

CNIC SECTION

Spanish National Centre for Cardiovascular Research (CNIC): pioneering a new model for funding biomedical research

Ginés Sanz and Valentín Fuster*

CARDIOVASCULAR DISEASE: HEALTH AND ECONOMICS

Recent decades have seen extraordinary progress in biomedical research. Advances in genetics, cellular and molecular biology, and biotechnology have generated a tremendous amount of information, much of which has been translated into new diagnostic and therapeutic tools. This has resulted in significant improvements in health-care delivery, life expectancy and quality of life in developed countries. For example, between 1940 and 2005 the life expectancy of Americans increased from 62.9 to 77.8 years.¹ However, during this same period the disease burden in developing countries increased.

Increased health and well-being also have clear economic benefits, since people are living longer and more productive lives. Health economists estimate that the saving of lives by preventive and therapeutic intervention in cardiovascular disease in the United States between 1970 and 1998 saved \$1.1 trillion each year.² Therefore, investment in biomedical research is considered essential to ensure progress and well-being.

Nonetheless, the cost of biomedical research, both basic and clinical, is increasing steadily as a result of the development of highly sophisticated technologies and the expense of training highly specialized researchers. Since the early 1980s, total funding for the biomedical sciences has exceeded that of engineering and the physical sciences.³ As therapies have become more effective, the discovery of new drugs and interventions has come to require considerable human and economic resources, exacerbated by the fact that very few of the potential drugs identified will reach the market. A related factor is the decline in the number of drugs registered in recent years. The number of new molecular drugs approved by the U.S. Food and Drug Administration (FDA) has fallen from an average of 35.5 per year between 1994 and

1997 to 23.3 per year between 2001 and 2004.⁴ This problem is especially severe for neglected diseases and conditions that afflict the world's poorest; the development of new drugs in these areas has been negligible in the past century.

BIOMEDICAL RESEARCH AND MECHANISMS OF FUNDING

Historically, three funding mechanisms have been dominant in biomedical research and drug development. At one extreme is the for-profit private funding by pharmaceutical and biotech companies, where investment in the development of a product or service must be exceeded by the income from sales. At the opposite extreme is public funding, which is in large part justified by the need to maintain a productive and competitive skills base in a country. The third means is charitable, not-for-profit funding by entrepreneurs and private foundations. A more recent approach to research funding is to combine public and private resources in a public-private partnership (PPP).

Governments have clearly understood that the limited resources available make it impossible for the public sector on its own to provide for the public good in an efficient, effective and equitable manner.⁵ Therefore, private funding of biomedical research is considered essential, and PPP is increasingly being seen as an effective means of increasing the efficiency of biomedical research, eventually leading to improved access to and outcomes of healthcare and social interventions.

A recent survey of biomedical research funding in the United States showed that total funding increased between 1994 and 2003 from \$37.1 to \$94.3 billion.⁴ U.S. biomedical research accounts for 5.6% of total healthcare spending. As shown in Figure 1, support from industry accounted for 57% of spending, followed by National Institutes of Health (NIH) funding with 28%. Private non-

Ginés Sanz is Chair of the Department of Translational Research at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain. Valentín Fuster is Scientific President of the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain, Editor-in-Chief of Nature Clinical Practice Cardiovascular Medicine, and Director of the Zena and Michael A Wiener Cardiovascular Institute, and the Marie-Josée and Henry R Kravis Center for Cardiovascular Health, and the Richard Gorlin, MD/Heart Research Foundation Professor, Mount Sinai School of Medicine, New York, USA.

Correspondence

The Zena and Michael A. Wiener Cardiovascular Institute and The Marie-Josée, and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574, USA
valentin.fuster@mssm.edu

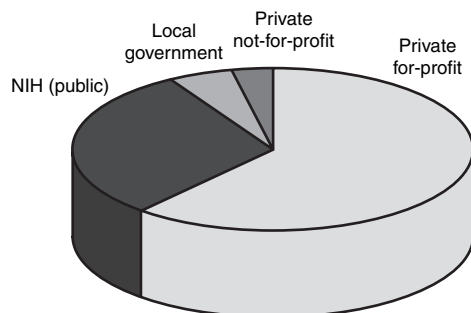


Figure 1 Contribution to biomedical research funding by different sectors in the United States.⁴ (NIH = National Institutes of Health)

profit organizations contributed \$2.5 billion in 2003, representing 3% of all biomedical research funds.

RESEARCH FUNDING IN SPAIN: PUBLIC AND FOR-PROFIT PRIVATE CONTRIBUTION

During the last decade the Spanish government has made considerable efforts to promote research and development (R&D). The total investment in R&D in 2006 was €11.8 billion, representing 1.2% of the country's gross domestic product (GDP). Moreover, a new «Plan Nacional de Investigación» (National Plan for Research) has been launched to increase spending on research to 2% of GDP by 2010⁶, bringing Spain into line with other Western nations, such as France (2.3%), Germany (2.5%) and the United States (2.57%). Public funding for biomedical research in Spain is coordinated by the Instituto de Salud Carlos III, which is the national agency for conducting and supporting medical research. The institute provides funding through a range of programmes, including funding for research networks and national centres such as the National Centre for Cardiovascular Research (CNIC). In addition, the strongest and most promising research proposals are identified and funded through an annual competitive call (the FIS programme).

Figure 2 shows the contribution of different sectors to the funding of biomedical R&D in Spain. Private for-profit business participation in R&D is 47% and has only increased 3 percentage points in the last 4 years, remaining far below the European Union average of 55%. Only 23 Spanish companies appear on the list of the top 1000 European private investors in R&D.⁷ The explanation for this divergence from the pattern typical of other Western economies probably lies in structural and legal issues, for example, tax exemption.

An important outcome of this is that only one out of five Spanish researchers works in the private sector.

The Spanish authorities are making efforts to remedy this situation. Recently, €200 million was assigned to fund 15 PPPs under the second call for proposals of the Strategic National Consortia for Technical Research programme (CENIT). This programme forms part of a broader Spanish government initiative called INGENIO 2010 and is designed to promote collaboration in R&D between public and private organizations. In total, 208 private companies and 246 research groups from the public sector participate in these projects.⁶ The final aim is to achieve the target of a 66% for-profit contribution from the private sector established at the Lisbon European Council meeting in 2000.

The pharmaceutical industry is a major contributor to this for-profit private sector national effort. The Spanish pharmaceutical market is the fifth largest in the EU behind Germany, France, Italy and the United Kingdom. The Spanish pharmaceutical industry reinvests 6% of its sales and employs 4300 professionals. In 2007 Spanish pharmaceutical laboratories invested €850 million in R&D, accounting for almost 20% of total private investment in Spain.⁸

NOT-FOR-PROFIT PRIVATE FUNDING FOR BIOMEDICAL RESEARCH: THE PPP

The escalating cost of research means that private funding is increasingly important, and indeed, irreplaceable. For many years such injections of private money have come from philanthropic donations by wealthy benefactors or charitable foundations. A common aim of this kind of investment has been to expand access to healthcare and education in emerging countries. In the field of biomedical research, another important goal has been the development of new drugs and vaccines

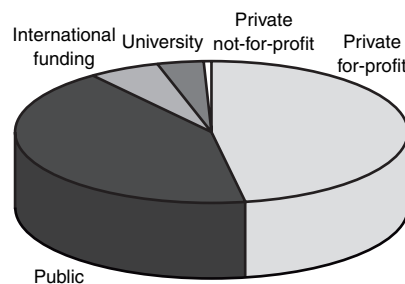


Figure 2 Contribution to biomedical research funding by different sectors in Spain.⁷

for neglected and communicable diseases in developing countries. In addition, several research institutes devoted to biomedical research in the United States and other Western countries are the result of generous donations by individual benefactors.

In the 1950s, the removal of legal and tax restrictions in the United States encouraged corporations to establish charitable foundations.⁹ More recently, the business community has recognized that it has broader obligations to society. However, until the late 1970s there was minimal collaboration between private and public sectors. Concern about the inability of international agencies to cope alone with the enormous health and social problems facing the world led to the establishment of PPPs to deal with specific issues.

A useful working definition of PPPs directed at improving healthcare is «arrangements that innovatively combine different skills and resources from institutions in the public and private sectors to address persistent global health problems».¹⁰ PPPs bring together skills, knowledge and resources from a variety of sectors, including academia, non-governmental organizations, philanthropists, government and intergovernmental agencies. Members of the for-profit private sector, such as pharmaceutical or biotech companies, may also be included in the PPP definition insofar as their objectives are to create a unique approach to solving health issues. Within this broad definition, two kinds of public-private collaboration in biomedical research can be identified. The first model of PPP involves an injection of finance into a public institution by private organizations with no expectation of a direct return on their investment. The benefits for the not-for-profit private partners might include the associated positive publicity and tax breaks. Their overriding motivation, however, is their social commitment. Companies that enter into these «social-commitment partnerships» do so because they recognize that science and technology will be the motor of the future economy and because they share the widely felt concerns about the social and economic costs of the growing epidemic of chronic diseases. The second entrepreneurial investment involves companies in the pharmaceutical or biotech sectors. In contrast to the not-for-profit model, in this second kind of PPP all parties seek some material benefit, with the objective of the private investors being a share in the eventual profits generated by some new product, technology or procedure. Examples of this kind of product-

development partnership include investment in start-up companies at university science parks or specific collaborations between a research group in the public sector and a private company.

In general, PPP initiatives can be categorized into three areas: (i) product distribution or disease-control programmes, (ii) product development, and (iii) policy/advocacy for health systems issues. PPPs have gained growing popularity as mechanisms for increasing access to essential drugs. With the creation of product development partnerships such as the international AIDS Vaccine Initiative, the Rockefeller Foundation's Medicines for Malaria Venture, and the support given by the Bill and Melinda Gates Foundation, there has been an enormously significant shifting of gears in the search for vaccines and drugs to treat these diseases.¹¹ However, there are not many examples of private-public cooperation in basic and clinical research programmes in developed countries.

THE CNIC: AN EXAMPLE OF PUBLIC-NOT-FOR-PROFIT PRIVATE PARTNERSHIP IN CARDIOVASCULAR RESEARCH

Cardiovascular disease, including heart and cerebrovascular diseases, are the principal cause of death in Spain. Research in this field is therefore considered a priority by health professionals and government authorities in this country. As part of a concerted response to this situation, the Carlos III Institute of Health, which was formerly dependent on the Ministry of Health, created a national centre for cardiovascular research in Madrid, the CNIC.

The main objective of this project is to create a centre of excellence that will be the nexus of an expanded Spanish contribution to cardiovascular research and play a leading role in the application of research results in clinical practice, both nationally and internationally.¹² As described in the previous issue (NCP Cardiovascular Medicine CNIC Edition October 2008 n 5 vol 10 CNIC-1), the CNIC has six departments: three are devoted to basic research and the other three have a more directly clinical orientation. This organization clearly reflects the priority of translational research for the CNIC.^{13,14} Another key strategic objective is the discovery and professional training of new researchers.¹⁵ This goal is being addressed through a range of tailored programmes for the discovery of young investigators as well as for teaching and training research staff at each stage of their careers. In this way, the CNIC aims

to create a wellspring of talented, highly-trained researchers who will become the scientific leaders of the future, enriching the intellectual life and medical practice in our country.

The funding of the CNIC is based on a PPP of the broader, socially committed model through the Pro CNIC Foundation (<http://www.fundacionprocnic.es>). To achieve the funding necessary for its ambitious plan, the CNIC appealed to the sense of social obligation of the largest businesses in the country by inviting these major players in Spanish civil society to make an active and long-term commitment to this project. The outcome was an agreement, signed in December 2005, between the Ministry of Health and a group of some of the most important Spanish businesses, the terms of which committed these businesses to funding the CNIC until 2012. Shortly after the agreement was signed, on January 24, 2006, this grouping of companies was formally constituted as the Pro CNIC Foundation. Since then, new companies have joined the group, and the Pro CNIC Foundation currently has 13 members: Acciona, Banco Santander, BBVA, Endesa, Fundación Abertis, Fundación Ramón Areces, Gas Natural, Grupo Prisa, Inditex, La Caixa, Repsol YPF, Fundación de Investigación Mutua Madrileña, and Telefónica. In this innovative PPP, the Spanish government has committed €450 million over the next 10 years and the Pro CNIC Foundation a further €180 million. This additional money can be invested in areas that may not be reached by public funding—for example, special programmes for the discovery and training of young investigators, extramural grants aimed at integrating basic and clinical research to answer specific questions, the acquisition of special research equipment that would otherwise be difficult to fund, and programmes to incentivize and retain valuable investigators.

The Pro CNIC Foundation not only provides the CNIC with funds, it also contributes its accumulated managerial and business expertise. Representatives of the Pro CNIC Foundation sit on the CNIC's Board of Trustees (Figure 3) and actively participate in the management, planning and decision making related to the Centre. In this way, some of the most important organizations in the private sector have committed themselves to a direct involvement in biomedical research and the fight against cardiovascular diseases.

A major strength of this socially committed PPP model is that it provides for a more solid base than traditional forms of charitable financing,

giving the CNIC a more stable financial support than if it relied on sporadic donations from benefactors. This stability gives the CNIC greater freedom to commit itself to long-term, high-return research strategies in collaboration with public and private institutions and allows for a more effective use of its own resources generated through competitive projects and the exploitation of intellectual property rights.

By joining the Pro CNIC Foundation, participating businesses are demonstrating their awareness of the importance of research as a motor of economic development and social well-being. The members are also providing pioneering support for an innovative model of research funding of enormous potential. Investment in research, especially in medicine and health, is essential for Spain's future international competitiveness, and the disinterested, not-for-profit contribution of the participating companies is testament to their high sense of social duty. Indeed, the Pro CNIC Foundation is a clear example of a new model of patronage in biomedical research and is a genuine example of collaboration between the public and private sectors.

The CNIC has also entered into product-development partnerships. The prime example is the collaboration with FERRER, a Spanish pharmaceutical company, aimed at developing a fixed-dose combination drug («polypill»). The aim is to improve secondary cardiovascular therapy by reducing patients' lack of treatment adherence and providing medication in emerging countries at an affordable price. This PPP brings together skills, knowledge and resources from a private for-profit pharmaceutical company and a public research institution to create a new approach to solving an important global health problem. The aim is to provide a three-component fixed-dose combination drug to patients from low-income countries with a history of myocardial infarction at a price lower than the cost of the three drugs purchased separately. The combination drug is expected to be available in early 2010.

CONCLUDING REMARKS

There is a general recognition in developed countries that biomedical research is essential for economic development and social well-being and is therefore a genuine social good. Nonetheless, the ever-increasing costs of research mean that all countries face limits to the proportion of their GDP they can devote to research in this area. In this situation, it is clear that the future direction



Figure 3 Pro CNIC Foundation Board of Trustees. Bottom row, left to right: César Alierta –Telefónica; Ignacio Polanco – Grupo Prisa; Emilio Botín - Fundación Marcelino Botín; José Manuel Entrecanales – Acciona, Pro CNIC Foundation President; Valentín Fuster – CNIC Scientific President; Isidro Fainé – La Caixa; Francisco González – BBVA; Luis Suárez de Lezo – Repsol YPF; Ignacio Garralda – Fundación de Investigación Médica Mutua Madrileña. Top row, left to right: Carlos Martínez Echevarría – Fundación Ramón Areces; Salvador Gabarró – Gas Natural; Luis de Carlos – Uría Menéndez; Rodolfo Martín Villa – Fundación Endesa; Miquel Roca – Fundación Abertis; Pablo Isla – Inditex.

Acknowledgments

CNIC is supported by the Spanish Ministry of Science and Innovation and the Pro CNIC Foundation (ACCIONA, BBVA, ENDESA, FUNDACIÓN ABERTIS, FUNDACIÓN DE INVESTIGACIÓN MUTUA MADRILEÑA, FUNDACIÓN MARCELINO BOTÍN, FUNDACIÓN RAMÓN ARECES, GAS NATURAL, GRUPO PRISA, INDITEX, LA CAIXA, REPSOL YPF and TELEFONICA). We thank Simon Bartlett for editorial assistance.

of biomedical research requires the participation of all sectors of society. This implies increased commitment of public funds, but also an active not-for-profit contribution from private businesses not involved in medicine and healthcare. Such an involvement by the private sector integrates businesses more closely into the social fabric and affirms a commitment to the future development of a country. Governments therefore have an important role in putting in place the legal framework to facilitate the formation of organisations like the Pro CNIC Foundation, which tie private money—mainly on a not-for-profit basis—into long-term social commitments of universal benefit.

REFERENCES

1. Kung HC et al. (2008) Deaths: final data for 2005. *Natl Vital Stat Rep* 1-120
2. Lasker Foundation. Investment in research saves lives and money. Available on line at <http://www.laskerfoundation.org/advocacy/pdf/factsheet2cardiovasc.pdf> (accessed 3 October 2008)
3. US Census Bureau (1999) Statistical Abstract of the United States, Science and Technology. Washington, DC: US Census Bureau.
4. Moses H et al. (2005) Financial Anatomy of Biomedical Research. *JAMA* 1333-1342
5. Nishtar S. (2004) Health research policy and systems. *Health Research Policy and Systems* 1-7
6. Clos J. (2008) La I+D+I como motor de la economía. *REDES de investigación en Medicamentos. Farma Industria* 10-11. Available on line at [http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/\\$FILE/REDES_10.pdf](http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/$FILE/REDES_10.pdf) (accessed 3 October 2008)
7. Cortina F, González B. (2008) El papel del INE en las estadísticas del I+D: evolución y perspectiva internacional. *REDES de investigación en Medicamentos. Farma Industria* 21-23. Available on line at [http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/\\$FILE/REDES_10.pdf](http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/$FILE/REDES_10.pdf) (accessed 3 October 2008)
8. Esteve A. (2008) El compromiso de la industria farmacéutica con la investigación biomédica. *REDES de investigación en Medicamentos. Farma Industria* 4-5. Available on line at [http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/\\$FILE/REDES_10.pdf](http://www.farmaindustria.es/farmaweb/7pb43811prod.nsf/5F10B81DD8C24C08C1257402005350E0/$FILE/REDES_10.pdf) (accessed 3 October 2008)
9. Ahn M et al. (2000) Public-Private partnerships in health care for developing countries: a new paradigm for change. *Managed Care Quarterly* 65-72
10. Meredith S, Ziemba E. (2008) The new landscape of product development partnerships (PDPs). *Health Partnerships Review* 11-14. Available on line at http://www.globalforumhealth.org/filesupld/hpr/HealthPartnershipsReview_Full.pdf (accessed 3 October 2008)
11. Croft SL. (2005) Public-private partnership: from there to here. *Transactions of the Royal Society of Tropical Medicine and Hygiene* S9-S14.
12. Fuster V. (2008) The CNIC, open to science and dissemination. *Nat Clin Pract Cardiovasc Med* CNIC Edition October 2008 vol 5 n 10 CNIC-1: 1.
13. Sánchez-Madrid et al. (2008) CNIC: A new approach to cardiovascular research. *Nat Clin Pract Cardiovasc Med* CNIC Edition October 2008 vol 5 n 10 CNIC-1: 2-6.
14. Sanz G et al. (2008) Translational research at the Spanish National Centre for Cardiovascular Research. *Nat Clin Pract Cardiovasc Med* CNIC Edition October 2008 vol 5 n 10 CNIC-1: 7-11.
15. Redondo J et al. (2008) Identifying and training the best and the brightest at the Spanish National Centre for Cardiovascular Research. *Nat Clin Pract Cardiovasc Med* CNIC Edition October 2008 vol 5 n 10 CNIC-1: 12-17.