedical research is growing. This is a benefit for all in the global world and instead of looking at each other as competitors the future calls for collaboration in Europe in ERA and in the global setting.

In Europe there is a huge difference between the research productivity among countries – some are among the highest producers in the world and others are lagging behind. A strong effort should be made to repair this difference and ensure the same high quality and productivity everywhere in Europe - through education, funding and best practice. Education along with collaboration is crucial across Europe.

The white paper recommends that citizens and patients should be closely involved with biomedical research, and that the results of biomedical research should be rapidly and efficiently brought to patient and healthcare. Biomedical research should be conducted with high quality in an open, honest and transparent way and investments should be at an appropriate level to create the right world-class biomedical research here in Europe.

Annexes

Annex 1. Scientific output: how much and what is published in the world in biomedical research?

Data sources

Apart from the bibliometric study comparing EU and US performed by Dr Glänzel and Dr Thijs (KU Leuven, Belgium), data for this chapter were extracted from:

- US National Science Foundation (NSF) *Science and Engineering Indicators 2010* report[67] (January 2010) and the appendix tables available from www.nsf.gov/statistics/seind10/appendix.htm (Tables 5-23 to 5-38).
- Observatoire des Sciences et des Techniques (OST) *Indicateurs de Sciences et de Technologies* 2010 report[68] (December 2010).
- UK Evidence Ltd *International comparative performance of the UK research base* report[69] (September 2009).

Useful definitions

1. US National Science Foundation (NSF)
Science and Engineering Indicators 2010 report:

The **list of fields and subfields** can be found in Table 5-24 "Fields and subfields of S&E publications data" available from www.nsf.gov/statistics/seind10/appendix.htm. For our analysis, the NSF field of 'medical sciences' was combined with the fields 'other life sciences' (including nursing and public health) and psychology. The NSF field of 'biological sciences' was used as such.

2. Observatoire des Sciences et des Techniques (OST)
Indicateurs de Sciences et de Technologies 2010 **report:**

- **Scientific specialisation index:** a specialisation index superior to 1 (= world average specialisation index) indicates that the country/region/economy is specialised in the discipline or sub-discipline studied. A specialisation index inferior to 1 (= world average specialisation index) indicates that the country/region/economy is under-specialised in the discipline or sub-discipline studied.
- The **impact index at 2 years (immediate impact)** measures the scientific impact of publications, reflecting their visibility. An impact index at 2 years superior to 1 (= world average impact index) indicates that the country/region/economy has a high impact in the discipline or sub-discipline studied. An impact index at 2 years inferior to 1 (= world average impact index) indicates that the country/region/economy has a low impact in the discipline or sub-discipline studied.

Bibliometric analysis performed by Wolfgang Glänzel and Bart Thijs (KU Leuven, Belgium)

Methodology

The results of this study are based on raw bibliographic data extracted from the 1996-2009 annual volumes of the Web of Science (WoS) of the Institute for Scientific Information (ISI, Thomson Scientific, Philadelphia, PA, US). The extracted data have been cleaned and then processed to bibliographic indicators. All publications of the document type *articles, letters, notes and reviews* indexed in the 1996 to 2009 annual

updates of the WoS have been taken into consideration. Citations received by these publications have been determined for the 3-year period beginning with the publication year. The last publication year that could be taken into account for the citation analysis was therefore 2007 (citation window: 2007-2009).

Publications were assigned to countries based on the corporate address given in the by-line of the publication. All countries indicated in the address field were thus taken into account. An integer counting scheme has been applied; each publication has been assigned as a full publication to all countries contributing to the publication.

The EU had 15 members until 2004. This is taken into account in the bibliometric data covering the period 1996-2003. In order to obtain consistent data, the EU with 25 members reflecting the situation between 1 May 2004 and 31 December 2006 was used for the period 2004-2009.

Subject classification of publications was based on the field assignment of journals (in which the publications in question appeared) according to the 12 major fields of science and 3 fields of social sciences and humanities developed in Leuven and Budapest (Glänzel and Schubert, 2003[70]).

Structure of the field as reflected by the WoS database

- **BIOSCIENCES (GENERAL, CELLULAR AND SUBCELLULAR BIOLOGY; GENETICS)**
  B0 multidisciplinary biology
  B1 biochemistry/biophysics/molecular biology
  B2 cell biology
  B3 genetics and developmental biology

- **BIOMEDICAL RESEARCH**
  R1 anatomy and pathology
  R2 biomaterials and bioengineering
  R3 experimental/laboratory medicine
  R4 pharmacology and toxicology
  R5 physiology

- **CLINICAL AND EXPERIMENTAL MEDICINE I (GENERAL AND INTERNAL MEDICINE)**
  I1 cardiovascular and respiratory medicine
  I2 endocrinology and metabolism
  I3 general and internal medicine
  I4 haematology and oncology
  I5 immunology

- **CLINICAL AND EXPERIMENTAL MEDICINE II (NON-INTERNAL MEDICINE SPECIALTIES)**
  M1 age and gender related medicine
  M2 dentistry
  M3 dermatology/urogenital system
  M4 ophthalmology/otolaryngology
  M5 paramedicine
  M6 psychiatry and neurology
  M7 radiology and nuclear medicine
  M8 rheumatology/orthopaedics
  M9 surgery

67. National Science Board. 2010. *Science and Engineering Indicators 2010*. Arlington, VA: National Science Foundation (NSB 10-01). January 2010.

68. Observatoire des Sciences et des Techniques. *Indicateurs de Sciences et de Technologies 2010*. December 2010.

69. UK Evidence Ltd report. *International comparative performance of the UK research base*. September 2009.

70. Glänzel W. and Schubert A. A new classification scheme of science fields and subfields designed for scientometric evaluation purposes. *Scientometrics*, 2003, 56:357–367.

Annex 1. Scientific output: how much and what is published in the world in biomedical research?

Glossary: measures and indicators

In order to shed light on the evolution, impact and competitiveness of European biomedical research, the following publication measures and citation-based indicators were used.

i) **Publication count**, that is, the number of publications published by the unit under study. For the European Union, duplicates caused by intra-European collaboration have been removed.

ii) **Share of publication output in the world total**.

iii) **Mean Observed Citation Rate (MOCR)**. MOCR is defined as the ratio of citation count to publication count. It reflects the factual citation impact of a country, region, institution, research group etc. A 3-year citation window has been applied.

iv) **Mean Expected Citation Rate (MECR)**. The expected citation rate of a single publication is defined as the average citation rate of all publications published in the same journal in the same year. Instead of the one-year citation window to publications of the two preceding years as used in the Journal Citation Report (JCR), a 3-year citation window to one source year is used, as explained above. For a set of publications assigned to a given country, region or institution in a given field or subfield, the indicator is the average of the individual expected citation rates over the whole set.

v) **Relative Citation Rate (RCR)**. RCR is defined as the ration of the citation Rate per Publication to the Expected Citation Rate per Publication, that is, RCR = MOCR/MECR. This indicator measures whether the publications of a country or institution attract more or less citations than expected on the basis of the impact measures, i.e., the average citation rates of the journals in which they appeared. Since the citation rates of the publications are gauged against the standards set by the specific journals, it is largely insensitive to the big differences between the citation practices of the different science fields and subfields. It should be stressed that in this study, a 3-year citation window to one source year is used for the calculation of both the enumerator and denominator of RCR. RCR = 0 corresponds to uncitedness, RCR < 1 means lower-than-average, RCR > 1 higher-than-average citation rate, RCR = 1 if the set of publications in question attracts just the number of citations expected on the basis of the average citation rate of the publishing journals. RCR has been introduced by Schubert *et al.* (1983), and largely been applied to comparative macro and meso studies since. It should be mentioned that a version of this relative measure, namely, CPP/JCSm is used at CWTS in Leiden (Moed *et al.*, 1995).

vi) **Normalised Mean Citation Rate (NMCR)**. NMCR is defined analogously to the RCR as the ratio of the Mean Observed Citation Rate to the weighted average of the mean citation rates of subfields. This indicator is a second expected citation rate; in contrast to the RCR, NMCR gauges citation rates of the publications against the standards set by the specific subfields. Its neutral value is 1 and NMCR >(<) 1 indicates higher(lower)-than-average citation rate than expected on the basis of the average citation rate of the subfield. NMCR has been introduced by Braun and Glänzel (1990) in the context of national publication strategy. A similar measure (CPP/FCSm) is used at CWTS (Moed *et al.*, 1995).

vii) **The ratio NMCR/RCR** reflects the average level of journals chosen for publication. In particular, NMCR/RCR>1 (>1) means that the journal impact of periodicals where the unit publishes is on average higher (lower) than the subject impact where the unit is active.

viii) **Share of author self-citations (%SCIT)** is used as an auxiliary indicator.

ix) **Share of highly cited publications in the world total**. The citation impact of each individual publication is compared with the seven-fold of the corresponding subject standard based on the 60 subfield classification scheme (Glänzel and Schubert, 2003). This threshold is derived from the method of characteristic score and scales (Glänzel, 2007). Indicators on highly cited publications defined on the bases of characteristic scores and scales can as such be considered subfield normalised, and can therefore be applied to larger domains as well.

List of potential biases

Bibliometric analysis is subject to **over- and under-estimation** before, at or shortly after the publication. Many examples can be cited where there was unjustified attention and appreciation, or the lack of it, but such exceptions should not disqualify the use of bibliometric analysis for most cases.

Reviews were taken into consideration in the bibliometric analysis although they generate a high level of citations.

All authors indicated in the by-line of the publication were taken into account. To have a better view of the publication impact, it could be useful to perform the analysis by taking into consideration only the first three authors and the last one.

Citations are assigned to **all countries** involved in the publication (based on the affiliation indicated in the by-line of the publication). Publications cannot thus be summed up across countries due to the large amount of collaboration between them (notably between EU and US) which usually results in more citations.

In the citation analysis, it should be taken into consideration that there is a high proportion of **self-citations** (around 18-26% for EU and the US in 1996-2007). However, this has considerably decreased over time as can be seen in the column '% SCIT' of Table A1 below: -3.3% for the US and even -6.7% in the EU. This makes the citation analysis even more accurate.

Other potential biases in the citation analysis include:
- conscious or unconscious preferential unscientific citations of specific publications
- US authors more frequently cite other US authors than authors outside the US[71]
- English language publications are favoured in citation databases[72]
- American scientists publish on average in journals with distinctly higher impact than their European colleagues (see column NMCR/RCR of Table A1)

However, all these biases were already potentially present in the bibliometric analysis performed for the White Paper I thus allowing a better comparison between the medical research output in 2007 and today.

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71. Glänzel W. and Schubert A. Domesticity and internationality in co-authorship, references and citations. *Scientometrics*, 2005, 65:323-342.

72. Winkmann G *et al.* Publication languages of impact factor journals and of medical bibliographic databank. *Deutschland Medizinische Forschungsrichte,* 2002,127:131-37.

Annex 1. Scientific output: how much and what is published in the world in biomedical research?
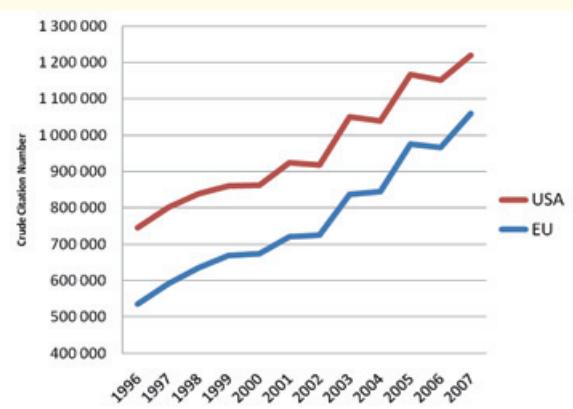

Figure A1.
Crude citation number: biomedical research output from US and EU15 or EU25 estimated from ISI citations to publications from 1996-2007.

Additional data on comparison of EU and US

Citations of scientific publications in other publications are used as a good marker for their visibility and scientific impact. The initial way to look into citations is to look at the **citation counts** (Figure A1). These counts for US publications in the field of biomedical research largely exceeded the citation counts for EU15 or EU25 publications during the time period 1996-2007, with a 64% growth witnessed in the US and 98% growth in the EU.

Table A1 below shows that the **mean observed citation rate** (MOCR, the citation count divided by the publication count) was always substantially higher for US than EU15 or EU25 publications with a steady difference of about 2 citations per publication. This relative difference remains important even when corrected for the journal standard citation rate (**MECR: Mean Expected Citation Rate**) and became even higher when corrected for the subfield standard citation rate (**NMCR: Normalised Mean Citation Rate**).

However, the increase from 1996 to 2007 in the journal-based relative citation rate (**MECR**) is higher for the EU (+50%) than for the US (+32%). The progression in the sub-field-based citation rate (**NMCR**) is also in favour of the EU as it increased by +8.1% vs. a decrease of 3.6% for the US.

The ratio of the two indicators NMCR/RCR (RCR: Relative Citation Rate, see Table A1) confirms that American scientists publish on average in journals with distinctly higher impact than their European colleagues. This difference remained stable throughout the observation period, although again in favour of the EU in terms of progression between 1996 and 2007 (+8.5% for the EU vs. −4.7% for the US).

The **impact of these publications after two years** as expressed by the immediate impact index[73] was superior by 20 to 40% in the US to the mean world impact index. Despite its

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73. The **impact index at 2 years (immediate impact)** measures the scientific impact of publications, reflecting their visibility. An impact index at 2 years superior to 1 (= world average impact index) indicates that the country/region/economy has a high impact in the discipline or sub-discipline studied. An impact index at 2 years inferior to 1 (= world average impact index) indicates that the country/region/economy has a low impact in the discipline or sub-discipline studied.

Year	US/EU	Papers	%Papers	Cites	%Cites	MOCR	MECR	RCR	NMCR	NMCR/RCR	%SCIT
1996	USA	117 764	37.7	745 519	53.2	6.33	5.87	1.08	1.38	1.28	21.3
	EU15	119 674	38.3	535 322	38.2	4.47	4.27	1.05	0.99	0.94	26.7
1997	USA	119 343	37.1	801 213	52.2	6.71	6.19	1.08	1.38	1.27	20.3
	EU15	124 208	38.6	591 509	38.6	4.76	4.58	1.04	0.99	0.95	25.3
1998	USA	122 660	36.8	838 425	51.9	6.84	6.33	1.08	1.38	1.27	19.8
	EU15	131 541	39.5	635 559	39.4	4.83	4.64	1.04	0.99	0.95	24.3
1999	USA	123 072	36.5	860 480	51.0	6.99	6.46	1.08	1.37	1.26	19.5
	EU15	131 980	39.2	668 585	39.6	5.07	4.89	1.04	1.00	0.97	23.3
2000	USA	122 375	36.4	861 225	50.9	7.04	6.48	1.09	1.36	1.25	19.1
	EU15	131 196	39.1	673 718	39.8	5.14	4.96	1.04	1.02	0.98	22.5
2001	USA	124 944	36.7	924 603	51.0	7.40	6.78	1.09	1.36	1.25	19.0
	EU15	133 182	39.1	720 266	39.8	5.41	5.21	1.04	1.01	0.98	22.1
2002	USA	121 892	36.2	918 449	50.6	7.53	6.88	1.10	1.37	1.25	18.3
	EU15	129 599	38.5	724 462	39.9	5.59	5.38	1.04	1.03	0.99	21.3
2003	USA	131 393	36.2	1 049 874	50.1	7.99	7.30	1.09	1.35	1.24	17.9
	EU15	138 913	38.3	837 218	39.9	6.03	5.79	1.04	1.03	0.99	20.8
2004	USA	128 178	36.9	1 039 854	50.0	8.11	7.42	1.09	1.33	1.22	18.0
	EU25	136 632	39.4	844 554	40.6	6.18	5.97	1.04	1.02	0.99	21.0
2005	USA	144 287	36.3	1 165 997	49.3	8.08	7.37	1.10	1.34	1.22	18.0
	EU25	155 593	39.1	975 318	41.2	6.27	5.98	1.05	1.05	1.00	21.0
2006	USA	142 280	36.4	1 151 110	48.7	8.09	7.42	1.09	1.32	1.21	18.0
	EU25	150 818	38.6	966 608	40.9	6.41	6.13	1.05	1.05	1.01	20.0
2007	USA	144 567	35.7	1 219 821	48.0	8.44	7.73	1.09	1.33	1.22	18.0
	EU25	156 726	38.7	1 058 684	41.7	6.75	6.41	1.05	1.07	1.02	20.0
2008	USA	161 222	33.8	:	:	:	:	:	:	:	:
	EU25	181 981	38.1	:	:	:	:	:	:	:	:
2009	USA	158 874	33.1	:	:	:	:	:	:	:	:
	EU25	180 913	37.7	:	:	:	:	:	:	:	:

Table A1.
Publication and citation indicators on biomedical research in the US and EU15 (1996-2003) and EU25 (2004-2009).
[Data sourced from Thomson Reuters Web of Knowledge (formerly referred to as ISI Web of Science)].
Note: The figures due to EU-US collaboration are not additive and may therefore not be summed up to the total.

Annex 1. Scientific output: how much and what is published in the world in biomedical research?

dominance the US impact index decreased between 2003 and 2008 contrary to the EU's impact index that increased during the same period.

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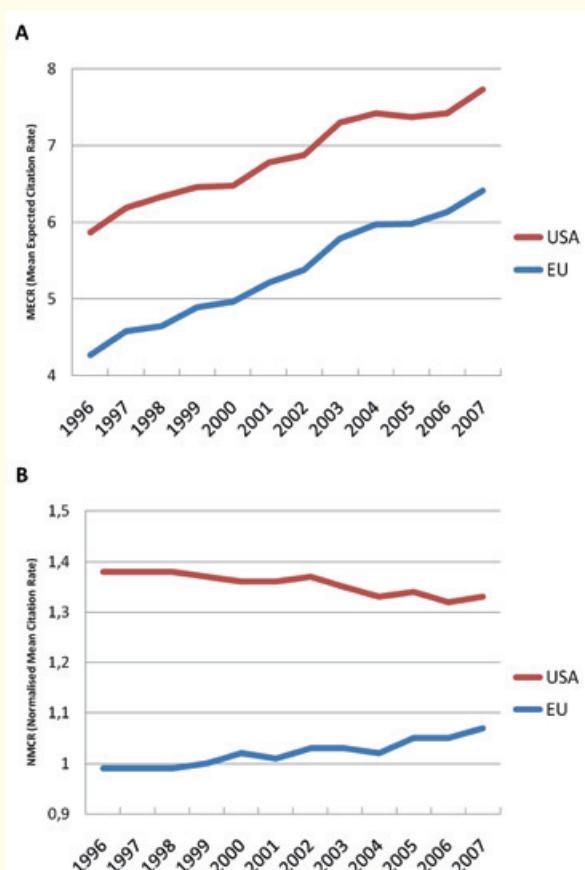
Figure A2.
Biomedical research output from US and EU15 or EU25 countries estimated from citations from 1996-2007 publications. **A.** Mean Expected Citation Rate (MECR) = average citations rate of all publications [in the same journal in the same year] during the subsequent 3 years. **B.** Normalised Mean Citation Rate (NMCR) = mean observed citation rate (MOCR) / weighted average of citation rate for the subfield. Data sourced from Thomson Reuters Web of Knowledge (formerly referred to as ISI Web of Science).
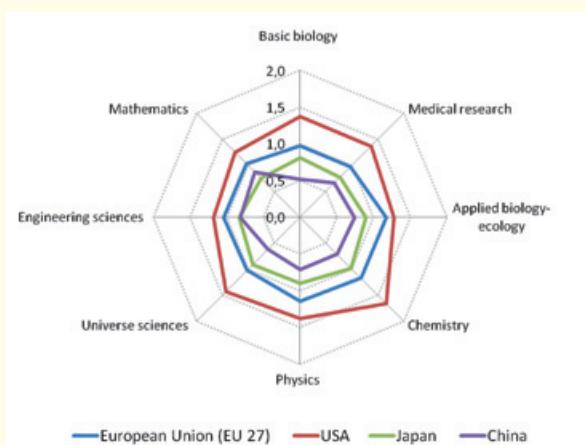
Figure A3.
Impact index at 2 years (immediate impact) per discipline: US, EU27, Japan and China (2008)
(Source: OST)

Annex 2. Funding for biomedical research in Europe and globally

Appendix A: Non-OECD countries' expenditures on health R&D

The Global Forum for Health Research (GFHR, 2009) has studied health R&D in a select number of non-OECD countries, including Argentina, Brazil, Bolivia, Chile, China, Cuba, India, Mexico, Paraguay, Russia, South Africa, Uruguay and Venezuela. Together, these 13 countries spent approximately 6.9 US$ billion or 4.3% of the world's total spending on health R&D in the business, government, higher education and private non-profit sectors in 2005.

Except for Brazil, where the official exchange rate is applied, all conversions of national currency values into US$ use country-specific PPPs. The individual countries spent approximately as follows (with the percentage share of each country's total R&D spending and the total R&D spending in parentheses): Argentina 315.2 US$ million (13.6% of 2,318 US$ million) in 2006; Brazil 616.9 US$ million (5.3% of 11.6 US$ billion) in 2005; Bolivia 1.6 US$ million (4.7% of 33.9 US$ million) in 2006; Chile 113.3 US$ million (7.0% of 1.6 US$ billion) in 2004; China 3.6 US$ billion (2.0% of 181.8 US$ billion) in 2006; Cuba 164.3 US$ million (37.0% of 449.8 US$ million) in 2008; India 1.2 US$ billion (4.5% of 26.8 US$ billion) in 2004; Mexico 566.7 US$ million (8.0% of 7.1 US$ billion) in 2006; Paraguay 0.1 US$ million (0.5% of 25.8 US$ million) in 2005; Russia 604.4 US$ million (2.1% of 28.7 US$ billion) in 2006; South Africa 712.7 US$ million (14.8% of 4.8 US$ billion) in 2005; Uruguay 1.6 US$ million (1.0% of 158.8 US$ million) in 2006; Venezuela 233.3 US$ million (22.5% of 1.04 US$ billion) in 2006.

These figures are based on the percentage shares of health R&D in total R&D and of total R&D in GDP, provided in GFHR (2009). The GDP figures measured in current PPPs (for all countries except Cuba) are from the World Development Indicators by the World Bank. Cuba's GDP measured in current PPP is from the CIA World Factbook. For Argentina, the PPP is based on the annual average exchange rate from the Argentine Central Bank and the index of PPP published by the World Bank. The annual average exchange rate used in figures for Brazil is from the Federal Bank of Brazil.

Appendix B: Methods

In spite of long-standing efforts by the OECD to impose the same standards for R&D surveys in all of its member countries, it should be noted that the international comparability of health R&D data may be compromised by the fact that some countries have developed rather idiosyncratic organisational structures for their medical research, which can make the task of tracing the flows of funds difficult. For this reason, OECD data tend to underestimate the flow of funds into health R&D in the US non-market sectors substantially. For example, large parts of what according to OECD definitions should be considered medical or human health-related R&D are classed as belonging to biology or other basic life sciences by major performers of this type of R&D in the US, such as national government agencies and universities. OECD data for Germany exhibit a similar problem: a large share of Germany's health-related R&D takes place outside the university system, in research institutes dedicated to basic sciences, such as the Max Planck institutes, the Helmholtz centres and the Leibniz organisation. These institutions often conduct research with the objective of developing applications to human health, but tend to classify their research in terms of basic scientific categories,

such as molecular biology and genomics, under the broad umbrella of biology and the life sciences. Data collection in France is also particularly difficult as the French non-market sector for medical research comprises a wide variety of regional and national institutes, such as the Institut national de la santé et de la recherche médicale, as well as relatively large private non-profit associations and endowed foundations, such as the Pasteur Institute. Funding flows into health R&D are hence subject to an unusual degree of heterogeneity in the case of France, too.

A more general caveat relates to the adopted method of converting national expenditures into a common currency. Instead of monetary exchange rates, purchasing power parities (PPPs) for countries' GDP, as provided by the OECD, are used. In principle, it would be desirable to apply more sophisticated PPPs that are specific to the basket of goods and services used as inputs in health R&D, but such sector-specific PPPs are not available. Against this background, the GFHR (2008) has rightly drawn attention to the need to develop specific PPPs for health R&D in the future.

1. PPPs

Economists and the OECD use purchasing power parities (PPPs) to determine how many units of a reference currency a given quantity of goods and services costs in different countries and to obtain a meaningful indicator for cross-country comparisons of income or expenditure volumes that aptly reflects the differences in the purchasing power of households, investors or governments. To do so, the OECD compares price levels for a basket of comparable goods and services that are selected to be representative of consumption or expenditure patterns in the various countries. Monetary exchange rates cannot be used because in addition to price differences, they are usually influenced by volumes of financial transactions between currencies and expectations in foreign exchange markets, among other factors. Given that price behaviour is different in different industries and sectors, the OECD publishes specific PPPs for a number of different types of goods and services, but specific PPPs for the inputs in health-related R&D are not available. We therefore use PPPs for GDP, as they can be considered the most generic PPPs. For the aggregates of various groups of European countries, we use annual PPPs to convert national expenditures into euros and then convert this aggregate into US$, the currency used as the standard unit for international comparisons by the OECD.

2. The Frascati Manual

The so-called Frascati Manual lays down international standards for the classification of research and development (R&D) activities, including the distinction between funder- and performer-reported data on countries' health-related R&D. Today's R&D statistics are the result of the systematic development of surveys based on the Frascati Manual that are part of the statistical system of OECD member countries. The manual's internationally accepted definitions have helped economists to identify "best practices" in science and technology policies. As a result of initiatives by the OECD, UNESCO, the European Union and various regional organisations, the Frascati Manual has become a standard for R&D surveys worldwide.

Annex 2. Funding for biomedical research in Europe and globally

3. NABS

The Nomenclature for the Analysis and Comparison of Scientific Programmes and Budgets (NABS) was developed in 1969 and first revised in 1975. It is linked to the Frascati Manual (OECD 2002) and mainly used for government budget appropriations or outlays on R&D (GBAORD) and R&D statistics at the national and international level, breaking down each country's annual spending according to the socio-economic objectives pursued, as defined and classified in NABS. The body responsible for maintaining and developing the NABS classification is Eurostat. With the revision of NABS 1992 into the 2007 version, Eurostat has further improved and updated many chapters according to user requirements, balanced with data availability at the country level, and brought them more closely in line with the Revised Field of Science and Technology Classification (FOS), the Classification of the Functions of Government (COFOG), Essential Public Health Functions (EPHF) and the Statistical Classification of Economic Activities in the European Community (NACE), while maintaining continuity with NABS 1992 as far as possible. As all NABS 2007 chapters correspond to a NABS 1992 chapter or sub-chapter, the content of the specific chapters has been largely maintained except for NABS 2007 chapters 12 "General advancement of knowledge: research financed from general university funds (GUF)" and 13 "General advancement of knowledge: research financed from other sources." In NABS 2007 chapter 7 "Health," the old content is used but harmonised with the EPHF.

Chapter 7 "Health" includes R&D related to protecting, promoting and restoring human health – broadly interpreted to include health aspects of nutrition and food hygiene. It ranges from preventative medicine, including all aspects of medical and surgical treatment, both for individuals and groups, and the provision of hospital and home care, to social medicine and paediatric as well as geriatric research. The following lists the sections within chapter 7 of NABS 2007 and their corresponding sections in NABS 1992 (in parentheses):

- Prevention, surveillance and control of communicable and non-communicable diseases (previously Code 4.2 – Preventive medicine);
- Monitoring the health situation (previously Code 4.7 – Social medicine);
- Health promotion (previously Code 4.5 – Nutrition and food hygiene);
- Occupational health (previously Code 4.4 – Occupational medicine);
- Public health legislation and regulations;
- Public health management (previously Code 4.8 – Hospital structure and organisation of medical care);
- Specific public health services (previously Code 4.1 – Medical research, hospital treatment, surgery); and
- Personal health care for vulnerable and high risk populations (previously Code 4.3 – Biomedical engineering and medicines).

The section "Public health legislation and regulations" is a newly created item in NABS 2007. The NABS 1992 sections "General research" and "Biomedical engineering and medicines" as well as "Other medical research" have no direct corresponding sections in NABS 2007.

NABS 2007 chapter 12 "General advancement of knowledge: R&D financed from GUF" has a subchapter on "R&D related to Medical Sciences – financed from GUF," which corresponds to the NABS 1992 subchapter "Medical Science" (Code 10.6).

4. List of European country groups used as aggregates in the graphs

EU9 includes Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and the United Kingdom.

EU12 includes Austria, Belgium, the Czech Republic, Greece, Hungary, Iceland, Ireland, the Netherlands, Poland, Portugal, Slovakia and Slovenia.

EU21 comprises EU9 and EU12.

5. Notes to Figure 2.d.1

In the cross-country comparison of absolute spending differences, all country-specific values of biomedical research expenditure in 2007 are from Alison Young except for (1) Japan's upper bar, which is from Japanese expert Tomohiro Ijichi, (2) France, which is from French expert Laurence Esterle and uses 2007-2008 data, and (3) Italy, which is from Eurostat.

For 2008, the country-specific values of the EU9 are from the OECD (Finland and Italy), A. Young (Spain), national experts (Denmark and Germany) and our own estimates using Eurostat data on R&D spending in all fields of science, based on the assumption that OECD-reported country-specific 2007 shares of non-market health R&D in spending for all fields of science remain constant (France, Norway, Sweden and the UK). The country-specific values of the EU12 are from Eurostat (Ireland and the Netherlands), the OECD (the Czech Republic, Hungary, Poland, Portugal, Slovakia and Slovenia) and our own estimates using Eurostat data (Austria, Belgium and Iceland), again based on the assumption of constant 2007 spending shares across fields of science. For Greece, we impute the 2007 value for lack of 2008 data. For Japan, the bar labelled "based on OECD" updates the 2007 value by applying the growth rate between 2007 and 2008 observed in the T. Ijichi series. For the US, the values are from A. Young (standard minimum and upper estimate) and Research America as indicated.

For 2009, the country-specific values of the EU9 are from the OECD (Italy), A. Young (Spain and Sweden), national experts (Finland and Norway) and our own estimates using Eurostat data (Denmark, France, Germany and the UK), again based on the assumption of constant 2007 spending shares across fields of science. The country-specific values of the EU12 are from Eurostat (the Netherlands), the OECD (the Czech Republic and Slovakia), national experts (Iceland) and our own estimates using Eurostat data (Austria, Belgium, Hungary, Ireland, Poland, Portugal and Slovenia), again based on the assumption of constant 2007 spending shares across fields of science. For Greece, we impute the 2007 value for lack of 2009 data. For Japan, the bar labelled "based on OECD" updates the 2008 value by applying the growth rate between 2008 and 2009 observed in the T. Ijichi series. For the US, a full assessment of biomedical research expenditures in 2009 is only available from Research America; the US standard minimum and upper estimate are 2008 data from A. Young, except for the direct federal government component in the standard minimum (which is already reported for 2009).

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6. Notes to Figure 2.d.2

In the time series, data for all countries provided by A. Young are consolidated values from the OECD, Eurostat and national sources. For countries outside the eurozone (Denmark, Norway, Sweden and the UK), we convert national currency values into euro using PPPs. For countries with missing observations, we compute estimates for the following countries and years based on the average annual growth rate between the years in parentheses: Austria 1999 (1998-2002), 2000 (1998–2002), 2001 (1998–2002), 2003 (2002–2004), 2005 (2004–2006); Belgium 1995-1999 (2000–2007); and Iceland 1996 (1995-1997), 1998 (1997–1999), 2006 (2005–2007). For France, we use data provided by A. Young augmented by an estimate for 2007 based on updated data from French expert L. Esterle. However, compared with previous years, the organisational basis she uses to obtain the 2007 value is narrower, neither including European and regional contracts nor expenditures of public research organisations which are involved in the biomedical field. To keep the time series consistent and include all research-performing organisations included in 2003, we partly estimate the 2007 figures for a subset of the relevant research organisations using the average growth rate of the observed spending components for any imputations required. For other missing values in the French series, we impute estimates based on the average annual growth rate between the years in parentheses for 1999 (1998-2001), 2000 (1998-2001), 2002 (2001-2003), 2005 (2003-2007) and 2006 (2003-2007) and use the 1997 value for 1995 and 1996. For Italy, A. Young provides accurate data for 2005 and 2006. In all years before 2005, the share of health R&D in the higher education sector is estimated as 25% of all R&D spending in the higher education sector. Since 2007, the OECD provides accurate data. For the UK, we use funder-reported data as a substitute since the published performer-reported data is known to be grossly incomplete. For Japan, a break in the OECD series, due to a change in definitions between 1995 and 1996, is eliminated by simply substituting the 1996 value for the OECD-reported value in 1995. Our series is based on data provided by A. Young for the years from 1995-2007. The values for the following two years are estimations extending the A. Young series by applying the annual growth rate between the years in parentheses in the T. Ijichi series: 2008 (2007-2008), 2009 (2008-2009). For all countries, the 2008 and 2009 values are calculated as described in the notes to Figure 1 and then rebased according to the respective index with base 100 in 1995.

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A STRONGER BIOMEDICAL RESEARCH FOR A BETTER EUROPEAN FUTURE

"Best Practice" for medical research in Europe:

Primary goals:
- Strong basic research
- Strong clinical research
- Strong translational research: bringing basic research knowledge into clinical practice, and vice versa -- all three of the above being facilitated by interdisciplinary research and public– private partnerships

Tools to reach these goals: people
- Career track schemes with attractive possibilities for researchers taking advantage of co-funding strategy
- European Medical Scientific Training Programme (EMSTP) for physicians and scientists scaling up existing successful initiatives
- The highest level of research ethics, and no scientific misconduct

Tools to reach these goals: research infrastructure
- Investment in national and European research infrastructure – covering the whole range from laboratory equipment in basic science labs and research facilities in hospitals, to the largest pan-European infrastructures, as outlined in the ESFRI Roadmap
- Launch a call for proposals to directly support on a highly competitive basis a league of top performing biomedical research centres of excellence, integrated into regional clusters
- Post-genomic clinical medicine
- Intelligent and coordinated use of Information Technology (IT)
- EC and national regulatory issues for clinical research adapted to facilitate research

Tools to reach these goals: research funding
- Adequate research funding – distributed on the basis of scientific excellence and through peer review
- Common criteria and methods for the evaluation of research outcomes

Tools to reach these goals: societal means
- Globalisation and collaboration: sharing of research and results
- Public engagement about medical research and its possible impacts
- Preparedness for the future

Annex 4. Glossary

4P medicine
Personalised, predictive, preventative and participatory medicine

Biobank
Also known as a biorepository, a place that collects, stores, processes and distributes biological materials and the data associated with those materials.

Biomarker
A cellular or molecular indicator of exposure, health effects or susceptibility. Biomarkers can be used to measure internal dose, biologically effective dose, early biological response, altered structure or function, susceptibility.

Clinical guidelines
Clinical guidelines are recommendations on the appropriate treatment and care of people with specific diseases and conditions. They are based on the best available evidence and help healthcare professionals in their work without replacing their knowledge and skills.

Clinical research
Patient-oriented research conducted with human participants or on material of human origin involving interaction with human participants in order to discover what causes human disease, and how it can be prevented and treated. Clinical research can include: mechanisms of human disease; therapeutic interventions; clinical trials; or development of new technologies. Epidemiological and behavioural studies, outcomes research and health services research can also be part of clinical research.

EU Clinical Trials Directive
The European Union published in April 2001 the European Parliament and Council Directive 2001/20/EC regulating clinical trials with medicinal products. By May 2004, all Member States were requested to have the Directive implemented in national regulations.

Effectiveness
A measure of the extent to which a specific intervention, procedure, regimen or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population; a measure of the extent to which a healthcare intervention fulfils its objectives. Has to be distinguished from efficacy.

Eurostat
A Directorate-General of the European Commission located in Luxembourg. Its main responsibilities are to provide the European Union with statistical information at European level and to promote the harmonisation of statistical methods across the Member States of the European Union, candidate countries and European Free Trade Association (EFTA) countries. The organisations in the different countries which actively cooperate with Eurostat are summarised under the concept of the European Statistical System.

Evidence-based Medicine (EbM)
According to Dr David Sackett and colleagues at McMasters University in Ontario, Canada, Evidence-based Medicine is "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (1996)

Global Forum for Health Research
Independent, international organisation committed to demonstrating the essential role of research and innovation for health and health equity, benefiting poor and marginalised populations.

Health Technology Assessment
Health Technology Assessment (HTA) as a term was first used already in the seventies. HTA systematically evaluates whether a technology works (i.e. is effective), is cost-effective, how it compares to other technologies and which risks it is associated with. One important method applied for HTA is EbM. HTA also addresses ethical, organisational and economic aspects of the technology. HTA thus addresses the direct, intended consequences of technologies as well as their indirect, unintended consequences. The results of HTA are mostly published as a report.

Immediate impact
See impact index at 2 years

Impact index at 2 years (immediate impact)
Measures the scientific impact of publications, reflecting their visibility. An impact index at 2 years superior to 1 (= world average impact index) indicates that the country/region/economy has a high impact in the discipline or sub-discipline studied. An impact index at 2 years inferior to 1 (= world average impact index) indicates that the country/region/economy has a low impact in the discipline or sub-discipline studied.

Innovation
Accumulation and transformation of knowledge

Knowledge
Knowledge is defined as information that is assembled according to commonly accepted rules in an accountable way, which is interpreted to a common cause and publicly accessible. Although robust knowledge is wider than research, scientific research is accepted as the most reliable way to build on such knowledge. The overview or synthesis of integrated results of scientific research is often indicated as evidence, mostly made available as guidelines.

Member States
27 European Union Member States

NUTS
The NUTS classification is a hierarchical system for dividing up the economic territory of the EU for the purpose of:
- The collection, development and harmonisation of EU regional statistics.
- Socio-economic analyses of the regions.
  - NUTS 1: major socio-economic regions
  - NUTS 2: basic regions for the application of regional policies
  - NUTS 3: as small regions for specific diagnoses
- Framing of EU regional policies.
  - Regions eligible for aid from the Structural Funds (Objective 1) have been classified at the NUTS 2 level.
  - Areas eligible under the other priority objectives have mainly been classified at the NUTS 3 level.

The current NUTS classification valid from 1 January 2008 until 31 December 2011 lists 97 regions at NUTS 1, 271 regions at NUTS 2 and 1303 regions at NUTS 3 level.

Scientific specialisation index

A specialisation index superior to 1 (= world average specialisation index) indicates that the country/region/economy is specialised in the discipline or sub-discipline studied. A specialisation index inferior to 1 (= world average specialisation index) indicates that the country/region/economy is under-specialised in the discipline or sub-discipline studied.

Systematic review

The application of strategies that limits bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic (Dictionary of Epidemiology, 2001).

The World Factbook (ISSN 1553-8133; also known as the CIA World Factbook)

Reference resource produced by the Central Intelligence Agency (CIA) of the US with almanac-style information about the countries of the world.

Translational research

The conversion of basic research advances into products that can be tested on humans.

Annex 5. **Abbreviations**

AAAs: Abdominal Aortic Aneurysms

ACAHO: Association of Canadian Academic Healthcare Organizations

AHRQ: Agency for Healthcare Research and Quality

AIDS: Acquired Immuno-Deficiency Syndrome

ALLEA: ALL European Academies

ARRA: American Recovery and Reinvestment Act

Aviesan: Alliance Nationale pour les Sciences de la Vie et de la Santé (French National alliance for life and health sciences)

AZT: zidovudine

BBMRI: Biobanking and Biomolecular Resources Research Infrastructure

BMBF: German Federal Ministry for Education and Research

BRDPI: Biomedical Research and Development Price Index

BRICSAM: Brazil, Russia, India, China, South Africa and Mexico

CDC: Centers for Disease Control and Prevention

CECR: Centres of Excellence for Commercialization of Research

CEO: Chief Executive Officer

CERN: European Organization for Nuclear Research

CFI: Canada Foundation for Innovation

CIA: Central Intelligence Agency

CIBER: Centro de Investigación Biomédica en Red (Networked Centre for Biomedical Research, Spain)

CIBERESP: Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública (Networked Centre for Biomedical Research on Epidemiology and Public Health, Spain)

CIHR: Canadian Institutes of Health Research

CMS: Center for Medicaid and Medicare Services

CNR: Consiglio Nazionale delle Ricerche (Italian National Research Council)

CNRS: Centre National de la Recherche Scientifique (French National Centre for Scientific Research)

COFOG: Classification of the Functions of Government

COST: European Cooperation in Science and Technology

CRC: Canada Research Chairs

CRT: Cardiac Resynchronisation Therapy

CSIC: Consejo Superior de Investigaciones Científicas (Spanish Council for Scientific Research)

CT: Computed Tomography

DFG: Deutsche Forschungsgemeinschaft (German Research Foundation)

DSc: Doctor of Science

EATRIS: European Advanced Translational Research Infrastructure in Medicine

EC: European Commission

ECRIN: European Clinical Infrastructure Network

EFPIA: European Federation of Pharmaceutical Industries and Associations

ELIXIR: European Life Sciences Infrastructure for Biological Information

EMA: European Medical Association

EMBL: European Molecular Biology Laboratory

EMBO: European Molecular Biology Organization

EMRC: European Medical Research Councils

EP: European Parliament

EPHF: Essential Public Health Functions

ERA: European Research Area

ERC: European Research Council

ERIC: European Research Infrastructure Consortium

ERINHA: European Research Infrastructure on Highly Pathogenic Agents

ESF: European Science Foundation

ESFRI: European Strategy Forum on Research Infrastructures

EU: European Union

EUCTD: European Union Clinical Trials Directive (EU 2001/20/EC)

EUROHORCs: European Heads of the Research Councils

FDA: Food and Drug Administration

FOS: Revised Field of Science and Technology Classification

FP: Framework Programmes for Research and Technological Development

FRSQ: Fonds de la Recherche en Santé du Québec

FWF: Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (Austrian Science Fund)

FWO: Fonds voor Wetenschappelijk Onderzoek-Vlaanderen (Belgian Research Foundation Flanders)

GAČR: Grantová Agentura České Republiky (Czech Science Foundation)

GBAORD: Government Budget Appropriations or Outlays on R&D

GC: Governing Council

GDP: Gross Domestic Product

GFHR: Global Forum for Health Research

GUF: General University Funds

HBV: Hepatitis B Virus

HHS: Department of Health and Human Services

HIV: Human Immunodeficiency Virus

HRSA: Health Resources and Services Administration

IAB: Institute Advisory Board

ICGC: International Cancer Genome Consortium

ICs: Institutes and Centers

IDCT: Investigator-Driven Clinical Trials

ILCOR: International Liaison Committee on Resuscitation

Annex 5. **Abbreviations**

IMI: Innovative Medicines Initiative

Inserm: Institut national de la santé et de la recherche médicale (French National Institute of Health and Medical Research)

IP: Intellectual Property

ISCiii: Instituto de Salud Carlos III (Spanish Health Institute Carlos III)

ISI: Institute for Scientific Information

ITER: International Thermonuclear Experimental Reactor

JPI: Joint Programming Initiative

JPMA: Japan Pharmaceutical Manufacturers Association

JPND: Joint Programming on Neurodegenerative Disorders

KT: Knowledge Translation

KU: Katholieke Universiteit (Leuven, Belgium)

LMB: Laboratory of Molecular Biology (Cambridge, UK)

MASS: Multicentre Aneurysm Screening Study (UK)

MCC: Multi-case Control study on Cancer (Spain)

MD: Medical Doctor

MOs: Member Organisations of the ESF

MRC: Medical Research Council (UK)

MRCT: Medical Research Council Technology (UK)

MRI: Magnetic Resonance Imaging

NABS: Nomenclature for the Analysis and Comparison of Scientific Programmes and Budgets

NACE: Statistical Classification of Economic Activities in the European Community

NAPHRO: National Alliance of Provincial Health Research Organizations

NCE/NBE: New Chemical and Biological Entities

NCE: Networks of Centres of Excellence

NCI: National Cancer Institute

NHLBI: National Heart Lung and Blood Institute

NICE: National Institute for Health and Clinical Excellence

NIH: National Institutes of Health (US)

NSERC: Natural Sciences and Engineering Research Council of Canada

NSF: National Science Foundation (US)

OECD: Organisation for Economic Co-operation and Development

OST: Observatoire des Sciences et des Techniques (France)

PAs: Priority Announcements

PhD: Doctor of Philosophy

PhRMA: Pharmaceutical Research and Manufacturers of America

PLoS: Public Library of Science

PPP: Purchasing Power Parity

PSRI: Public-Sector Research Institutions

R&D: Research and Development

RAID: Rapid Access to Interventional Development

RCN: Norges Forskningsråd (Research Council of Norway)

SARS: Severe Acute Respiratory Syndrome

SDs: Scientific Directors

S&E: Science and Engineering

SMEs: Small and Medium Enterprises

SNSF: Schweizerischer Nationalfonds (Swiss National Science Foundation)

SSHRC: Social Sciences and Humanities Research Council

SWOT: Strengths, Weaknesses, Opportunities, Threats

TRND: Therapeutics for Rare and Neglected Diseases

UN: United Nations

UNESCO: United Nations Educational, Scientific and Cultural Organization

WHO: World Health Organization

WoS: Web of Science

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Dr Joaquín Casariego	General Director CAIBER	*Instituto de Salud Carlos III (ISCiii)*	*Spain*
Dr Rafael de Andrés-Medina	Head of the Documents & Technical Studies Department	*Instituto de Salud Carlos III (ISCiii)*	*Spain*
Professor Michael Stolpe	Scientist	*Kiel Institute for the World Economy*	*Germany*
Dr Stephane Berghmans	Head of Biomedical Sciences	*European Science Foundation (ESF)*	*France*

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Österreichische Akademie der Wissenschaft:
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Bulgarian Academy of Sciences:
Bogdan Petrunov, *National Center of Infectious and Parasitic Diseases, Sofia*

Croatia

Croatian Academy of Sciences and Arts:
Krešimir Pavelić, *"Rudjer Boskovic" Institute, Zagreb*

Cyprus

Cyprus Research Promotion Foundation:
awaiting nomination

Czech Republic

Academy of Sciences of the Czech Republic and Czech Science Foundation:
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Estonian Academy of Sciences and Estonian Science Foundation:
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Finland

Academy of Finland:
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France

Centre National de la Recherche Scientifique:
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Institut National de la Santé et de la Recherche Médicale:
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National Hellenic Research Foundation:
Andrew Margioris, *School of Medicine, Heraklion*

Hungary

Hungarian Academy of Sciences and Hungarian Scientific Research Fund:
János Réthelyi, *Semmelweis University, Budapest*

Iceland

Icelandic Research Council:
Jona Freysdottir, *University Research Hospital, Reykjavik*

Ireland

Health Research Board:
Catherine Godson, *University College Dublin, Dublin*

Italy

Consiglio Nazionale delle Ricerche:
Giovanni Pacini*, *Institute of Biomedical Engineering, Padova*

Lithuania

Research Council of Lithuania:
Limas Kupčinskas, *Lithuanian University of Health Sciences, Kaunas*

Luxembourg

Fonds National de la Recherche:
awaiting nomination

The Netherlands

Nederlandse organisatie voor wetenschappelijk onderzoek:
Marcel Levi, *Academic Medical Center, University of Amsterdam, Amsterdam*

Norway

The Research Council of Norway:
Stig Slørdahl*, *Norwegian University of Science and Technology, Trondheim*

Poland

Polish Academy of Sciences:
Anna Członkowska, *Institute of Psychiatry and Neurology, Warsaw*

Portugal

Foundation for Science and Technology:
Isabel Palmeirim, *Department of Medicine, University of Algarve, Faro*

Romania

National Research Council:
Simona-Maria Ruta, *"Carol Davila" University of Medicine, Bucharest*

Slovakia

Slovak Academy of Sciences:
Richard Imrich, *Center for Molecular Medicine, Slovak Academy of Sciences, Bratislava*

Slovenia

Slovenian Academy of Sciences and Arts:
Uroš Skalerič, *University of Ljubljana, Ljubljana*

Spain

Consejo Superior de Investigaciones Científicas:
Isabel Varela-Nieto*, *Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid*

Ministerio de Ciencia e Innovación:
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Sweden

Vetenskapsrådet:
Mats Ulfendahl, *Swedish Research Council, Stockholm*

Switzerland

Swiss National Science Foundation:
Stéphanie Clarke, *Centre Hospitalier Universitaire Vaudois, Lausanne*

Turkey
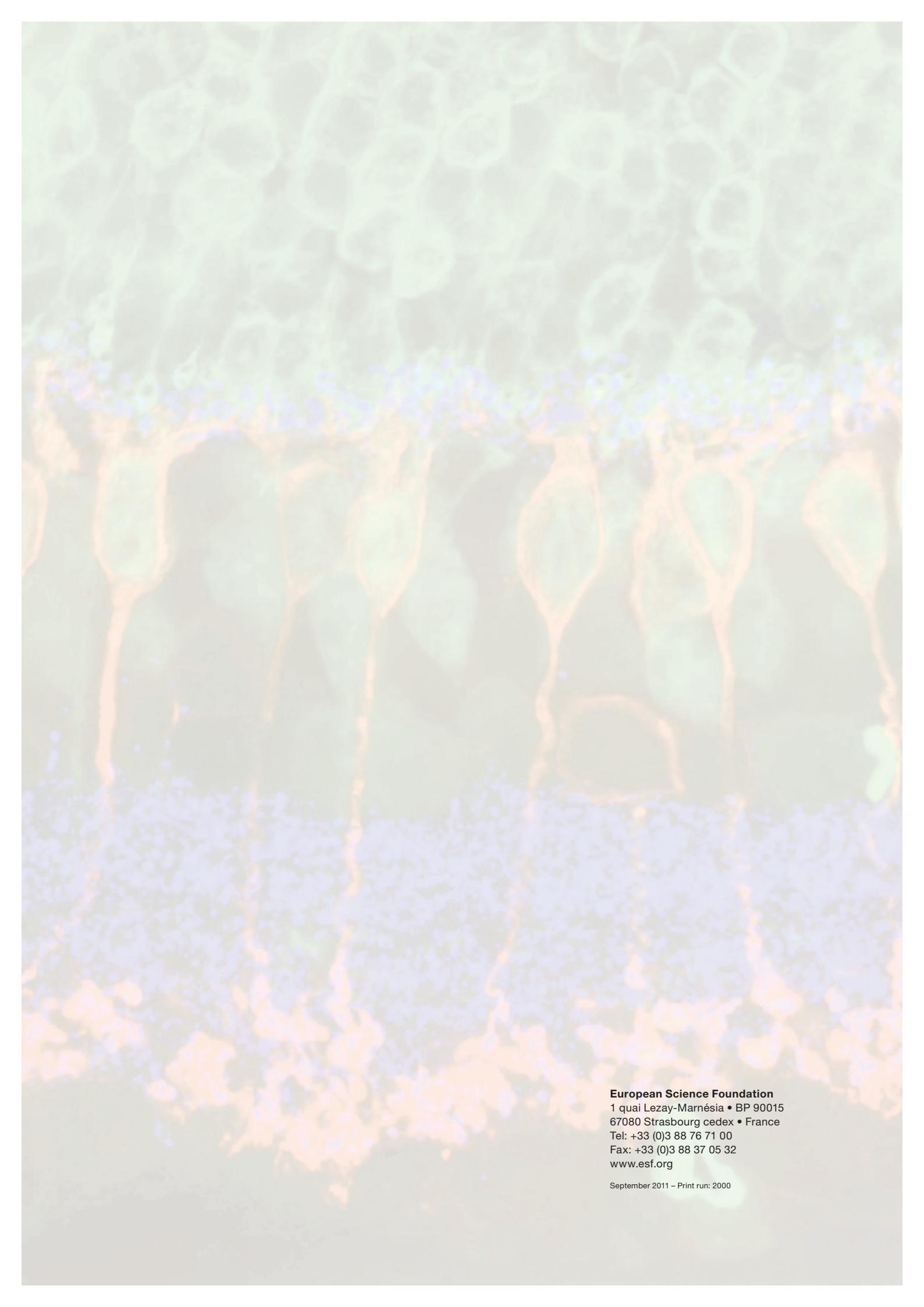
The Scientific and Technological Research Council of Turkey:
Haluk Aydın Topaloğlu, *Hacettepe Children's Hospital, Ankara*

The United Kingdom

Medical Research Council:
Mark Palmer*, *MRC, London*

*The delegate is also a Core Group member