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Market challenges facing academic research in commercializing nano-enabled implantable devices for in-vivo biomedical analysis

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ABSTRACT

This article reports on the research and development of a cutting-edge biomedical device for continuous in-vivo glucose monitoring. This entirely public-funded process of technological innovation has been conducted at the University of Barcelona within a context of converging technologies involving the fields of medicine, physics, chemistry, biology, telecommunications, electronics and energy. The authors examine the value chain and the market challenges faced by in-vivo implantable biomedical devices based on nanotechnologies. In so doing, they trace the process from the point of applied research to the final integration and commercialization of the product, when the social rate of return from academic research can be estimated. Using a case-study approach, the paper also examines the high-tech activities involved in the development of this nano-enabled device and describes the technology and innovation management process within the value chain conducted in a University–Hospital–Industry–Administration–Citizens framework. Here, nanotechnology is seen to represent a new industrial revolution, boosting the biomedical devices market. Nanosensors may well provide the tools required for investigating biological processes at the cellular level in vivo when embedded into medical devices of small dimensions, using biocompatible materials, and requiring reliable and targeted biosensors, high speed data transfer, safely stored data, and even energy autonomy.

1. Introduction

1.1. Nanotechnology and economy

It is widely recognized that the welfare of the most advanced economies is at risk, and that the only way to tackle this situation is by controlling the knowledge economies and dealing with the convergence of sciences and technologies (Linstone, 2011). To achieve this ambitious goal, we need to improve the performance of each dimension in the "knowledge triangle": education, research and innovation. Indeed, recent findings point to the importance of strategies of adding-value and marketing during R+D processes so as to bridge the gap between the laboratory and the market and so ensure the successful commercialization of new technology-based products (Musso, 2009; Walsh, 2004; Linton and Walsh, 2003). Moreover, in a global economy in which conventional manufacturing is dominated by developing economies, the future of industry in the most advanced economies must rely on its ability to innovate in those high-tech activities that can offer a differential added-value, rather than on improving existing technologies and products. It seems quite clear, therefore, that the combination of health (medicine) and nanotechnology in a new biomedical device is very capable of meeting these requisites.

Nanotechnology provides breakthroughs that support endless sources of innovation and creativity at the intersection between medicine, biotechnology, engineering, the physical sciences and information technology, and the discipline is opening up new directions in R+D, intellectual property and knowledge management, and technology transfer (Lüthje and Herstatt, 2004; Linton and Walsh, 2004; Kostoff et al., 2007; Yanez et al., 2010; Allarakhia and Walsh, 2011). A number of nanotech products are already in use and analysts expect markets to grow by hundreds of billions of euros during the present decade. After a long R+D incubation period, several industrial segments are already emerging as early adopters of nanotech-enabled products (Fuji-Keizai, 2007); in this context, surprisingly rapid market growth is expected and high mass market opportunities are envisaged for targeted research sub-segments (Salermo et al., 2008; Linton and Walsh, 2008a). Findings suggest that the Bio&Health market will provide some of the greatest advances over the next few years and that, as a result,

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the applications of nanoscience and technology to medicine will benefit patients by providing new prevention assays, early diagnosis, nanoscale monitoring, and effective treatment via mimetic structures. Doubtless, there are considerable challenges in the design of nanostructures which can operate reliably over extended timescales in the body.

The scale-length reduction that has been achieved through nanosynthesis (bottom-up technology) and nanomachining (top-down technology) has the potential to interact with the biological world as never before. The bio-nanotechnologies operate at the interface between organized nanostructures and biomolecules, which are key control routes for achieving new breakthroughs in medicine; dentistry and therapeutics; in food of animal and vegetable origin; and in daily care products such as cosmetics. According to the GENNESYS White Paper (2009), this new field of research will provide significant breakthroughs in the near future in the realms of bioreactors, biocompatible materials and lab-on-chip technologies. As a result of the very novelty, diversity and transdisciplinary nature of nanotechnologies, some researchers require a social science agenda for nanotechnology (Wood et al., 2008) as well as to take into account the social risk and the precautionary principle within nanotechnologies (Glenn, 2006; Throne-Holst and Stø, 2008).

1.2. Convergence of technologies in nanomedicine

For the purpose of this paper, nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale. Nanomedicine has a potential impact on the prevention, early and reliable diagnosis, and treatment of diseases. In the nanomedicine case, there is a wide range of technologies that can be applied to medical devices, materials, procedures, and treatment modalities. A closer look at nanomedicine introduces emerging nanomedical techniques such as nanosurgery, tissue engineering, nanoparticle-enabled diagnostics, and targeted drug delivery. Still in its infancy, much of the work in the discipline involves R+D and it is, therefore, crucial that health institutions, research institutes and manufacturers work together efficiently. In particular, multidisciplinary research groups and technology transfer offices are playing a key role in the development of new nano-enabled implantable biomedical devices through an advanced understanding of the microstructure/property relationship for biocompatible materials and of their effect on the structure/performance of these devices. To proceed further, a general framework is required that can facilitate an understanding of the technical and medical requirements so that new tools and methods might be developed. Moreover, in medicine there is a pressing need to ensure close cooperation between University–Hospital–Industry–Administration while specific tools and procedures are developed for use by clinicians. Drawing on the experience of the authors, in this case study we seek to demonstrate the importance of cooperation and collaboration between these four stakeholders and the citizens involved in the innovation process leading to the development of new biomedical products ready for the market.

The interaction between medicine and technology allows the development of diagnostic devices to detect or monitor pathogens, ions, diseases, etc. Today, the integration of rapid advances in areas such as microelectronics, microfluidics, microsensors and biocompatible materials allows the development of implantable biodevices such as the Lab-on-Chip and the Point-of-Care devices (Ghafar-Zadeh and Sawan, 2008; Barretino, 2006). As a result, continuous monitoring systems or event detectors are available to develop faster and cheaper clinical tasks—especially when compared with standard methods. It is in this context that we present an integrated front-end architecture for in-vivo detection.

1.3. The biomedical device for in-vivo analysis

The system introduced in this paper is conceived to be implanted under the human skin. The powering and communication between this device and an external primary transmitter are based on an inductive link. The architecture presented is designed for two different approaches: defining a true/false alarm system based on either amperometric or impedance nano-biosensors. Among the diseases that might be monitored by in-vivo analysis, it is the aim of this paper to focus on diabetes given that its incidence and prevalence is increasing worldwide, reflecting lifestyle changes and aging populations. Specifically, this growing prevalence is closely linked to that of obesity, creating significant market opportunities as reported in the World Diabetes Market Analysis 2010–2025 (Visiongain Ltd., 2010), and, especially, because the World Health Organization estimates that the number of diabetics will exceed 350 million by 2030.

For this in-vivo implantable biomedical device, we also examine an ambitious approach that covers the entire value chain (from basic research, through engineering and technology, to industry), the infrastructure required and the implications for society of these and similar current market challenges. In this instance, the entire value chain is hosted by the university system, which highlights the social turnover of public research investment. We also consider the extent to which recent technological innovations in the biomedical industry have been based on academic research, and the time lags between investment in such academic research projects and the industrial application of their findings—i.e., so as to estimate the social rate of return from academic research. Because the results of academic research are so widely disseminated and their effects so fundamental, subtle and widespread, it is often difficult to identify and measure the links between academic research and industrial innovation. Nevertheless, there is convincing evidence, particularly from industries such as drugs, instruments, and information processing, that the contribution of academic research to industrial innovation has been considerable (Mansfield, 1991).

In summary, the entire value chain is analyzed for a cutting-edge product developed at the University of Barcelona and at the Institute for Bioengineering of Catalonia: a new nano-enabled implantable device for in-vivo biomedical analysis. In the interests of the present case study, we consider its radical application for glucose threshold measurement as one of the main effective applications of a device transferred to the market aimed at enhancing the quality of life of those facing diabetes.

2. Paper's aim, methodology and structure

The aim of this paper is to provide a broad overview of the innovation process from the use of fundamental research through to the technological commercialization of, in this case, a biomedical device, culminating in successful technology transfer. Moreover, the social return of the investment in public R&D is highlighted, since the final product enhances the well-being and safety of its end-users.

The innovative process presented in this paper has been supported mainly by public R&D and as such it should serve to promote innovation and technology transfer in public research centers and universities, and help confront the new market and technological challenges in a context of converging research disciplines and organizations. Broadly speaking, this example of technology transfer should enhance economic activity and commercial incomes in

public research groups by following the steps of a 'research value-added' process which integrates technology description, the innovation model and the final product within a context of disruptive and or emerging technologies, such as nanotechnologies (Linton and Walsh, 2008b).

As discussed above, there are currently huge opportunities to be exploited by researchers and innovation managers in the development of high-tech products, above all in the field of medical devices, an area heavily funded by public and private agencies that merits the approbation of the whole society. As such, the University–Hospital–Industry–Administration (plus Citizens) system should emerge as an essential five-helix engine for economic growth and social benefits.

In this paper we use the case study methodology as a research method to understand the complex issue of nano-related products commercialization within the daily context of a particular university research group. The case-study method has a long and respected history in the mainstream management literature and this method is also gaining acceptance, along with other qualitative methods, within the small business and entrepreneurial research community (Perren and Ram, 2004; Hamel et al., 1993; Yin, 1990; Yin, 2003). The case study reported here deals with networking and cross-fertilization among several research organizations and its proactive strategy in order to add value to the R&D activities and bridge the market. The case study methodology through the cooperation and own experience of all the participants has been widely recognized among the university-to-industry technology transfer literature (Goldhor and Lund, 1983; Anderson et al., 2007). The authors have considered multiple sources of data for this study (organizational documents, technical articles as well as research and market reports), and open-ended interviews have been also conducted with key members of each organization taking part of the value chain of the nano-enabled implantable device for in-vivo biomedical analysis.

In seeking to develop a pathway for technology transfer that includes nanobiotechnologies in a medical device, this paper presents the following structure:

- Within the next section, the innovative product itself is presented. Section 3 describes the design, performance and application of the implantable biomedical device developed by the team. The conceptual and experimental process employed in developing this medical device is presented so as to provide a better understanding of all the R&D and innovative activity that was involved. Its specific application for the monitoring of blood glucose is also considered.
- Section 4 turns its attention to examine nanotechnology and nanomedicine and provides a scientific and technical overview of various aspects related to the processing–microstructure–property–structure–performance–investment relationships in nanotechnology activity as a whole, in the field of nanomedicine and in the final product described in this paper.
- Section 5 introduces the value chain followed by the biomedical device from a publicly funded research project to the market. This section provides the theoretical framework and the overview of the technology transfer process as illustrated by this example drawn from the life sciences.
- Section 6 focuses on the commercialization of the device and management of the university research. Within this section, the convergence of technologies is analyzed when market and healthcare challenges are both considered in the fight against diabetes.

Finally, we offer a number of conclusions and recommendations regarding technology transfer and the market challenges in the case of nano-enabled biomedical devices.

3. The innovative biomedical device

3.1. State of the art

Many different problems need to be overcome in obtaining the ideal implantable device (Sadik et al., 2009). First and foremost, the device must be biocompatible to avoid unfavorable reactions within the body. Secondly, the medical device must provide long-term stability, selectivity, calibration, miniaturization and repetition, as well as power in a downscaled and portable device. In terms of the sensors, label-free electrical biosensors are ideal candidates because of their low cost, low power and ease of miniaturization. Recent developments in nanobiosensors provide suitable technological solutions in the field of glucose monitoring (Nim Choi et al., 2007), pregnancy and DNA testing (Erdem et al., 2009). Electrical measurement, when the target analyte is captured by the probe, can exploit either voltmetric, amperometric or impedance techniques. Ideally then the device should be able to detect not just one target agent or pathology, but rather different agents and it should be capable of working in a closed-loop feedback, as described by Wang (2008) in the case of glucose monitoring.

Several biomedical devices for in-vivo monitoring are currently being developed. Thus, highly stable, accurate intramuscular implantable biosensors for the simultaneous continuous monitoring of tissue lactate and glucose have recently been produced, including a complete electrochemical cell-on-a-chip. Moreover, with the parallel development of the on-chip potentiostat and signal processing, substantial progress has been made towards a wireless implantable glucose/lactate sensing biochip (Rub et al., 2009). Elsewhere, implantable bio-micro-electromechanical systems (bio-MEMS) for the *in situ* monitoring of blood flow have been designed. Here, the aim was to develop a smart wireless sensing unit for non-invasive early stenosis detection in heart bypass grafts (Steeves et al., 2007). Interestingly, this study examines the use of surface coatings in relation to biocompatibility and the non-adhesion of blood platelets and constituents. In this case, nanotechnology presents itself as being a useful tool for improving the biocompatibility of silicon bio-MEMS structures when nanoscale metallic titanium layers are used, since it enhances biocompatibility.

The next step involves developing a configurable application-specific integrated circuit (ASIC) working with a multiplexed array of nanosensors designed to be reactive for a set of target agents (enzymes, viruses, molecules, chemical elements, molecules, etc.). Multiple sensors of the array can then be used for one specific target, while other arrays can be prepared for the other targets, while also seeking a redundant response. Thus, a panel of biomarkers needs to be developed. In this way, the reproducibility and accuracy can be improved for each target, and different targets can be assayed simultaneously.

3.2. Architecture of the implantable device

At this juncture, the architecture presented represents an initial approach for the development of applications based on biosensors aimed at detecting the presence or absence of certain levels of proteins, antibodies, ions, oxygen, glucose, etc. These in-vivo detection circuits, or true/false applications (Gore et al., 2006), work as an alarm. When the concentration level under analysis falls outside a range of accepted values, a threshold value activates the alarm. For instance, in the case of glucose monitoring, the detection of a threshold decrease in glucose levels would be mandatory for avoiding critical situations such as hypoglycaemia (Haider et al., 2007; Wolpert, 2007). Such detection would be achieved when the amplitude of the measured signal falls below a specified threshold value.

The generic implantable, front-end architecture is based on inductive coupling for the in-vivo monitoring of the presence or absence of pathogens, ions, oxygen concentration levels, etc.

The system in Fig. 1 shows a platform with a true/false alarm or event detector for the monitoring of different targets. The data are transferred to a central database where all the inputs can be personalized for each patient. The data collected can be measured in different scenarios: when the patient is at rest, undertaking a certain type of physical activity, etc., depending on the particular medical interest, and hence an accurate prognosis and diagnosis can be obtained (Lin Tan et al., 2008). The system has a research application in the constant monitoring of patients as they carry out their daily activities in normal conditions (outdoors) and in this way secondary effects such as the psychological alterations caused by the stress of being in a hospital, with unknown people, etc., can be avoided. The proposed architecture (see Fig. 2) is at this stage analyzed as a threshold detector for one sensor, working amperometrically, and includes on-chip biasing, the potentiostast to drive the biosensor, a conditioning module, and the modulation and data-processing block. The conditioning module is designed to adapt to the level of the signals measured. The detection of targets using the threshold methodology needs to guarantee sufficient signal level so as to ensure a sufficiently high signal-to-noise ratio (SNR).

This modulation and data processing block is designed to analyze and send to the external reader the levels it detects.

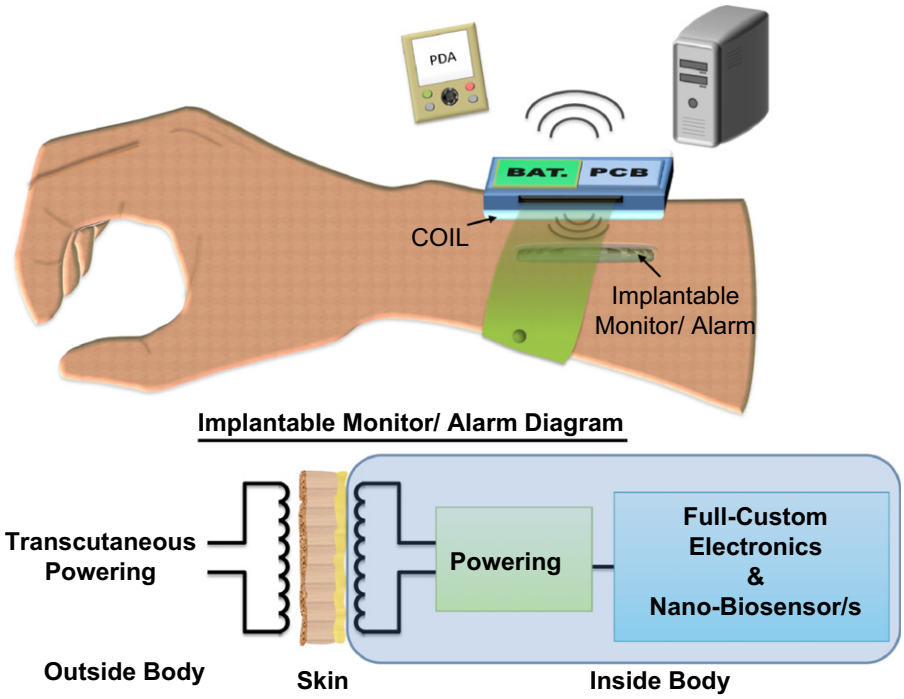

Fig. 1. Conception of the implantable device.

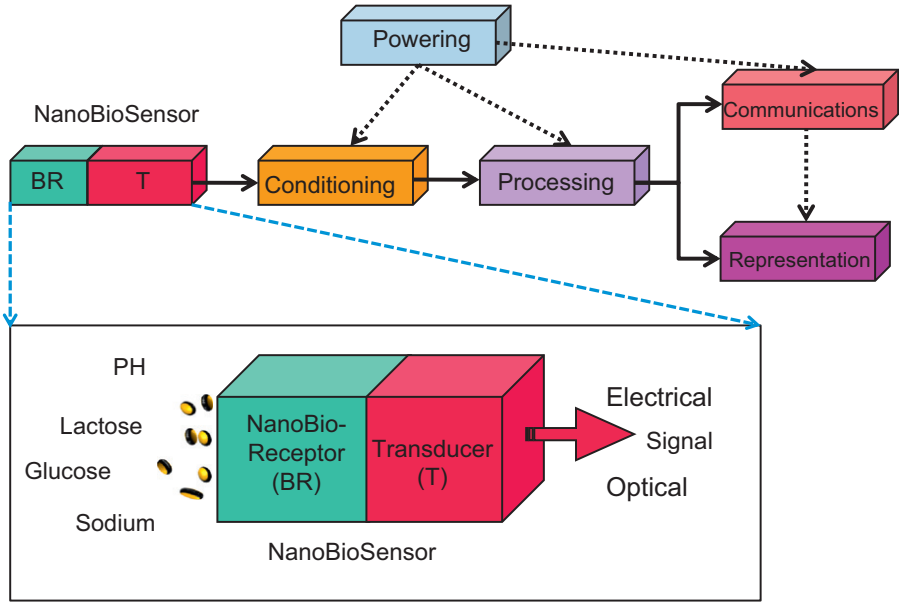

Fig. 2. Block diagram of the implantable device.

Two different approaches are defined: a generic amperometric biosensor application and an impedance biosensor, for label-free systems, based on an integrated analog lock-in amplifier, which will proceed with analog processing on the sensor for detection and transmission. For future implementation, this module will be designed so that it can be re-configured.

To validate the first proposal (amperometric), a full custom IC has been designed including several modules of the architecture and a PCB-transponder antenna, tuned to 13.56 MHz, to provide the power and communication link. The design also incorporates an integrated analog lock-in amplifier in case of impedance detection.

The medical device block diagram is presented in Fig. 2 and its front-end architecture is introduced in the Fig. 3. It comprises a nanobiosensor, an antenna and the electronic modules.

A nanobiosensor or nanosensor is generally defined as a nanometer size scale measurement system comprising a probe with a sensitive biological recognition element, or bioreceptor, a physicochemical detector component, and a transducer in between. Two types of nanosensors with potential medical applications are cantilever array sensors and nanotube/nanowire sensors and nanobiosensors, which can be used to test nanolitres or less of blood for a wide range of biomarkers. In our work, a nanobiosensor with three electrodes has been selected to explain and develop the system. Its topology can be readily adapted for any kind of sensor. The three electrodes making up the sensor are: (a) the working electrode (W), which serves as a surface on which the electrochemical reaction takes place; (b) the reference electrode (R), which measures the potential at the W electrode, and (c) the auxiliary or counter electrode (A/C), which supplies the current required for the electrochemical reaction at the W electrode.

The system is designed as a wireless powered active RFID Tag (Tesoriero et al., 2008; Lin et al., 2007) where the inductively coupled link, generated by the implantable and the external antenna, is able to supply enough energy to power the entire system and to provide wireless bidirectional communication through the human skin. Thus it can transmit the information obtained by the nanobiosensor and receive data from the external reader who in turn can configure the implanted electronics and read the data acquired.

Fig. 4 shows the final product focusing on its size, main components and the interaction in/out-body.

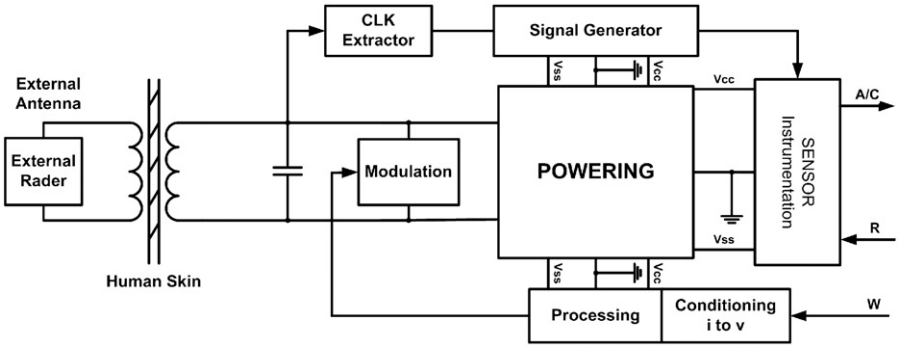

Fig. 3. Proposed generic implantable front-end architecture.

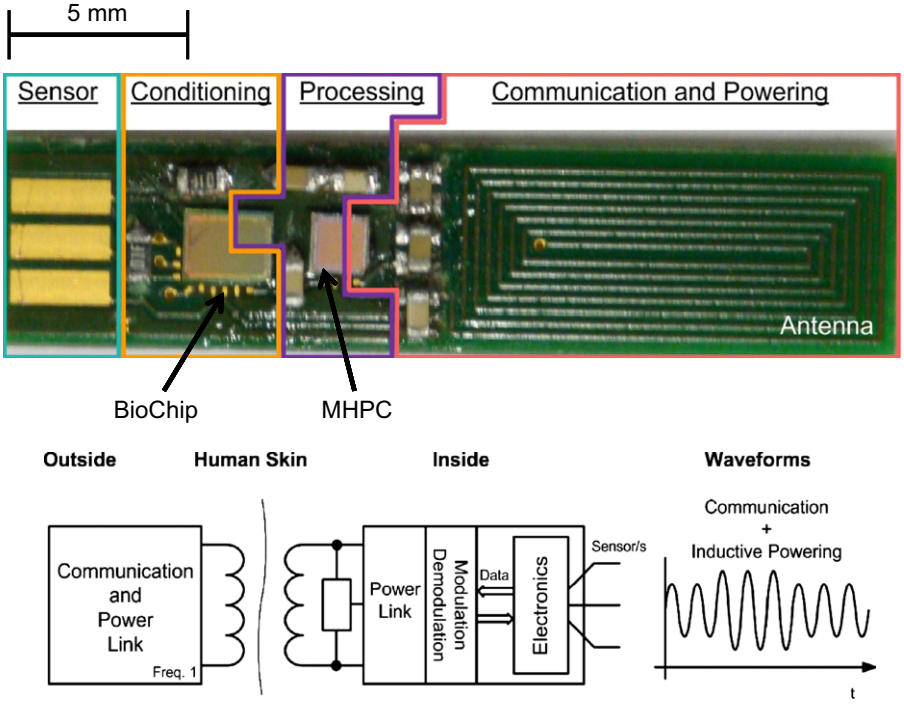

Fig. 4. Prototype of the implantable device.

4. Nanobiotechnology and nanomedicine

4.1. Scientific policies and global investment

The availability of in-vivo biomedical devices, such as the one described above, is closely linked to advances in nanobiotechnology. Nanotechnology is expected to have a rapid impact on society (Roco and Bainbridge, 2005): creating future economic scenarios, stimulating productivity and competitiveness, converging technologies, and promoting new education and human development. Evidence of this rapid impact of nanotechnology can be seen in government investment figures for nanotechnology R+D activities, facilities and workforce training. The 2011 US National Nanotechnology Initiative budget request for nanotechnology R+D across the Federal Government was over US$1.8 billion (NNI, 2010). In Europe, the VIIth Framework Program (FP) will contribute about €600 million per year to nanotechnology research until 2013, with an additional, similar amount being provided by individual countries. This gives Europe a larger yearly expenditure on nanotechnology than the United States or Japan (Swarup, 2007).

In the context of European policy, N&N is a key area for the European Commission: the VIIth FP (2007–2013) provides a specific program for the nanosciences, nanotechnologies, materials and new production technologies with a budget of €3475 million (10.72% of the VIIth FP total budget). Moreover, several specific programmes are involved in nanoscale research, and thus the total budget invested in nanoactivities will be increased by several thousands of €millions (Meur) coming from the following programmes: Health (6100 Meur); Food, agriculture and biotechnology (1935 Meur); ICT (9050 Meur) and Energy (2350 Meur).

4.2. Nano-related papers and patents

Several overviews and comparative studies of the worldwide expansion of nanopublications and nanopatents are available (Heinze, 2004; Braun et al., 1997; Hullmann and Meyer, 2003). Scientific papers and patents in the nanotechnology sector have grown exponentially over the last two decades. The relative growth in number of "nano-title-papers" in various bibliographic databases, i.e. the increase in the number of "nano-title-papers" as a proportion of all papers has been dramatic: if we take the Science Citation Index as being representative of all the sciences (albeit that chemistry is somewhat underrepresented), the proportion of "nano-title-papers" grew from 1985 to mid-2003 by about 1.2% at an average annual growth rate of about 34%, which means it has doubled every 2.35 years. Since the mid-1990s the speed has slowed somewhat to an annual growth rate of about 25% (doubling every 3.1 years) (Schummer, 2004). In 2007 over 15,000 nanoscience and nanotechnology-related papers were published, and there is now intense activity as regards intellectual property (IP) – the ownership of innovations, inventions, ideas and creativity – in the nanoscale field. Nanotechnology is increasing the shift towards a knowledge-oriented economy and so intellectual property is in a position to increase wealth creation, growth and development across the world (Aditeya, 2007). Several reports have sought to map nano-related patents (Scheu et al., 2006), and figures for nanotechnology-related IP are startling. In the European Patent Office a nanotechnology working group (NTWG) was created in 2003 and 90,000 patents were tagged to class Y01N. The proportion of nanotechnology patents more than doubled between the mid-1990s and the mid-2000s (USA 40%, Japan 19%, and Germany 10%). The Compendium of Patent Statistics 2007 (Dernis, 2007) provides internationally comparable data on patents. Before 1980, 250 nanotechnology-related patents were granted annually to universities worldwide, but by 2003 this number had increased 16-fold to 3993 patents, which have been filed for the fundamental building blocks, materials and tools required to develop this technology. The US patent office has received applications regarding the composition of matter, devices, apparatus, systems and control of nanomaterial and devices, and methods. Cross-industry patent claims are being made for single nanoscale innovations that may have diverse applications. Thus, applications have been identified in major patent classes such as electricity, human necessities, chemistry and metallurgy, performing operations and transporting, mechanical engineering, physics, fixed construction, fabrics and paper. In order to analyze the impact on the industrial sector, the OECD has categorized nanotechnology patents into six fields of application: Electronics, Optoelectronics, Medicine and biotechnology, Measurements and manufacturing, Environment and energy, and Nanomaterials.

As the research of Miyazaki and Islam (2007) revealed, universities account for a particularly large share of the research in nanotechnologies (representing 70.45% of nanotech-related research worldwide). In this they are complemented by public research institutes (who account for 22.22% of articles). Thus, it is estimated that universities now hold 70% of key nanotechnology patents. The private sector plays a more limited role (7.33% of articles globally), but it is a more prominent player in the US (12.41%). In Asia, Japan holds a strong share (12.30%) in the private sector, while South Korea (8.25%) and to a lesser extent India (3.52%) compete with Japan. In the future, nanotechnology development is likely to shift from large publicly funded organizations and universities to small start-up companies that seek to exploit the earlier publicly funded research efforts to generate the first commercial applications, in a similar way to what we have witnessed in the biotechnology industries.

4.3. Research challenges for nanobiotechnologies

Nanobiotechnology is a rapidly developing area of scientific and technological opportunity that provides advances in the food industry, energy, environment and medicine. In nanomedicine, there is a wide range of technologies that can be applied to medical devices, materials, procedures, and treatment modalities. A closer look at nanomedicine identifies such emerging nanomedical techniques as nanosurgery, tissue engineering, nanoparticle-enabled diagnostics, and targeted drug delivery. According to an expert group of the European Medicines Evaluation Agency (EMEA), the majority of current commercial applications of nanotechnology to medicine are devoted to drug delivery (Amir-Aslani and Mangematin, 2010). More novel applications of nanotechnology include tissue replacement, transport across biological barriers, remote control of nanoprobes, integrated implantable sensory nanoelectronic systems and multifunctional chemical structures for targeting of disease. Thus, nanobiotechnology can provide not just the miniaturization of implantable biomedical devices (microfluidics, microelectronics, etc.) but also reliable multifunctional arrays for disease detection. There is probably no better example of the technological convergence of the top-down (miniaturization) and bottom-up (design and creation of new functional structures) strategies, which seek the point of equilibrium where technological advances and market demands might meet.

Finally, it has been argued that current nanoscale research reveals no particular patterns and degrees of interdisciplinarity and that its apparent multidisciplinarity consists of different, largely mono-disciplinary fields which are quite unrelated to each other and which have little more in common than the prefix "nano" (Schummer, 2004). At this point, the discussion regarding the discontinuous or incremental nature of nanotechnology might arise in the innovation and technology transfer process. Based on the empirical findings of the survey conducted by Nikulainen and

Palmberg (2010), it seems that, at the moment, there is no need for nano-specific technology transfer related initiatives. This conclusion may nonetheless have to be revisited if nanotechnology becomes more radical and discontinuous. Today, chemists developing drugs, reactors and catalysts are working at the nanoscale, as they have for many years, even though they simply refer to their work as chemistry. Certainly, policymakers need to take into account relevant environmental, health and safety issues by setting standards and implementing regulations to facilitate the diffusion of nanotechnology.

5. The R&D value cycle

5.1. A new university role in R&D commercialization

It is widely accepted that the university's role has evolved from one of performing conventional research and education functions to serving as an innovation-promoting knowledge hub (Youtie et al., 2008). In this role, universities have become deeply embedded in the regional innovation system and are key actors in promoting technological innovation and economic development in their regions of influence (Juanola-Feliu and Samitier, 2009). Today, universities actively seek to foster interactions and spillovers so as to link research with application and commercialization. As a result, the processes of the creation, acquisition, diffusion and deployment of knowledge are at the core of the university's functions (Juanola-Feliu, 2009).

Although nanotechnology is still very scientist-driven, interestingly, it has been found that the most nano-oriented researchers are actually more keen to apply their results in the private sector. However, it is widely acknowledged that their basic research orientation could hinder any actual interaction with firms. Thus, the role of the University Office for Technology Transfer (UOTT) and its innovation managers are essential for promoting technology transfer and engaging researchers to ensure their achievements attain market integration. By way of a case study, this paper provides a successful example of nanotechnology embedded in a commercial product in which public R&D investment has played a key role. The product under study is a new integrated implantable nanobioelectronic device developed following the value chain of R&D implemented within the Department of Electronics at the University of Barcelona, with the participation of other publicly funded organizations: the Institute for Bioengineering of Catalonia (nanobiosensors) and the Spanish Biomedical Research Network in Diabetes and Metabolic Diseases (diagnostics and clinical research).

Medical innovations depend heavily on the breaking down of barriers that have long prevailed in the academic world in the form of the boundaries that have seen the discipline coalesce into separate departments. To be specific, some of the most significant breakthroughs in the Life Sciences have come from the realm of the Physical Sciences (Rosenberg, 2009). Here again, to strengthen medical and clinical infrastructures geographically and organizationally, schools with university departments have generated new opportunities for transfers of instrumentation and techniques across disciplinary boundaries.

One way to ensure success in such attempts at cross-disciplinary interaction is to examine the way scientific knowledge flows between engineers, researchers and physicians while involved in efforts to develop or improve diagnostic devices. Clearly, the main characteristic of a nano-enabled biomedical project is its multidisciplinary context and the need to foster integration of knowledge of various dimensions (Linton and Walsh, 2008a). Fig. 5 shows the R&D value chain leading to the nano-enabled implantable device for in-vivo biomedical analysis introduced in this paper, and Fig. 6 shows the main actors and activities leading to a successful technology transfer and commercialization of public-funded nano-enabled medical devices.

Basic and applied research is hosted within university departments and research institutes, where the convergence of science and engineering disciplines at the nanoscale is the current trend for solving new scientific and technological challenges. The university services that promote technology transfer and innovation management play a key role in the subsequent industrialization of this research. In this regard, the sharing of facilities at Scientific and Technology Parks combined with incubation support for technology enhancement add value to the process. Clinical research is developed at the university hospitals in a multidisciplinary-based, technology feedback process that leads

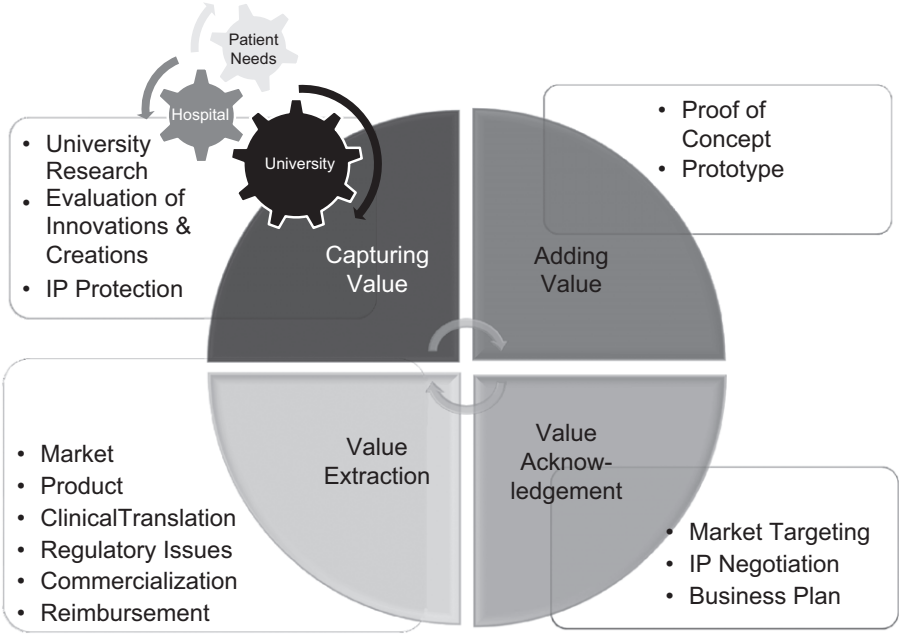

Fig. 5. Overview of the value cycle from research to the commercialization of a new medical device.

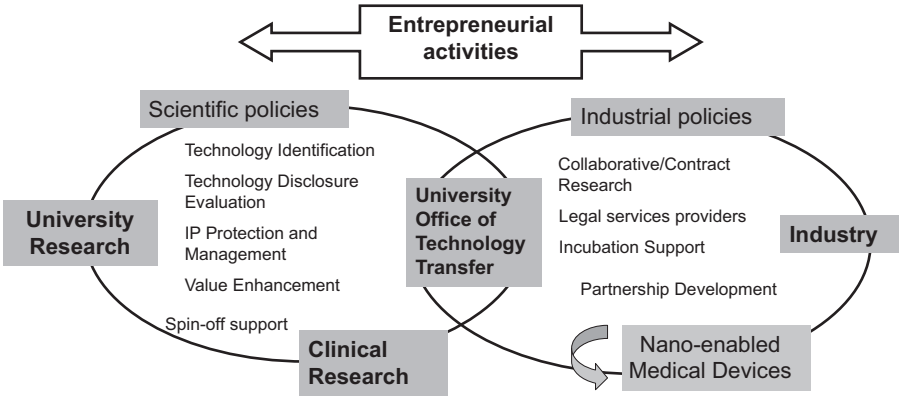

Fig. 6. Overview of the main actors and activities involved into the technology transfer process of public-funded research.

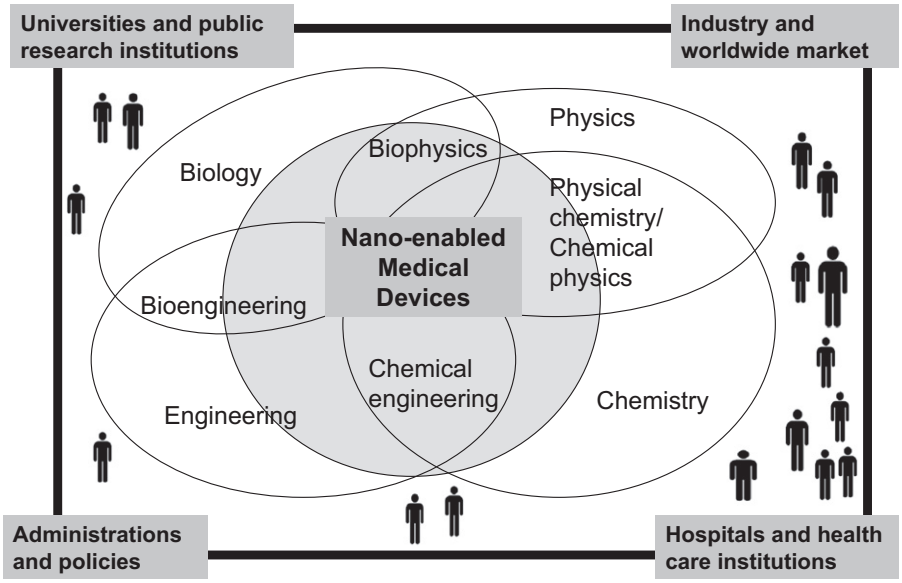

Fig. 7. Innovation ecosystem in biomedical engineering for nano-enabled medical devices: cross-fertilization and blurred disciplines.

to the development of safe, useful biomedical products. Market penetration is supported by business agencies that provide funding, IP protection and help with successful commercialization, as well as by ethical observatories. As a result, the product's technological attributes are a continuous flow of product ideas and technologies embodied in the final product in which the organizational environment and the interdisciplinary research define their social and economic assets. In this way, firms obtain ideas that later lead to the creation of new products and processes, and the university identifies new areas of research.

When employing a method for identifying creative scientific research accomplishments in two fields (nanotechnology and human genetics), it was found that creative accomplishments are associated with small group size; organizational contexts that enjoy sufficient access to a complementary variety of technical skills; stable research sponsorship; timely access to extramural skills and resources; and facilitating leadership (Heinze et al., 2009).

5.2. A new ecosystem for nano-enabled biomedical innovations

Over the last four decades, research in biomedical engineering has led to the manufacture of cutting-edge medical instruments. For example, the introduction of endoscopes into surgical practice is considered one of the biggest success stories in the history of medicine. However, in order to develop appropriate medical instruments or procedures, a key issue for successful biomedical research is the ability to understand effectively the requirements of the medical practitioner (Arntzen-Bechina and Leguy, 2007). Furthermore, the two main actors, namely universities and industry, involved in the development of new technologies need to collaborate and cooperate to a much greater extent (Gilsing and Duysters, 2008; Messeni Petruzzelli, 2011; Bianchi et al., 2011). Hence, the process of knowledge flow between the various stakeholders involved in the design of medical instruments is of utmost importance. Fig. 7 shows the framework for a balanced innovation ecosystem in biomedical engineering in which nanotechnology is gaining increasing relevance, as the manipulation at the nanoscale provides new innovative products and processes thanks to cross-fertilized knowledge. Thus, a general framework should be delineated to facilitate the understanding of both technical and medical requirements.

As a result, new tools and procedures for the public good can be developed by ensuring close cooperation between University, Hospital, Industry and Administration (Islam and Miyazaki, 2009; Hernández-Espallardo et al., 2011). As such, it is vital to understand the mechanisms and channels of knowledge sharing and transfer between the University–Hospital–Industry–Administration–Citizenship 5-helix engine, as well as to identify and support entrepreneurs within the innovative ecosystem (Hoye and Pries, 2009).

There are close research ties between industry and academic institutions in the biomedical field. This observation might be further amplified by noting that there is no significant distinction between the more academic institutions, such as hospitals and firms, in their production of medical devices (Mackenzie et al., 1988). When alliance activity was examined in a large sample of biotechnology firms (Stuart et al., 2007), it was found that many young biotechnology firms were exploiting this framework by acting as intermediaries in tripartite alliance chains: they enter by establishing partnerships with public upstream research institutions, and later they initiate a commercialization process by establishing alliances with downstream firms. Although this analysis is undertaken in the biotechnology sector, it is believed that the processes described are relevant to other, science-driven high-technology industries such as the emerging field of nanotechnology. Further evidence for strengthening public–private alliances comes from the new role of the university: many universities have seen their traditional missions of educating students and advancing understanding evolve to include the patenting and commercialization of research discoveries, as they become much more proactive in their commercial efforts, particularly during the last few decades (Di Gregorio and Shane, 2003). Actually, the modes of interaction between university researchers and firms can take on a broad range of formal and informal shapes enhancing technology transfer from universities to firms. The common approach in the literature is to focus on tangible outcomes such as patenting and the licensing of research results, but in the case study presented in this paper we argue that a broad perspective of the outcomes of technology transfer should be used including both tangible and intangible outcomes. This means technology transfer also involves the related knowledge whereby firms receive ideas that later lead to new products and processes, and universities can identify new research areas (Bozeman, 2000; Landry et al., 2007). Whatever the case, the rate of commercialization of university inventions is very low, particularly in those instances where there is a lack of adequately trained staff and insufficient capacity to process inventions in the University Office of Technology Transfer (UOTT). High-tech inventions originating from university labs may well need market space/niche identification, new market creation, and the translation of the lab result into an "investor friendly" business plan (Swamidass and Vulasa, 2009). Although technology transfer to the new biomedical firm involves certain familiar components, including the background of the entrepreneur and the "spin-off" effect, previous studies suggest that the technology transfer process is quite specific in the field of biomedicine (Roberts and Hauptman, 1986).

Specifically, we encounter a highly ambitious process for in-vivo biomedical implantable devices that covers the entire value chain from basic research, through engineering and technology, to industry and the required infrastructure, and to the implications for society and current market challenges. In this context, the whole value chain is hosted by the university system, which highlights the societal turnover of the public research investment.

6. Nanobiotechnology commercialization and management challenges

6.1. Commercialization of the university research

Nowadays, the commercialization of university-generated knowledge is closely linked to the recently emerging, highly scientific component of technology present in key industries. Since the universities are generating a large share of the production of scientific results, the interface between academia and industry has had to be brought into sharp focus. To facilitate technology transfer from the university to the commercial sector, the active involvement of university inventors with strong incentives from the technology market is required, at the same time as steps are taken to ensure that the disincentives from within the university environment are not excessive (Goldfarb and Henrekson, 2002). Thus, in order to reach the final lap of commercialization in the value chain described in Section 5, significant academic freedom to interact with industry, including significant involvement in new firms, is highly recommendable. Moreover, recent findings suggest that nanotechnologies and emerging markets present unique challenges and opportunities for those entrepreneurs (from research groups and firms) focusing on the competitive advantage of the current scenario of emergence of technologies (Malanowski and Zweck, 2007; Thukral et al., 2008).

Various authors claim, however, that current data do not support the widely held expectations that biotechnology will have a revolutionary impact on healthcare and economic development (Nightingale et al., 2007). Yet, nanotechnology advances could increase productivity and enhance the speed and coverage of diagnostics and therapeutics following a well-established incremental pattern of technological change and 'creative accumulation' that builds upon, rather than disrupts, previous drug or medical device development.

Needless to say that nanobiotechnology commercialization gives special emphasis to nanomedicine outputs, where research and medical applications are heavily funded by governments and the private sector. The focus on nanomedicine enhances the high value chain for applications of this kind that are emerging from a context of converging technologies in which nanotechnology is establishing itself as a new industrial revolution and as a global economic model of "green growth".

6.2. Management of the university innovation

Although nanotechnology and biotechnology exhibit similar technological evolutionary patterns (Rothaermel and Thursby, 2007), nanotechnology has the potential to affect a broader range of industrial sectors than biotechnology (Youtie et al., 2008; Juanola-Feliu et al., 2004). In another study, conducted for a similar model (Nikulainen, 2007), it was found that nanotechnology is linked to a variety of industries, and in particular to those with higher than average R&D intensity. These findings suggest that nanotechnology is connected in a variety of ways to a diverse set of industries. What remains unclear in the literature, however, is whether nanotechnology transfer between different actors takes unique forms. In particular, very little is known about nanotechnology transfer from universities to firms. Any further development of nanotechnology will depend largely on the degree to which existing firms and industries are able to identify commercial applications. This will, in turn, depend on the degree to which the scientific knowledge that is being created can be transferred from public sector to private sector research (Nikulainen, 2010). Though nanotechnology remains very basic research-oriented, it is still important to understand whether there is demand already from the private sector for this potentially revolutionary technology.

According to market research information provided in the report World Diabetes Market Analysis, 2009–2023 (Bharat Book Bureau, USA, February 2009), in 2007, the diabetes treatment market worldwide was worth over $25 billion, and had double-digit growth from the year before. Consequently, it is one of the largest sectors in the global healthcare industry. All segments of the diabetes therapy market have been expanding, but the area that is expected to grow most rapidly in forthcoming years is the

needle-free devices for diabetes diagnostic, specially for periodic, regular glucose level monitoring and insulin dispensing.

Thus, the Department of Electronics at the University of Barcelona, in collaboration with the Institute for Bioengineering of Catalonia (IBEC), the Biomedical Research Networking Centre in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN) and the Biomedical Research Network in Diabetes and Metabolic Diseases (CIBER-DEM), have promoted an alliance with the aim of developing a cutting edge multidisciplinary research and commercial team covering the entire range from applied research to clinical diagnostic. In this way, research centers, hospitals, firms, health policies and citizens share the same goal: launching onto the market safe, reliable and affordable biomedical devices for the diagnostic and therapy of diabetes, improving the quality of life of those who have to control their blood sugar level by on-line monitoring and keeping the requested glucose level constant (by using a Radio Frequency activated clock-alarm or with exact doses administered directly from an insulin reservoir). The aim of this section was to describe the huge market challenges for a wide product segmentation of biomedical devices, and how to manage them into a public-funded R&D&I environment; the medical conditions and indications themselves have not been considered in this paper as they lie beyond its scope.

7. Conclusions and final recommendations

In this paper, the design of a generic in-vivo implantable biomedical device capable of detecting threshold values for targeted concentrations (i.e. detection of glucose levels) has been presented. Given the speed with which diabetes can spread and the improvements that are possible in its diagnosis and control if needle-free systems are available, the medical device introduced in this paper is designed to reach a huge market over the next few years. Moreover, when the entire value chain is publicly funded, this means that the goals of technology transfer from university to industry and the social returns on the public investment have been fully realized. Thus, a successful model for research, innovation and technology transfer can be introduced to a particular scenario typified by the convergence of technologies and disciplines, as well as by the convergence of various stake-holders combining representatives from research centers, hospitals, market, policy centers and citizens as well.

Although the case study reported in this paper is complex because it involves multiple organizations and sources of data, it contributes to extend experience to the best practices and models on nanotechnology applications and commercialization. Moreover, this case study could provide a basis to apply solutions to commercialize nano-related products understanding the complex real-life situations and learning from the everyday experience on facing market challenges by academic research.

The complete overview provided here of the value chain of research and technology transfer processes highlights the importance of a common framework in which multidisciplinary teams and organizations can work together directed by determined scientific leadership. In this specific case, the Department of Electronics at the University of Barcelona has had overall charge of the research and commercialization activities. The resulting biomedical device is nano-enabled in a dual sense: when miniaturizing the system (fluidics, electronic, energy autonomy) and when new functional structures are included (nanobiosensors developed by the IBEC). The CIBER-DEM joins the value chain when clinical research and commercialization are considered. Still an emerging technology, the future ASIC will work with an array of nanobiosensors with different targets, and it will define the configuration of the measurement method. Each array will be used to detect a specific type of target, and the multiplexed system will be used to analyze each array focusing on a particular target. Then, top down approaches using nanoengineering and nanofabrication and bottom up approaches using supramolecular chemistry can produce novel diagnostics which will increasingly focus on delivering a personalized solution based on the analysis of array data in real time, and where appropriate, applying this decision to deliver an automated therapy (theranostics).

This paper has sought to contribute to the analysis of the interaction between the various factors involved in the process of technology diffusion by extending the discussion to the commercialization of nanotechnology, an issue that has gone largely unaddressed in the literature on nanotechnology. What is required is closer and more regular collaboration between industry, hospitals and scientific facilities to guarantee the commercial success of biomedical research. Clearly, the speed of change being recorded in markets, products, technologies, competitors, regulations and even in society means there are significant structural variations and public R&D challenges in commercializing nano-enabled implantable devices for in-vivo biomedical analysis.

In conclusion, despite the somewhat limited availability of information discussing the safety of medical nanomaterials, the case study presented in this paper is a clear demonstration of how to strengthen the bonds between the science community, hospitals and industry. The process described offers an efficient method for performing experiments at large test and clinical facilities, within an innovative framework that takes advantage of new scientific tools and discoveries. Biomedical devices represent a strategic gamble for the future of Spain's scientific and technological policy areas as they seek accelerated economic growth within the knowledge-based society. In this way, the country's regions can strengthen the network links between their R&D agents – science and technology parks, institutes and research centres, hospitals, technology platforms and incubators – as they explore and confront the new scientific and market challenges presented by the nanotech life sciences.

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