GRUP

Connect-EU

Nanobio + Nanomed

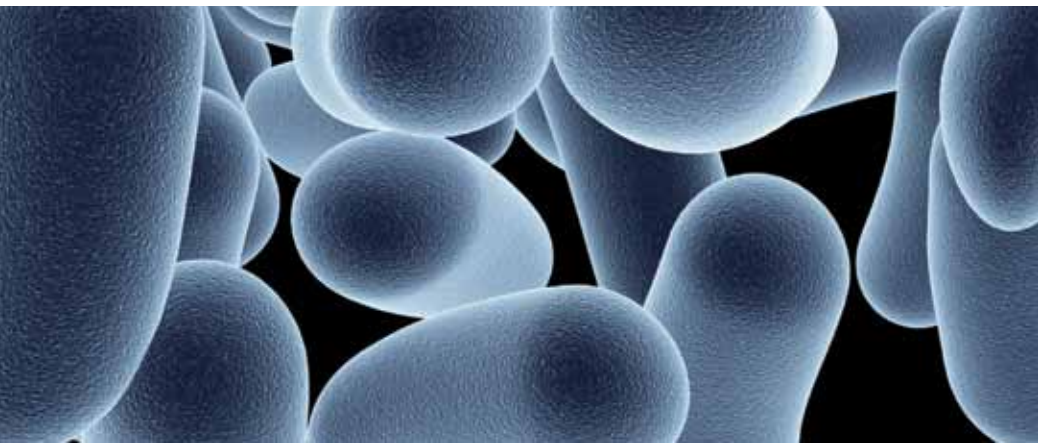
Strategic Research Agenda (2011)

Connect-EU Nanobio + Nanomed
Institute for Bioengineering of Catalonia (IBEC)
c/Baldiri Reixac, 10-12
08028 Barcelona
e-mail: info@ibecbarcelona.eu

www.connecteu-nanobionanomed.cat

This document was designed and produced by the Communications Office of the Institute for Bioengineering of Catalonia (IBEC).
www.ibecbarcelona.eu

With the support of:



Contents

1. Introduction 7

1.1 Nanobiotechnology definition 7
1.2 Nanobiotechnology applications: impact and opportunities 8
1.3 Current state of nanobiotechnology in Europe: policy-making aspects 10
1.4 Nanobiotechnology in FP7 programmes 12
1.5 HORIZON 2020: Common strategic framework 13

2. Nanobiotechnology in Catalonia 17

2.1 The Connect-EU Nanobio + Nanomed group of experts: Why and what for? 17
2.2 Current status 17
2.3 Research landscape 19
2.4 Industrial landscape 22

3. R&D priorities 23

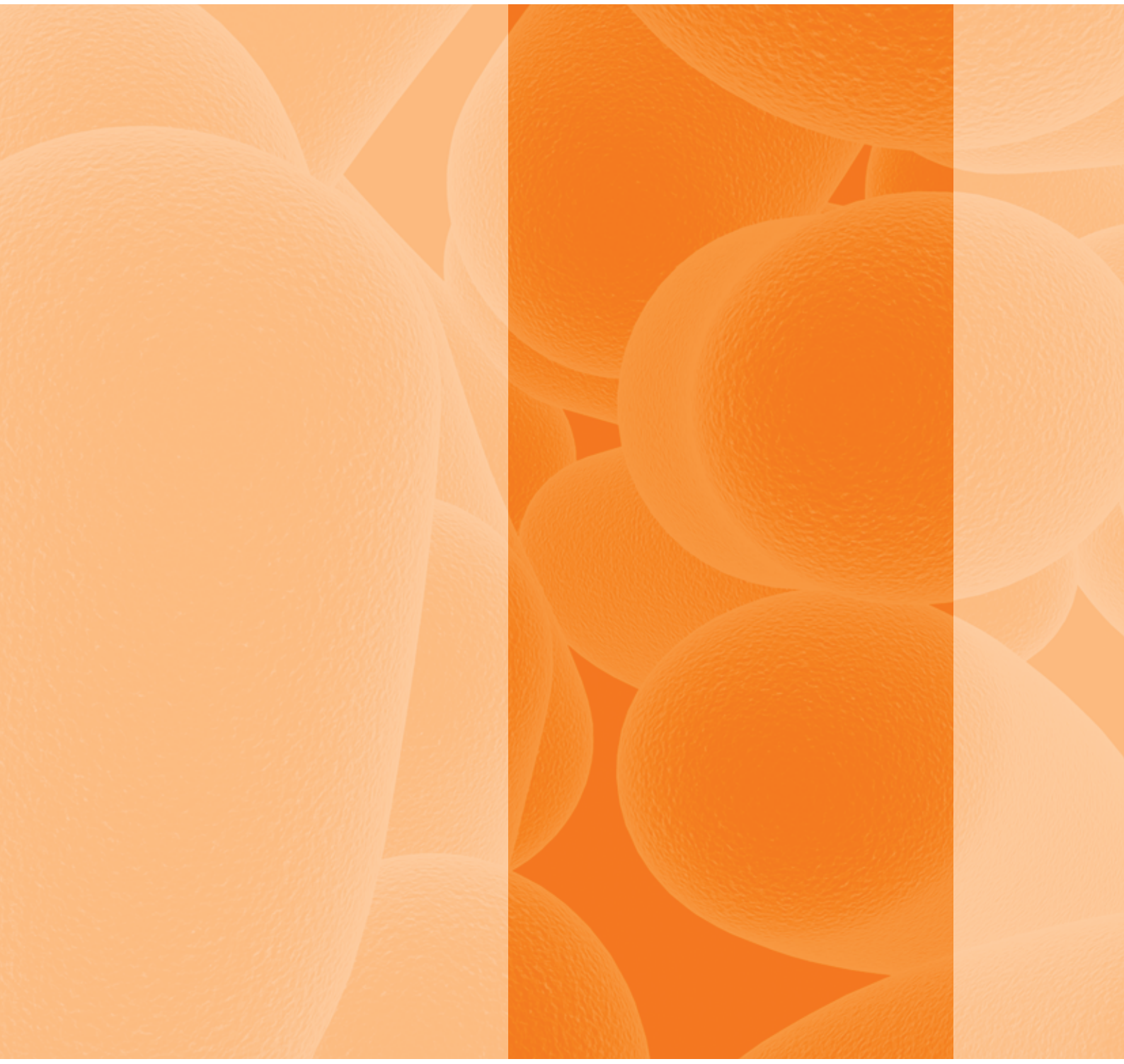
3.1 Pharma: Human and animal health 24
3.2 Medical Technologies: Diagnostics 26
3.3 Medical Technologies: Biomaterials and regenerative medecine 28
3.4 Food technology 30
3.5 Nanosafety and environment 32

4. Strengthening the research base 33

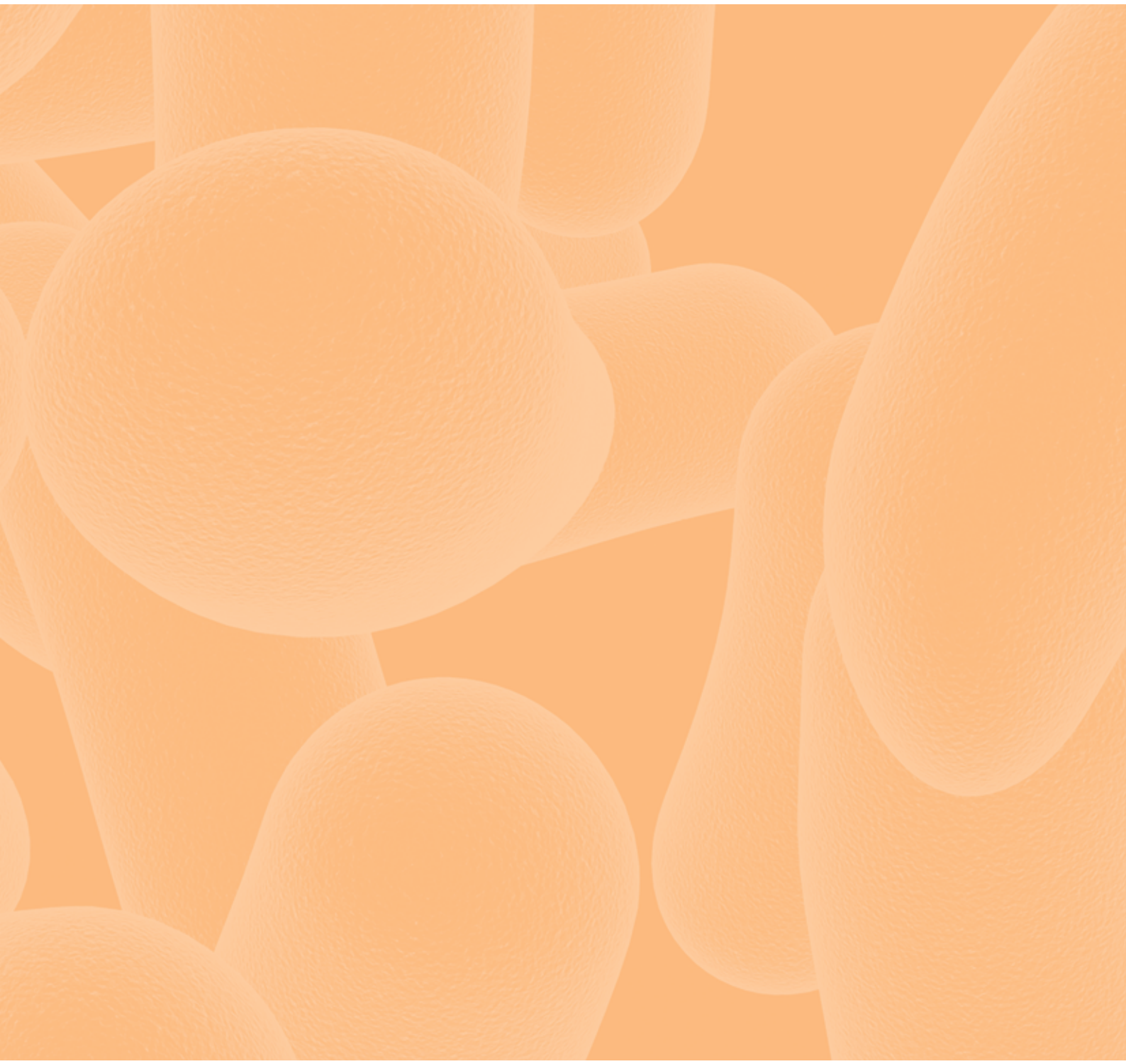
4.1 Interdisciplinary talent 33
4.2 Support to infrastructures 34
4.3 Coordinating activities 35

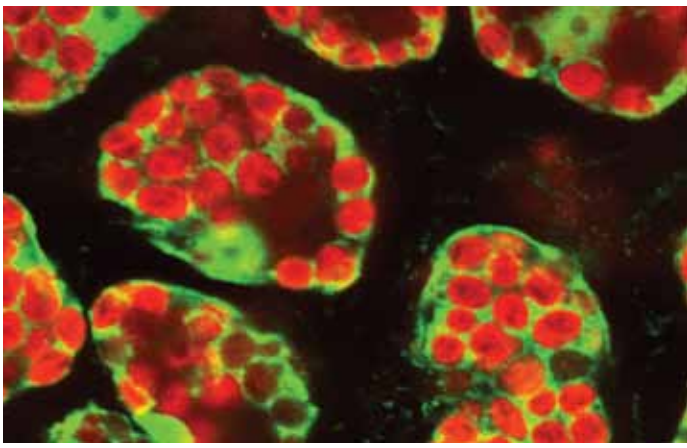
5. Conclusions 37

Contributors 39
Bibliography 40
Appendices 43



Strategic Research Agenda (2011)





1. Introduction

1.1 Nanobiotechnology definition

Nanobiotechnology represents the convergence between nano- and biotechnology and includes all methods and techniques at the nanoscale (10^{-9}m) that can serve to control and characterize biological matter. These techniques are therefore used to study and modify biomolecules (proteins, acids nucleics and others) and cells. Much of what is known about bulk properties of materials breaks down at these scales. Nanomaterials such as carbon nanotubes and gold nanoparticles have physical properties that are different from their bulk counterparts. These divergences generate new opportunities and applications.

Besides the application to study biosystems, researchers also learn from biology to create new micro-nanoscale devices and better understand life processes at the nanoscale. Nanobiotechnology encompasses three core research capacities:

- **Synthesis and fabrication of nano-structured materials:** Due to quantum effects, increase of surface vs. volume and the capability to auto-organize observed at nanoscale, nano-structured materials interact accurately with cells and biomolecules. This behaviour enables the detection of molecular scale phenomena and opens up new avenues in the modification of molecules and cells individually.

- **Characterization:** The use of nano-tools to explore matter (microscopy techniques with nano-scale resolution) unveils specific properties of the complex architecture of biomolecules, their dynamics and topography.

- **Nanobioengineering:** Accurate observation with nano-tools combined with the fabrication and synthesis of nano-structured materials creates biomimetic materials with improved biocompatibility and surfaces with specific nano-patterns. Biology provides concepts of natural construction and self-assembly that inspire revolutionary possibilities to structure matter.

Nanobiotechnology is the most complex sub-area of nanotechnology. Conceptually, its successful implementation requires the integration of nano- and biotechnology. Progressing with nano capabilities and subsequently applying them in biological systems is not the right approach. With an intrinsic interdisciplinary nature, the advance of nanobiotechnology is dependent on a close collaboration between life scientists, physical scientists, and engineers, with the contribution of clinicians in the aspects of medical applications. Nanotechnology applied to healthcare – usually called nanomedicine – is one of the key enabling technologies to achieve and enable earlier and more precise, individual diagnosis (the sooner, the better the treatment), better targeted therapies (fewer side effects) and better therapy monitoring (faster recovery). Thus, nanomedicine is understood

to be a fundamental instrument for personalized and sustainable medicine.

1.2 Nanobiotechnology applications: impact and opportunities

The next decade will see the advent of a new phase in nanotechnological research, encompassing not only "conventional" applications (for example, in nanoelectronics) but also many new applications in a diversity of products, situated in the area of humans and their environment. It is also expected that nanotechnology will make a major contribution to several problems on a global scale, such as energy supply and public health.

Nanotechnology is considered as a main enabling technology for the 21st century and the basis for a new industrial revolution. At the moment, nanotechnology is making an entrance in various application areas, ranging from food, health and energy provision to water purification, for example. Figure 1 reflects the application areas of nanotechnology companies in the European market. The figure demonstrates the diversity of the application areas within nanotechnology. It clearly shows that public health and life sciences form an important economic driving force for nanotechnology.

Many sectors will benefit of the nanobiotechnology application in products from sectors such as pharmacy, medical technologies, veterinary, environment, cosmetic, food and industrial biotechnology.

Regarding the environmental management, the benefits to be gained from nanobiotechnology are particularly important. The nanobiotechnology contributes with tools and protocols to study effects of fabrication and the use of nano-structured materials in the environment and animal/human health. These concerns are included under the "nanosafety" concept. The proper implementation of this framework is fundamental to ensure the Europe competitiveness in nanotechnology commercial development, as well as representing new opportunities by themselves for the services and manufacturing industry.

World public health will definitely benefit from the continued development of nanotechnology. Nanomedicine is thought to be the instrumental for improved and cost effective healthcare, one crucial factor for making medicines and treatments available to all. Therefore, it is regarded as an important set of tools to deal with the major challenge of an aging population. Disruptive technologies such as nanotechnologies in

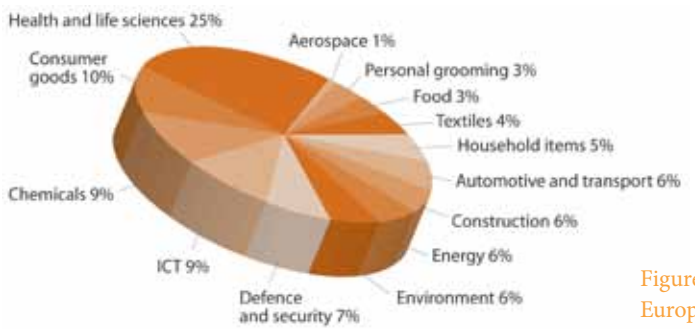


Figure 1: Application areas of nanotechnology per sector in the European market (2007). Source: "Strategic Research Agenda – Nanotechnology", Netherlands Nano Initiative, 2008

medicine create or pull on new supply chains, and thus it is most important to implement measures that help this supply chain being created in Europe.

Nanomaterials and devices provide unique opportunities to advance medicine and could impact diagnosis, monitoring, and treatment of diseases as well as to control and understand biological systems. On the one hand, it is estimated that nanobiotechnology techniques implementation in pharmaceutics and medical products will impact in a $197 million worldwide market (Datamonitor studies 2009). In recent years, the interest in basic knowledge on cell-substrate interaction has grown increasingly, as it has now been recognized to play a key role in the differences observed in cell behavior when comparing *in vitro* and *in vivo* culturing. This represents a crucial factor in the fields of tissue engineering, drug development and regenerative medicine. Cells in their natural environment are surrounded by nanostructures when contacting with each other (membrane have nano-size features) or with the extra-cellular matrix. The knowledge of these interactions is the basis of developing new and more suitable scaffolds for implants applied to tissue engineering. Moreover, in combination with the capabilities of stem cells we are at the beginning of a new era of clinical therapies based on regenerative medicine.

New diagnostics based on nanotechnology could offer an earlier and more personalized assessment before symptoms show up. It's clear that the main advantage of nanomedicine on quality of life and healthcare budgets is earlier detection of disease, leading to less severe and costly therapeutic demands, and improved clinical results. Nanobiotechnology-based devices and procedures will provide crucial input for clinical decision talking and therapy planning by new *in vitro* and *in vivo* test and diagnostic lab-on-chip or imaging systems. Finally, nanotechnology can also improve therapeutic systems by means of the development of targeted delivered drugs.

Nanotechnology application in clinical medicine not only will enforce European enterprises competitiveness in sectors where they currently lead, but also will contribute with exceptional solutions of European interest. These contributions will ensure the quality of health services sustainability and maintain the patient cost-profit balance in the framework of European population aging problem.

The fact that biomedical applications have to validate used materials biocompatibility generates lots of knowledge and know-how. At the same time, this is a high regulated sector that strictly tests fabrication processes. Therefore, it fosters new technologies in cosmetic sector, animal health and biotechnology in food and industry. These more accessible sectors, which sometimes are used to market new products, have been used first nanotechnology applications.

Biotechnology's contribution is key to industry development and to progress. Europe, with the aim of competing with the USA and bringing together a critical mass that can compete in the knowledge-economy field, has decided to bet on the life sciences sector as a driver of the new economy, knowing that in the near future the healthcare and wellbeing market, which is key in 21st century society, will be dominated by biotech products.

1.3 Current state of nanobiotechnology in Europe

The application of nanofabrication techniques contributes improved functionality, portability, integration, communications capacities, and intelligence in materials to breakthrough innovation in many sectors, as commented in the previous sections. Nanotechnology deployment and transfer to the market has been a priority for the European Commission since the beginning of the past decade, and lately, it has been pointed out as a pivotal area to overcome Europe global financial crisis. Several policy measures have accompanied three stages in this deployment.

During an initial adoption period (2004-2007) a variety of materials and products with some business success and notables failures started to emerge. Nano-structured materials and nano-particles have been incorporated into a growing range of products and processes. This initial stage was simultaneous to the beginning of the Seventh Framework Programme (FP7) as the cornerstone of the funding of R&D at European level.

Several public/private initiatives have been created to build a coordinated scenario. European Technology Platforms are examples of efforts to gather all related stakeholders (industry, academia, government) to work in the same direction. European Technological Platforms gather R&D stakeholders from a specific sector, and are led by industry. As starting point, the Technological Platforms are expected to define a Strategic Research Agenda (SRA) about social relevant themes in a specific sector where European growth, competitiveness and sustainability objectives, in the middle- to long-term, depend on technological advances.

In the area of interest, the ETP-Nanomedicine platform launched its SRA at the end of 2006 and delivered the document "Roadmaps 2020" in October 2009, guiding medical and pharmaceutical product development. Both documents have been the basis of many calls in the period 2007-2011 under the programmes of NMP and HEALTH in the Nanobio+nanomed topic. In the area of health, efforts have been focused on detection and diagnosis, where the European Technology Platform Nanomedicine (ETPN; **www.etp-nanomedicine.eu**) has a key role establishing a strategic vision, identifying priorities and boosting innovations in nanotechnologies for medical use.

One of the novelties funding instruments and programmes in FP7 was linked to the ETP's creation, namely the Joint Technological Initiatives (JTIs). JTIs have been created to facilitate industrial participation and improve private-public cooperation in European level research. These research programmes are co-funded for private sector, European Commission and member states. JTIs are linked to European Technological Platforms and can be considered an evolution of the aforementioned platforms. Two of

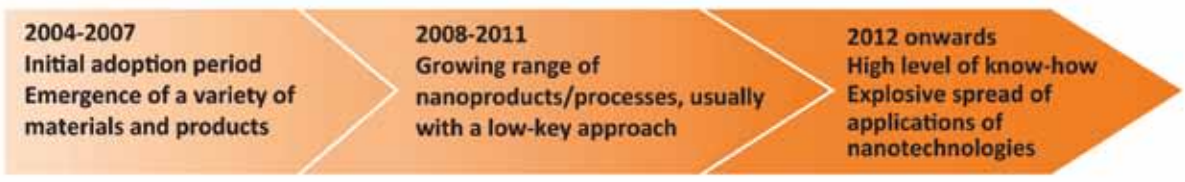


Figure 2: The three stages of nanotechnology in Europe. Source: Burton Lee and Innovarium Ventures 2010, May 2010

the original seven JTIs work on the nano and biotechnologies cross-over and their applications: 1) ENIAC Joint Undertaking (JU) and 2) Innovative Medicines (IMI). ENIAC-JU was created in 2008 with the purpose to implement a research programme oriented to improve integration and miniaturization of devices and increase their functionality. ENIAC-JU gathers members from EC, represents from member states as well as members from AENEAS business association. AENEAS represents manly actor of R&D in nanoelectronics in Europe (Enterprises and research institutions). IMI is a public-private partnership between the European Union, represented by the European Commission, and the pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The European Union and the pharmaceutical industry have joined forces to make the drug discovery and development process in Europe more efficient and to enhance Europe's competitiveness in the pharmaceutical sector.

However, introduction of these new technologies raised ethical and safety problems. In this second state appeared new public and private initiatives to deal with above problems and coordinate future research and funding. In this second stage (2008-2011) Europe has prioritised three major areas: health, environment and energy. Fragmentation of resources, affecting allocation and knowledge transfer, was identified as an issue affecting the advance of nanotechnology. This was particularly incumbent to areas such as standardization and regulatory affairs for new products and manufacturing processes.

In this direction, several "project clusters" have been created in this second period, aiming to coordinate projects and improve knowledge exchange in related topics, under the auspices of the Directorate of Research at the CE. Nanobiotechnology-related examples include the EU NanoSafety Cluster, the Drug Delivery Cluster and the Micro Nano Bio Systems (MNBS) Cluster. The Nanosafety Cluster aims to maximize the synergies between the existing FP6 and FP7 projects addressing all aspects of nanosafety including toxicology, ecotoxicology, exposure assessment, mechanisms of interaction, risk assessment and standardization. The MNBS cluster gathers projects targeting micro/nano-systems and applications that have, or interact with, biological components. The MNBS cluster includes applications in health, environment and the food and beverage industry. The projects follow different strategies but with the same major target of achieving substantial improvement on system integration (e.g. miniaturization and reduced power consumption, integration of molecular and cell biology) on system quality and/or reliability and shorter time-to-market.

The establishment of NANOFUTURES has also to be highlighted. It is a coordination platform with the mission to overcome the sector-wise fragmentation and accelerate the commercialization of nano-based products. NANOFUTURES gather stakeholders representing all the previously existing technology platforms with an interest in nanotech, to join forces in carrying forward industrialization to benefit the European economy and all of its citizens.

Nowadays, in the third stage of European nanotechnology, an explosive spread of application is expected with a deeper penetration of nanotechnologies in many markets. Within this context, new issues such as regulating problems and translation of research results into products are positioned as top priorities.

In the area of nanomedicine in particular, it has been seen that the majority of European projects often turn out to be non-translatable from the outset. When tackling the problem of translation in nanomedicine

two questions arise: Why is translation a problem in Europe? What is missing? These are the current challenges.

1.4 Nanobiotechnology in FP7 programmes

The 7th Framework Programme for Research, Technological Development and Demonstration activities (FP7) is the main EU's research support instrument for the period 2007-2013. Of the €54.6 billion total sum, 25.8 billion was committed over the first four years (2007-2010), while the remaining €28.8 billion must still be programmed in the final period 2011-2013, which amounts to €9.6 billion a year on average. Beyond 2013, a new Common Strategic Framework (CSF) will be launched, with a new name: HORIZON 2020, to be built up from FP7 results as well as European Innovation Technologies (EITs) and Competitive and Innovation Framework Programme (CIP), in order to eliminate fragmentation and make sure EU-funded projects better complement each other, covering the whole value chain of innovation and help coordinate national efforts. HORIZON 2020 Multiannual Financial Framework was presented on 29 June 2011 and the strategy as a whole will be worth €80 billion.

FP7 is organized into several thematic programmes and four axes: COOPERATION, IDEAS, PEOPLE, CAPACITIES. Large scale R&D collaborative projects are funded under COOPERATION. The multidisciplinary character of nanobio/nanomedicine activities allows multiple funding programmes consideration, whose obvious shortcoming is fragmentation. Nanobio/nanomedicine related topics are usually funded under the NMP (Nanotechnologies, Materials and Production) program, but also can be included in funding programmes such as HEALTH, ICT and KBBE. The specific calls in NMP, HEALTH, ICT and KBBE (2007-2010) and corresponding allocated budgets are listed in Appendix 1. Adding the budgets allocated per theme, the overall funding devoted to nanobiotechnology just through COOPERATION is higher than €400 million in this period.

The European Commission has allocated a total budget of €3.5 billion (in the period 2007-2013) to R&D in Nanotechnologies, Materials and Production (NMP). Approximately one-third is devoted to the nanotechnology "pillar". In addition to these opportunities, the pillar "Materials" provides useful funding for the Nanobio+nanomed group-related topics, mainly focused on "Novel biomaterials" (NMP2.3).

Under HEALTH, these opportunities are focused in "Pillar I", aimed at emergent technologies applied to health. Predictions for the second period of FP7 predict more funding in clinical trials of nanodrugs and medical products based on nano. These topics are included in "Pillar II" of the HEALTH program. Projects that include nanobiotechnologies applications in food, environment management and animal health are funded in the KBBE programme, in particular, under the "pillars" KBBE-2 and KBBE-3. In the ICT programme, a significant number of projects that merge nanoelectronics, computing and nanophotonics with biotechnology are funded (Challenge 5.1). Nanobio+nanomed topics can also be funded under the FET and FET-OPEN programmes focused in the exploratory research. These programmes give opportunities to high risk and creativity projects (also known as "frontier" projects).

Funding opportunities channelled by means of ERANETs programmes, with the contribution of the

state members, must be added to the amount above. In particular, ERANET EURONANOMED (2009-2011) has been a remarkable instrument to foster innovation in nonomedicine with the participation of 24 agencies and 18 states. These projects funding were aimed to collaborative consortiums with members from technological research, hospitals and industry. These projects were mainly focused on the technology transfer part, to the market and to the clinic.

On top of the private-public collaboratives, existing opportunities in the generic (transversal) PEOPLE, IDEAS and CAPACITIES programmes. In particular, concerning frontier research in an emergent area such as nanobiotechnologies, it is worth commenting the IDEAS programme results. The European Research Council (ERC) was created in 2007 with the objective to fund frontier research in any area of knowledge. ERC activities are framed in the FP7 IDEAS programme with a budget of €7500 million in the period 2007-2013. ERC manages two funding calls: Starting Grants and Advanced Grants programmes. They should involve new, ground-breaking or unconventional methodologies, whose risky outlook is justified by the possibility of a major breakthrough with an impact beyond a specific research domain. Starting Grants are addressed to young researchers with 2-9 years of doctoral research experience and fund proposals with a maximum of €400.000 annually during five years. In 2009, 16 Starting Grants (out of 244 in all domains) with a core focus on nanobiotechnology/nanomedicine were funded. Advanced Grants are addressed to active researchers who have a track-record of significant research achievements in the last 10 years. Advanced grants will be up to €2.5 million for a period of 5 years. In 2010, 15 Advanced Grants proposals were accepted (out of 266 in all domains). However, the previously commented fragmentation is also evident in the ERC Grants management process: some of the nanobiotechnology projects are submitted to the Life Sciences Panel, whereas others are presented as Physical Sciences topics.

1.5 HORIZON 2020: Common strategic framework

The road towards HORIZON 2020 Financial Framework started in June 2010 with the adoption of Europe 2020 Strategy. Since then, diverse White Papers and public consultations have been launched during 2010-2011 to define the priorities of HORIZON 2020. Programmes reviewed above must be updated with new elements from next framework HORIZON 2020, new funding scenario in EU R&D until the year 2020.

Europe 2020 is the EU's growth strategy for the coming decade. In a changing world, the EU must be a smart, sustainable and inclusive economy. These three mutually reinforcing priorities should help the EU and the Member States deliver high levels of employment, productivity and social cohesion.

Concretely, the Union has set five ambitious objectives (employment, innovation, education, social inclusion and climate/energy) to be reached by 2020. Each Member State has adopted its own national targets in each of these areas. Concrete actions at EU and national levels underpin the strategy.

Europe's future economic growth and jobs will increasingly have to come from innovation in products, services and business models. This is why innovation has been placed at the heart of the Europe 2020 strategy for growth and jobs. With over thirty action points, the Innovation Union aims to improve conditions and access to finance for research and innovation in Europe, to ensure that innovative ideas can be turned

into products and services that create growth and jobs.

Recommendations related with the "**Key Enabling Technologies**" (KETs) and their implementation in the European industry are elements to keep in mind. It is also important to consider the new "**European Innovation Partnerships**" (EIP) created by the Commission stating that:

"Innovation contributes to tackling the most critical societal challenges we are facing. Europe's expertise and resources must be mobilized in a coherent manner and synergies between the EU and the Member States must be fostered in order to ensure that innovations with a societal benefit get to the market quicker. Joint programming should be developed."

The European Innovation Partnerships will aim to bring together key stakeholders from the demand and supply side; all actors in the innovation cycle, from research to translation (adaptation), deployment and final users, along with those engaged in standardization and regulation. It also wants to improve coordination and coherence between funding for research and innovation at European, national and regional level in Europe. This altogether will foster innovation in prod-

Figure 3: HORIZON 2020: objectives and structure (Source: European Research Area 2011)

ucts, processes and services, and in parallel facilitate the innovation chain and reduce the time to market for innovative solutions.

The launch of the pilot Innovation Partnership on active and healthy ageing is an important step in that context, with particular relevance to nanomedicine and its contribution to a different approach to healthcare.

The European Commission has identified active and healthy ageing as a societal challenge common to all European countries, and an area which presents considerable potential for Europe to lead the world in providing innovative responses to this challenge.

With the Innovation Union strategy, the European Commission aims to enhance European competitiveness while tackling societal challenges.

First traces of this new framework can be observed in HEALTH 2012 programme where many topics have been lastly modified to include references to EIP objectives. EIP detected impact is related with amount of funding already assigned on EIP defended topics.

The Europe 2020 strategy clearly signaled the importance of industrial competitiveness for growth and jobs as well as for Europe's ability to address above mentioned grand societal challenges in the coming years. Mastering and deploying **Key Enabling Technologies** (KETs) in the European Union is central to strengthening Europe's capacity for industrial innovation and the development of new products and services needed to deliver smart, sustainable and inclusive European growth.

The High-Level Expert Group (HLG) considers that the success of such a policy requires KETs to be positioned as a technological priority for Europe and for this to be demonstrably translated into the EU's main political and financial instruments in the next financial perspective 2014-2020.

The European Union (EU) identified six Key Enabling Technologies (KETs) for their potential impact in strengthening Europe's industrial and innovation capacity: **nanotechnology, micro and nanoelectronics, advanced materials, photonics, industrial biotechnology** and **advanced manufacturing systems**. In particular, KETs were recognized as playing an increasingly vital role in developing the required industrial and technological base indispensable for the delivery of smart, sustainable and inclusive European growth.

The report clearly highlights the vital role of applied nanotechnology and industrial biotechnology in furthering competitiveness and addressing the grand challenges facing the EU, as well as photonics. Scientific and Industrial Policies must be focused and aligned in order to to create more synergies between the diverse instruments to boost Europe's capabilities.

Combinations of KETs are embedded at the core of most advanced products, a nano-bio-info convergence example might be a real-time avian flu test instrument, incorporates biotech labels, microelectronics chips, laser based photonic detection, and nanotechnology optimized surfaces for fluidic processing. Mastering of KETs is absolutely required to ensure that we can produce within Europe, future innovative products and is therefore a strategic priority to ensure the competitiveness of European industry.

2. Nanobiotechnology in Catalonia

2.1 The Connect-EU Nanobio + Nanomed group of experts: Why and what for?

The Connect-EU Nanobio + Nanomed group is working to foster Catalan participation in European-level collaborative projects where nano-biotechnology can add value, such as healthcare, animal health, environment and other industrial sectors. Furthermore, the group works in the identification of the topics of major interest to improve this participation in FP7 projects (2012-2013), and define the most useful instruments beyond 2013, under the HORIZON 2020 framework. The mapping of the research capacities, industrial interests and subsequent R&D+I priorities are the basis for this Strategic Research, which summarizes the current potential and the future intentions.

Applications of nano-biotechnology represent huge innovative possibilities for all life sciences sectors. Moreover, nanobiotechnology is the base of nanosafety, which has to serve as a horizontal tool to the chemical and materials-users sectors (construction, automobile, aeronautics, etc). However, the life sciences sectors (see section 2.4, Industrial landscape) are, as a whole, one of the pillars of Catalan economy, and the ones more highly dependent in research-based innovation.

This Strategic Agenda aims to become a reference document for the next national decisions and a route map for the relevant stakeholders in nanobiotechnology. This document has been written at the request of ACC1Ó (Catalan Government agency for competitiveness), and points out the generic research themes and application areas that are crucially important to Catalonia. The agenda describes the Catalan research scene in the area of nanobiotechnology, particularly in the sub-area of Nanomedicine; identify necessities and capacities and sets out the new European research programmes (HORIZON 2020) which can fit better with Catalan industry needs and boost Catalan research capacities.

2.1 Current state

Catalonia has become one of the top hubs of excellence in nanoscience research and development in southern Europe, as proven by publication statistics. The metropolitan area of Barcelona is the third European district (behind Paris and Munich) in the number of scientific publications in nanobiotechnology. The Catalan leader position in nanomedicine, in particular, is the result of the synergic opportunities between investments in nanoscience and biomedical research, with clinical excellence with wide tradition in this region.

Catalonia is a highly attractive biocluster for the international sector due to its many assets, strategic location, and skills in nanotechnology, clinical research, structural biology and technology platforms, applied in key fields like oncology, neurosciences, personalized medicine and cardiovascular diseases. The international sector has high hopes for the BioRegion, as they

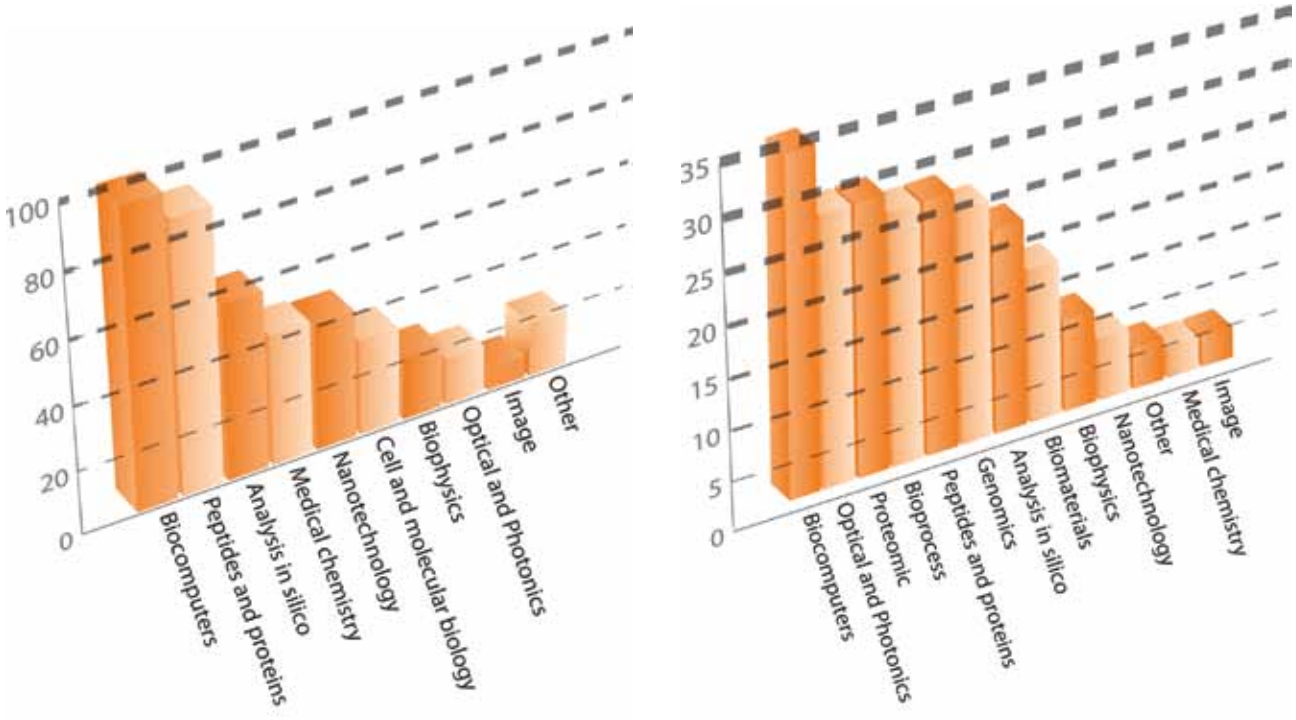


Figure 4: (left) Technologies used in research by Catalan companies (Biocat report 2009); (right) technologies used by Catalan research groups

see Barcelona being one of the key cities in the global biotech panorama in the next years. There is no other region in Spain with more potential than Catalonia: political participation, critical mass of researchers, prestigious universities, hospitals with proven research, developed science and technology parks, a renowned biotechnology industry, and the commitment of all participants involved.

Biocat, the organization driven by the Government of Catalonia and the Barcelona City Council that coordinates, promotes and drives the BioRegion – the Catalan biocluster – has a joint strategy for the life sciences, biotechnology, pharmaceutical, medical technology, diagnostic systems and bioinformatics sectors with the aim of concentrating, innovating and identifying need and solutions; with the desire to react to opportunities and promote synergies, networking and collaborations. In short, we aim to make our research and innovation sectors drive the economy and position Catalonia and Barcelona at the forefront of the international stage.

The region has a leading position in the Spanish scientific research panorama, especially in the life sciences areas: biotechnology, biomedicine and medical technology. Catalonia has nine biomedical research centers and 12 hospital research institutes, four of which – the Vall d'Hebron Hospital Research Institute (VHIR), the Bellvitge Institute for Biomedical Research (IDIBELL), the Health Sciences Research Institute of the Germans Trias i Pujol and the Hospital Clínic (IDIBAPS) – have been accredited as Health Research Institutes by the Ministry of Science and Innovation, which is equiva-

lent to a "centre of excellence" on clinical research. (Only one other Spanish hospital has received this recognition, Virgen del Rocío in Seville). Barcelona has the second highest number of nanotechnology publications in the world (2009, 2010, behind Boston) and Catalan centers that carry out research in this discipline – such as the Institute for Bioengineering of Catalonia (IBEC), the Catalan Institute of Nanotechnology (ICN), Center for Nanoscience and Nanotechnology Research (CIN2) and the Center for Research in NanoEngineering (CRnE) – are international references in the field.

Despite the indisputable overall improvement in research, which Catalonia has led in many fields, the Spanish innovation levels are still among the lowest scores in Europe. In the Global Competitiveness Report 2009-2010, Spain was ranked 33rd in competitiveness – of the 133 countries analyzed – with a score of 4.6 out of 7, and one of the weakest factors was innovation. The current situation shows a world-class research system but are still far from economic productivity. Furthermore, there is a general consensus on the part of economic theorists and political leaders that only an innovation-based change in the productive model will allow us to overcome the current economic crisis and lay the foundation for sustainable growth.

Research centres in Catalonia mainly carry out research related to biomedicine and nanotechnology. New biomaterials and the environment are areas with growing interest.

Catalonia is a pioneer in Spain and has created specific centers devoted to this discipline, which are now international benchmarks: Catalan Institute of Nanotechnology (ICN), Institute for Bioengineering of Catalonia (IBEC), Center for Nanoscience and Nanotechnology Research (CIN2) and Molecular Biology and Biochemistry Research Center (CIBBIM), specialized in nanomedicine. Currently in Catalonia there are 37 registered groups at different Catalan centers and universities with nanotechnology as the core activity of research. Nanotechnology, which is a transversal tool, is used as an enabling technology in 30% of the research centers, according to the report issued by the Department of Economics of the Universitat of Barcelona.

Taking into account this potential, a new initiative was launched in May 2011 to make best of the many opportunities that nanobiotechnology presents Catalonia, fostered by the Catalan Biorregion: BioNanoMed Catalunya, the Alliance for Bionanomedicine development in the region. The initiative is a joint effort of the aforementioned leading institutes, companies from the sectors of interest and other stakeholders, such as hospitals, technological centres and Government. The work of the Connect-EU is part of the internationalization axis within the mission of the Alliance (see Section 4), whose ultimate goal is to promote the uptake of the nano-based innovation by the biotech and healthcare sectors, and increase the visibility of the Catalan cluster.

2.3 Research landscape

A growing number of centres, university labs and departments are working on the interface of nano and biotechnology in Catalunya. The academic membership of the largely inclusive CONNECT-EU group includes most of them, with the leaders as core members of the former (IBEC; ICFO; ICN; ICMAB-CSIC; IQAC-CSIC; CIBBIM-VHIR; Barcelona Science Park).

R&D/Biotech

- In Catalonia €3,286 million was invested in R&D in 2008 (up 12.9% from 2007). This is 1.61% of the Catalan GDP. R&D investment in Catalonia can be broken down as follows: 60.9% from the business sector (€2,001 million, up 9.5% from 2007); 16.8% from the public sector (€554 million, up 39.2% from 2007) and 22.3% from the academic sector (€724 million, up 6.9% from 2007).
- The Department of Health earmarked €209 million (€24.5 million for projects and €184 million in indirect expenditure) in 2009, up 28% from 2008 (€16 million for projects and €132 million in indirect expenditure).
- The Department of Innovation, Universities and Enterprise earmarked nearly €110 million for research centers (2008). The budget for biotechnology-related CERCA centers was €220 million.
- ACC1Ó earmarked €6.7 million for the sector: one million for projects in research centers, €4.1 million for R&D subsidies in pharmaceutical, biotechnology and medical technology companies, and the rest for support structures (2009).
- Biotechnology generated direct, indirect and induced employment for 63,300 people. There are 22,210 researchers, of which 13,783 worked in the public sector (75% of the total) (2008). The direct, indirect and induced economic impact of the biotechnology sector is an estimated €8,189 million in turnover, or 0.8% of the GDP, accounting for 60,000 jobs in 2007.
- The number of biotechnology companies (EB) and related companies (EBR) totals 669 in Spain. Of these, 168 (47 EB and 121 EBR) are located in Catalonia, according to the Genoma España report Relevance of the Spanish biotech sector in 2009. The Biocat Directory lists 65 biotech companies and 150 related companies.
- Human capital: In Spain 4,240 people work in the biotechnology sector, with personnel expenditure at €180 million (2008). Annual growth of occupation in the sector over the past decade has been above 35%. An estimated 1,200 people work in the sector in Catalonia.
- Turnover of biotechnology companies in Spain was estimated at €706 million for 2008, of which Catalonia contributed 22.7% (€160.3 million). Annual growth over the past decade has been above 30%.
- Venture capital invested in biotechnology totaled 0.8% (€25.4 million) of all venture capital invested in Spain in 2008.
- Private capital (venture capital & private funds) invested in Catalan companies in 2008 was an estimated €21.3 million.
- The average investment is €1 million for companies with 20 workers (in the EU-15 the average is €6.7 million per company and in the USA, more than €15 million per company).

Figure 5: Biocat report 2009

As a starting point to the priorities setting, a description of the skills and techniques contributing to the development of nanobiotechnology has been carried out. This series of skills and techniques (see Appendix 2) has been used to map the current landscape of research in this interdisciplinary area in the region. Using these forms, a survey across the group members and all the interested parties has been undertaken. The mapping results are available as a PDF, "Mapping – Biotechnology Research Capabilities.pdf" from the Connect-EU Nanobio + Nanomed website.

The mapping was organized by four vertical research lines: new characterization tools (photonics, micro/nanoscopy); nanofabrication and nanomaterials synthesis capacities; nanoelectronics, including sensors and integration; biotechnological related capabilities, mostly in toxicology and pre-clinical development, adapted to the assessment and study of the interaction of nanomaterials with the human body and the environment.

According to this mapping, fifteen research centres in Catalonia are currently active in the area of nanobiotechnology, as well as approximately ten university labs, implying four different universities. A significant critical mass of approximately 250 researchers is involved. A great number of the listed research groups are members of the CIBER-BBN, a networked centre of excellence focusing on bioengineering, biomaterials and nanomedicine, an initiative supported and funded by the Spanish Ministry of Science and Innovation, with a largely translational mission. More accurately, eighteen of forty-seven groups in CIBER-BBN are working on nanomedicine and are based in Catalonia.

In this context of transfer from "bench to bedside", it is also worth highlighting clinical expertise in the Catalan-based academic hospitals shows that oncology and the nervous system are the two therapeutic areas with the highest concentration of research activity, both in Catalan companies and research centers. The critical mass of the world-class research in the area of oncology, with centres such as VHIR/VHIO and ICO-IDIBELL, can be regarded as a very strong asset for the future of the nanomedicine in the region.

2.4 Industrial landscape

The industrial sectors benefiting most straightforwardly from the application of nanobiotechnology convergence are the health-sciences related sectors (human and animal pharma; medical technologies), followed by other life sciences sectors, such as environmental management and food.

The picture (BIOCAT report 2008) of the Catalan biotech sector is that of a growing, dynamic, though still immature, sector. An extraordinary capacity for scientific research is finding its way to market products and, therefore, lead industrial innovation and economic development. The efforts in recent years have been focused on fostering tech transfer from academia to industry, as well as internationalization (first in Europe, second in USA and China).

Red biotech, which is generating new therapies, drugs, diagnostic procedures and treatments for human health, leads the sector in Catalonia. In fact, 60% of research carried out in our research centers focuses on this area, as does the business activity of 64% of companies analyzed. Healthcare is a non-cyclic sector and a priority for public administrators and residents alike because advances in this area have the most direct impact on the wellbeing of society. Biotechnology is also

the field in which the pharmaceutical industry – which invested more than €1000 million in R&D in 2008 in Spain – turns to in search of much-needed innovation for its pipeline, earmarking 19% of investment directly to biotech projects. Herein lies the economic potential of red biotech.

However green biotech – which has agrifood and environmental applications – and white or industrial biotech can also contribute notable social benefits and important economic growth, despite their less notable presence in the BioRegion of Catalonia. The importance of green biotech applications is clear: from improved animal or plant genetics to transformation and preservation of food, which directly affects economic activity in sectors like agrifood (the most important in Spain with production value of €80,000 million in 2008, accounting for 17% of the industrial GDP).

Biotech research and production are, at the same time, areas where technological advances that are not bio in origin can be applied. Informatics and engineering have thus become bioinformatics and bioengineering, two key elements in current biomedical research. The medical technology subsector is made up of a wide range of companies, from laboratories that produce biological diagnostic kits to companies specializing in telemedicine or image diagnostics, to companies in traditional industrial sectors – plastics, metals, etc – that have been subcontracted to produce elements for medical devices. In 2008, roughly one hundred companies were working in the medical technology field (*in vitro* diagnostics, medical devices, bioengineering, etc). In 2008, 65 biotechnology companies and 70 pharmaceutical companies – including the top five companies in the sector in Spain – focused on medical products.

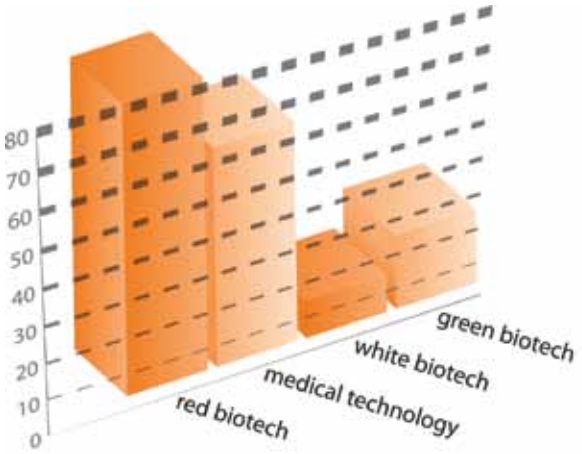
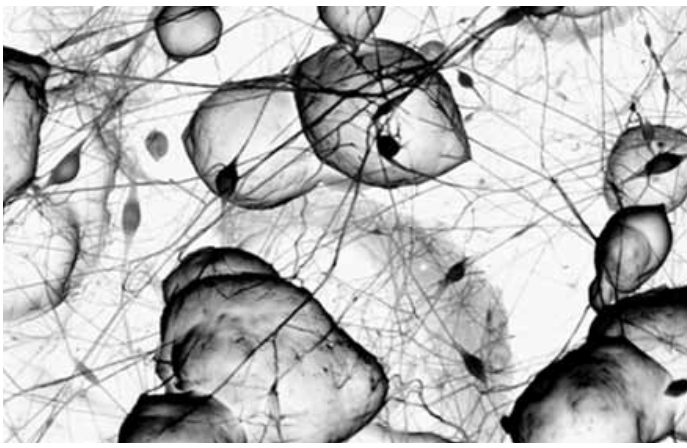


Figure 6: Catalan companies using nanotechnology in their processes/products (2009). Source: Biocat Report 2009



3. R&D Priorities

As it has been stated and discussed in the previous sections, some of the most sought-after products for the future pipelines of the health and life-science sectors can be enabled using nanobiotechnology. The priorities of the Catalan research agenda will be determined by these market/clinic goals. The needs pointed out by companies and requirements for new applications and solutions have been surveyed directly through interviews and questionnaires (see Contributors, page 39).

First, the survey confirmed that the participation of industrial partners in FP7/European consortia is directly linked to projects whose final or intermediate goals are related to these interests. They would also be projects that require an international and in most cases, multidisciplinary, consortium, given their scope, scientific-wise or policy-wise (case of projects in nanosafety). The group has reviewed if the products in the future pipelines could be nano-enabled/nano-improved, and discard certain interests which go beyond nanotechnology possible results. For instance, better data management for drug discovery in the case of pharmaceutical industry.

The R&D priorities detailed in the next section have been singled out matching the industry interests with the academic/research capacities. The Catalan research organizations would be more likely to participate in projects requiring partners excelling in the skills that have been highlighted. They can also work like innovation engines in this case. The role played by research and technological non-profit organizations can be key as well in the sense of their expertise as coordinators of complex framework-funded projects and initiatives, and/or contacts at the highest level.

The results of the matching and analysis exercise to identify areas of high potential for the Catalan community are summarized in the following tables. With a goal-oriented starting point, the capabilities that can be contributed from nanobiotechnology knowledge are emphasized, in particular those available in the region. Some of these topics are already present in the current 2012 FP7 working programmes, mostly in HEALTH, NMP or ICT. This information has also been highlighted in the tables. It is stressed as well in which future actions funded under HORIZON 2020 agenda related projects could be framed. Pushing further the technological development and into pre and clinical stages is one of the goals of the current research agenda, which would be greatly aided by participation in HEALTH-related working programmes.

It is worth stressing that the identified priorities feature in most cases as “major challenges” in the Strategic Research Agendas and related documents issued by the European Technology Platforms in the respective areas (Nanomedicine, FoodForLife, Photonics21, ENIAC).

3.1 Pharma: human and animal health

The pharma sector is a pioneer in the uptake of the nanotechnology possibilities for the development in the new products. Liposomes have been used to enhance drug-delivery since the 1980s, in particular in the area of oncology.

However, beyond the use to improve the delivery of small molecules (Lipinski molecules; conventional drugs), usually to improve side-effects or for new therapeutical applications facilitating what is known as "reprofiling", the red biotech is particularly interested in the possibilities of nano-based systems to ensure the bioavailability and delivery of macro/biomolecules. Industrialization/scale up/uptake of new technologies and the concern of R&D projects focused on the use of materials not yet approved by the FDA are two topics that have been remarked by the industrial partners. The involvement of industry at an early stage of the innovation process would be highly recommended.

The request for adequate animal models, in particular for biological barriers, as part of the pre-clinical and clinical efforts is another striking point to be regarded in R&D projects. The investment and participation in other related areas, such as regulation and cost-benefit studies have also been pointed out as significant contributions to lower the innovation barriers in these sectors.

Product	Applications / Clinical Areas	Needs / projects
Nanosystems for drug delivery/ injection, topics	Cancer, inflammatory problems, Alzheimer's / neurodegenerative diseases, etc (there is not a preferential clinic area)	Nanoparticles to encapsulate macromolecules (peptides, proteins, nucleic acids)
Therapies monitoring (see diagnosis part)		Industrial production scale
Nanovaccine		Regulatory topics: validation methods
Animal Health: Nanosystems that allow complement addition in food		Nanosystems capable to cross barrier (nasal, BHH, intestinal, epidermis, etc)

Capacities	Technological challenges	Calls FP7 – 2012 Working programmes
Synthesis of liposomes/ vesicles/micro-nano polymeric/noble metal nanoparticles Functionalisation (chemical/ bio)	Industrialization: nanosystems design which can be manufactured with acceptable economic, energy costs	HEALTH 2012.1.4-4: Targeted nucleic acid delivery as an innovative therapeutic or prophylactic approach 4th IMI Call 2011: Delivery and targeting mechanisms for biological macromolecules
Production/biomolecules isolation	Systems development that improve controlled release in materials already approved by regulatory agencies	NMP 2012 1.4-3 Nanoscale mechanical metrology for industrial processes and products NMP 2012 LARGE: Large-scale Integrating Collaborative Projects
Animal models	Encapsulation systems that allow the re-profiling of drugs already in use (by other routes of administration, other therapeutic applications)	
Preclinical toxicology: development of appropriate protocols		
Clinical capacities: oncology		
Characterization: microscopy		

3.2 Medical technologies. Diagnostics

In the area of diagnostics, the most remarkable fact is that the Catalan companies are focused on *in vitro* diagnostics. The absence of both companies working on imaging systems and pharmaceutical companies developing imaging markers are two fundamental points. The priorities, therefore, would be projects contributing to the deployment of latest generation point-of-care diagnostic devices (POC), based on lab-on-a-chip approaches. Integration and assembly, as well as testing of prototypes, is remarked as the most needed area of improvement, as well as the industrialization of the nano-fabrication tools. Early involvement of engineers and design departments in the projects is outlined as an important factor, as well to contribute to the improvement of integration-related aspects.

Cost-benefit evaluation studies are very much sought and requested as well (see page 24, Pharma).

Product	Applications / Clinical Areas	Needs / projects
***In vitro* Molecular Diagnostics: applications point-of-care (POC) for the detection of biomarkers**	Oncology-monitoring/prediction	Improving speed (vs. current tests and clinical trials), ensuring reproducibility, cost-effectiveness, improving sensitivity and specificity
	Rapid detection of infectious diseases/ linked to administration of antibiotics	Ensuring tests' reliability: reproducibility guaranteed with improved sensitivity and specificity
	Personalized medicine: targeting defined treatments (Companion diagnostics)	

Capacities	Technological challenges	Calls FP7 – 2012 Working programmes
Characterization: Electron microscopy (TEM / SEM / e-beam lithography) Scanning probe microscopes (AFM / STM / LFM / CSAFM / MFM / EFM / PFM / Nanolithography) Spectroscopy (UV-Vis / IR / EPR / fluorescence)	Speed of diagnosis, especially in infectious diseases, without pre-treatment sample; alternative diagnostics with fluid other than blood or urine (saliva, etc)	Call 8 ICT 2012: Challenge 5.1 Personal Health Systems (PHS)
Manufacturing: NANOBIOELECTRONICS micro and nanoelectronics (nanowires, nanoarrays) and communications; nanobiosensors: electrochemistry, photonics, nanomechanics Manufacturing technologies (screen-printing and ink-jet technologies) Nanoimprint lithography (dip-pen) Functionalization surfaces with biomolecules: nano-bio materials	Integration (of all components: sensor, communication, etc) Encapsulation of multiple systems Industralization (cost, ECO, reliability, etc)	HEALTH-2012 1.2-1: Development of technologies with a view to patient group stratification for personalised medicine applications
Production/isolation of biomolecules (nucleic acids, proteins, peptides etc) functionalization	Multiplexing/multimarkers (especially in cancer-metastasis stage)	FP7-HEALTH-2012-INNOVATION-2-2.3.0-1: Diagnostics for infectious diseases in humans
Integration / microfluidics		
Clinical capacities: infectious diseases, cancer (animal models, clinical trials capacity in hospital)		

3.3 Medical technologies. Biomaterials and regenerative medicine

Therapeutic area-wise, the interests and priorities of the Catalan companies are focused on bone and dental regeneration systems. Smart biomaterials, going beyond compatibility, and promoting healing of the tissue are the main application of interest. Diverse materials and techniques can contribute to these products, starting with polymer-based nano-structured surfaces. Scaffolds to promote angiogenesis, optimized with sensors to detect if the cell growth is successful, represent another milestone to the realization of regenerative medicine. *In vitro* 3D cell culture systems are a second product that can derive from the scaffolds development. Though these advanced cultures systems, which could facilitate enormously pre-clinical testing and reduce costs, have been pointed out as a tool with enormous potential for the drug discovery process, pharma companies themselves are not strictly interested in participating in consortia working on their development.

Product	Applications / Clinical Areas	Needs / projects
Smart biomaterials for implants	Bone / cartilage regeneration, cardiovascular	Ensuring biocompatibility: design, validation, testing
Antibacterial coatings for clinical materials	Intelligent dental implants Catheters, stents, implants, etc that can work as anti-infective barrier	Self-healing materials Non-invasive clinical protocols
Scaffolds for cellular growth	3D Cell Models	*In vitro* cellular environments similar to *in vivo*

Capacities	Technological challenges	Calls FP7 – 2012 Working programmes
Synthesis and characterization of polymers and other materials (CNTS, etc)	Tuning and control of nano-structured materials properties. Reproducibility.	NMP2012 2.1-3 Self-healing materials for prolonged lifetime NMP2012 2.2-1 Biomaterials for improved performance of medical implant
Nanofabrication and characterization of bio / non-bio surfaces and interfaces Synthesis of Biomolecules: Proteins and antibodies Systems of optical /magnetic integrated sensors (i.e to detect angiogenesis) Bacterial inclusion bodies	Achieving massive production and industrialization with acceptable costs Pre-clinical and clinical validation: Tissue regeneration promoted by intelligent implants	
Porous materials, multi-model stacks	Reduce time and cost of new biomaterials clinical trials	

3.4 Food technology

The less RTD intensive sector of the food and drink industries can also benefit greatly from the application of nanobiotechnologies. In this particular case, it was pointed out that bringing together the research and industry stakeholders through coordination and support actions would be convenient, as the companies are still largely oblivious to the possibilities of nanotechnology.

The development of more sustainable and safer processes through eco-innovation (new products and production systems and processes, including everything related to packaging) is one of the major trends. It is pointed out, that it has happened with the adoption of the first wave of biotechnology, food industries can gain from the tech and knowledge transfer from the health-related sectors.

Nanoencapsulations and improved delivery can also contribute to develop personalised and healthier foodstuffs, thinking of particular niches of the market, which is one of the goals of the research agenda of the sector at the European level. Sensorial qualities, whereas ensuring safety and sustainability of the products, can also be enhanced by means of these approaches.

Product	Applications / Clinical Areas	Needs / projects
Fast respond detectors devices	Detection of spoiled food	Detection of bacteria, micro-organisms, etc.
Bioactive materials for packaging	Detection of the presence of contaminants	Improving the taste and sensory properties of food
Nanoencapsulation (additives, nutraceuticals complements, ingredients)	Improve the absorption of certain components Improve sensory and nutritional properties	Targeted delivery of bioactive compounds with beneficial properties.

Capacities	Technological challenges	Calls FP7 – 2012 Working programmes
High production volumes at low prices	Nanobiosensors: technology transfer from diagnostic area	
	Synthesis of nano-structured materials (films)	
Crossing stomach barrier	Liposomes, nanovesicles, NPs and other systems of nano-encapsulation	

3.5 Nanosafety and environment

The biological effects of engineered nanomaterials are currently a topic of considerable debate. Nanobiotechnology has to provide the knowledge base to ensure the safety of products containing nanomaterials by means of validated assays. This necessary framework of methods to produce reliable data, essential for both producers and consumers, has been named "nanosafety".

Nanosafety concerns many and diverse industrial sectors: chemistry, materials, energy, building, aeronautical, etc. The chemical industries are particularly interested, as responsible for the synthesis of the raw nano-structured materials and nanoparticles to be assembled into many different products. At the beginning of the third stage of nanobiotechnology in Europe (2011-2012, see Figure 2 in the Introduction), the regulatory and standardization affairs are lagging behind compared to the technological development of the nano-capacities, and the lack of coordination could become a barrier to adopt nano-enabled products in the near future. It is expected and required that the significant investments in R&D in nanosciences and nanotechnology by the European Union and the state members yields an equally sizable number of breakthrough innovative products and opens new markets. In order to achieve this objective, an adequate and clear regulatory framework has to be enforced. Consequently, at the end of FP7, nanosafety has become a core funding topic, and the coordinated knowledge exchange across funded projects, with the set up of the Nanosafety Cluster, and initiatives such as the network NanoImpactNet, a priority theme for the Commision.

The design and validation of robust protocols is currently an unmet demand to set up such a framework. Abundant research efforts are under way to establish suitable test methods and to understand mechanisms potentially leading to a detrimental impact of nanomaterials on human health and on the environment, but they are leading to scattered data, often not very comprehensive. Appropriate and well-documented characterization of the physical/chemical parameters of the nano-objects is a first step to ensue the definition of "gold standards" in nanotoxicology, the major issue. This implies going beyond the adaptation of conventional toxicology tests to the study of nanoparticles fate, along with the centralization of the obtained data, properly labeled and stored (i.e. the creation of European databases, accessible by researchers, producers, regulators). Coordination of efforts from member states is also called for.

Out of the interviewed companies and industrial associations in Catalonia (pharma and chemical sector), none of them are yet working on the synthesis/production nor on commercialization of engineered nanomaterials. The nanosafety issue is perceived as a topic of interest, but not for them to be involved at this stage, but rather to be settled by research centres and regulatory agencies. Individual companies are not expected to join European consortia on these topics (NMP2012 WP 1.3-1 Systematic investigations of the mechanisms and effects of engineered nanomaterial interactions with living systems and/or the environment; 1.3-2 Modelling toxicity behaviour of engineered nanoparticles; 1.3-3 Regulatory testing of nanomaterials), neither they suggest particular high-priority topics as a consequence, though they endorse the participation of Catalan research stakeholders in related programmes and projects. Industrial associations show however interest in the dissemination of results, or later training activities to keep abreast with future changes.

4. Strengthening the research base

Priorities in training, infrastructures and coordination of research activities

Beyond the definition of a set of priority topics in applied R&D to exploit the current potential of Catalonia in nanobiotechnology, the present document aims to provide guidelines to sustain and strengthen such possibilities.

In this sense, the leverage of the Catalan scientific capacities in the convergence of nanotechnology, biotechnology and photonics (three of the six KETs highlighted by the European Union as the source of the European innovation capacity for the next future, june 2010), to generate novel knowledge, which will be the basis for applied research projects is fundamental. The long-term policy measures should address both the attraction and nurture of talent as well as the development and update of research infrastructures and equipments.

The implementation of these measures can also be partially funded by FP7/HORIZON 2020 programmes. They should imply the participation of the Catalan Government agencies (regulators, policy makers or R&D funding bodies). National and regional policy makers and administrations play a central role in ensuring an effective exploitation of the potential for synergies between the diverse European funding programmes in aspects such as infrastructures management and coordination at European level of research activities and high-level training.

4.1 Interdisciplinary talent

Nanobiotechnology is interdisciplinary by definition, as a merge of expertise arising from physics, chemistry, materials engineering and biology. On top of that, there is a myriad of industrial sectors which can benefit from its application: pharma, medtech, animal health, food technology, biotech, as well as most manufacturing sectors through the implementation of nanosafety. The exchange of highly trained scientists and engineers across the academia/industry interface is another key factor in the development of the Innovation Union document goals. In this area, as new professional profiles are required, in order to achieve the expected results from industry adopting and exploiting nanobio-related knowledge, this exchange is a nearly obvious demand. The exposure should be ideally started at the Master/PhD level, though in-career training programmes for professionals should also be implemented. For instance, toxicologists should be exposed earlier on to the nanotechnology needs to design appropriate testing protocols; also, clinical research managers familiarised with new regulatory schemes, or manufacturing engineers engaged with new methods of nano-fabrication will be sought. The national programme International Campus of Excellence (CEI) must facilitate the public-private connection of talent around campuses. The international projection of the CEIs based in the Barcelona nano-bio district (including most mapped research organisations, companies and hospitals) is essential to achieve this goal.

Regarding the European Funding schemes for researchers training, the participation in actions such as Industry-Academia Partnerships (IAPP; PEOPLE programme in FP7) and the European Innovation Doctorate (EID; PEOPLE) can be a particularly useful vehicle for this aim. Bringing close together expertise from the nano environment to industries such as pharma, biotech, food or cosmetics, it is highly advisable to upgrade industry-academia cooperation in terms of research training and knowledge sharing to accelerate the uptake of nano-based products into the market.

In terms of Catalonia as a region, to explore the possibilities of actions such as COFUND to inforce postdoctoral/PhD fellowships and grants with a clear interdisciplinary focus, involving more than one institution etc, would be also an interesting opportunity for the area of nanobiotech.

4.2 Support to infrastructures

Regarding infrastructures, the connection of research facilities such as cleanrooms, ultra-high level microscopy and nanochemical characterization services with biological labs is recognized as a fundamental step for the advance of nanobiotechnology. Foundries for nanofabrication must not only be adjacent to large scale facilities for analysis, but also to cell and molecular biology laboratories. For the nanomedicine researchers, such integrated facility offers the opportunity to carry out all the patterning, characterization and biological processes in a clean environment, avoiding the problems of contamination encountered when moving devices between laboratories and buildings.

Therefore, the optimisation of the use and connection of existing facilities is a differential factor in the evolution of such an interdisciplinary effort, more than the construction of a single-site to achieve these purposes, with regular upgrades for each of them and its connection. The initial effort and investment in nanosciences and biotechnology in Catalonia during the past decade should be sustained thanks to the participation in European initiatives targeted to achieve these goals. The participation of science and technology parks and other singular-strategic research facilities in the area in projects funded through the INFRASTRUCTURES programme should be encouraged. The promotion of initiatives in this area will grant the Catalan-based researchers access to facilities located in other world-class European clusters.

Taking the example of the nanopharmaceuticals, as pointed out in earlier sections, the scale-up and manufacturing, as well as the realisation of pre-clinical/clinical validation protocols are two key factors that should not hinder the development of their enormous potential. The fabrication under Good Manufacturing Practices (GMP) is a must in this context, and lab facilities validated at this level are a missing factor in the current infrastructures landscape.

As pointed out in the Section 3, the set-up of a clear regulatory framework for the manufacturing and use of nano-engineered materials is a must for the nano-based products to arrive to the market. The adoption of a scheme similar to the Nanotechnology Characterization Lab at NCI (USA) would aid the coordination of the characterization and toxicology-related studies of nano-engineered objects. It is likely that this will be a "virtual" centre in the European version, with a "real-life" central ad hoc database to be fed by "certified" research labs and to be accessed by end-users such as manufacturing companies. This initiative is drafted in the NMP2012 Working Programme, and it is expected

to be funded by the Commission with the contribution of member states and regions.

The CE has agreed that to ensure nano-based innovation, a European central policy for Risk and Safety Management should be established. It might be supported by some sort of global, core information centre to provide advice and expertise. Regulatory testing topics in the NMP2012 Working Programme are more aligned with these efforts. The location of such centre depends on the engament of the diverse member states. ERA schemes, with involvement of the regions, will be key to the development of these initiatives, beyond the INFRASTRUCTURES (currently under CAP programme) call. However, the involvement of the authorities and other Government-related stakeholders as applicants is crucial in this case.

4.3 Coordinating activities

In the final report of the EURONANOBIO FP7 project, "Concept for a European Infrastructure in Nanobiotechnology", it was proposed that the most efficient model for fast and efficient nano-based discoveries into health and life sciences sectors would be a connected network of research-driven innovation clusters.

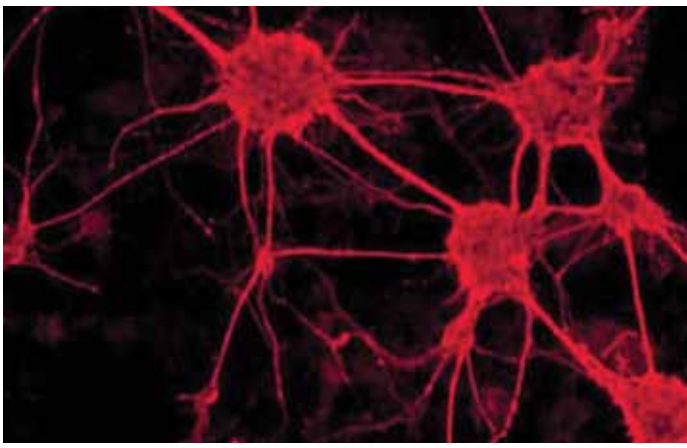
Given the very diverse know-how that is required, for instance, in the development of a new nano-based pharmaceutical product, the cluster turns out to be a more efficient building block, as opposed to isolated large facilities or research centres, for the European nanobiotechnology infrastructure at large. For the translation to market and clinic of such product, it would also very much in need expertise probably located in other regions (i.e. multicentric clinical trials), so European-funded actions to connect and coordinate these regional clusters were called for. This coordination would help to move forward in aspects such as standardization, regulation and adoption of health-related innovation, which demand European-level agreement.

Following these recommendations, the BioNanoMed Catalunya Alliance was launched in May 2011. The Alliance, within the Catalan Biorregion, BIOCAT, is created and fostered by the leading organisations carrying out research in nanotechnology and nanobiomedicine in the region, with the aim of developing and promoting this sector. The vision of this initiative envisages promoting synergies between Catalan research groups and centres, hospitals and companies, in order to create new research and business opportunities in nanobiomedicine, and increase their international impact. The Alliance aims to becoming a platform to promote the research performed on nanobiomedicine in Catalonia; defining the position of Catalonia in research, innovation and knowledge transfer; establishing internationalisation strategies and increasing the efficiency of the system; defending the common interests of the alliance members before local, national and international administrations to ensure inclusion in their work programmes and funding instruments.

The participation in initiatives such as the "Regions of Knowledge" (CAPACITIES; FP7) would be an excellent boost to the coordination of activities and reinforce the links with other top clusters/regions in nanobiotechnology at European-level. The Regions of Knowledge action responds to a need at European level to increase the overall capacity of European regional players to boost innovation based on research andtechnology development (R&D). Topics on nanobiotechnology, such as nanohealth and nanosafety,

would be of particular interest for the development of the Catalan cluster.

The goal of this programme is to enable regions to strengthen their capacity for investing in and conducting research and technological development activities in a way which can contribute significantly to their sustainable economic development. Throughout FP7 so far 'Regions of Knowledge' has successfully initiated a process of transnational collaboration of clusters in emergent technological sectors that will harness R&D for regional development in synergy with the EU regional policy and the related structural funds.



5. Conclusions

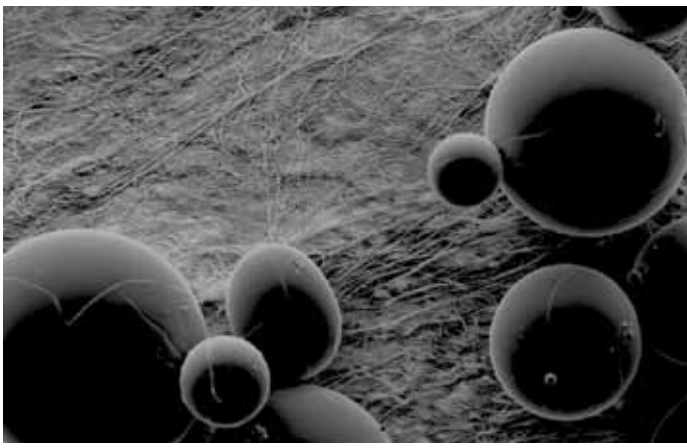
Nanobiotechnology applications offer a great opportunity to some of the most relevant industrial sectors in Catalonia, such as healthcare, fine chemistry and food technologies. Initial significant investment from the Catalan and Spanish Government in infrastructures and facilities, purpose-built and located to favor the convergence of nano and biotechnologies, has spawned a significant research capacity. According to the survey supporting the recommendations in this document, the next steps should be focused on the development phase, regarding industrialization/prototyping/integration topics. In the same direction, ensuring the safety of nano-based products and the subsequent contribution for an adequate standardization methodology/framework are other issues which should be tackled in the immediate future. The potential products of interest are mostly in the pharma (targeted delivery of macromolecules and reprofiling) and medical devices area (*in vitro* diagnostics), with significant interest from the food sector.

The highlight on the development phase is aligned with the policies currently being deployed at the European level. Catalonia is not alone in trying to make best of a sufficient and capable academic sector in nanobiotechnology. Insufficient innovation levels have been identified as the pending issue. The follow-up of FP7, HORIZON 2020, is currently being designed in order to improve these results, with a commitment to transfer novel knowledge effectively to the European industries. As for nanobiotechnology, two points in the agenda are not to be missed: the focus provided EIP for Healthy and Active Aging and the commitment to the alignment of policies, streamlining of funding programmes very much sought by the participatns in interdisciplinary topics.

The goal will be to improve the solid performance of Catalunya in this area during the FP7, in particular the industries participation in international projects, it is highly advisable to engage with the diverse structures such as Project clusters (Nanosafety Cluster and MNBS Cluster are two examples closely related to the nanobiotechnology applictions) and changing Technology Platforms (ETP Nanomedicine; IMI; Nanofutures) providing feedback to the policy makers. The involvement of Catalan industry in earlier-stage projects, prior to the immediate transfer, would be highly beneficial to the quality of applied research. A good example of this is the issue of manufacturing/scale up issues in nano-based pharaceuticals and delivery systems.

Internationalization of research at industrial level, with the added benefit of open innovation with the best, and gaining access to new markets with lower barriers. SMEs are particularly sought-after for their role in the innovation process for emergent technologies, with new business models likely to be created under the auspices of new standards. Participation in large-scale initiatives (ERA integration space; infrastructures support) since the inception phase.

Thinking in the long-term, and not only in the immediate application, frontier research to feedback the roots of the "nanobiotechnology" tree on the three interacting KETs (nanotechnology, biotechnology, and also photonics) should not be neglected. Catalan support to FET Flagships initiatives related to the area should be foreseen as the participation in the schemes to benefit from ERC Grants results, triggering innovation at regional level from breakthrough science.



5. Contributors

Coordinator: ibec Institute for bioengineering of Catalonia

Core group members: Vall d'Hebron Institut de Recerca; ICFO Institut de Ciències Fotòniques; CSIC ICMAB QAC; ICN Institut Català de Nanotecnologia; aromics; Parc Científic de Barcelona; ADVANCELL

Non-core group members:

- Grup BIOCENIT- Universitat Rovira i Virgili (URV)
- Institut d'Investigació Biomèdica de Bellvitge (IDIBELL)-ICO
- Institut de Recerca Biomèdica de Lleida
- Institut Químic de Sarrià
- Institut de Recerca Biomédica (IRB)
- Institut de Recerca Hospital Sant Pau
- LEITAT
- Activery
- Andrés Pintaluba
- Bioibérica
- Biokit
- Cosingo Imagine Optic Spain S.L
- ENDOR Nanotechnologies
- GP Pharma
- Grupo Ferrer
- NTE-Sener
- Reig Jofré
- STAT Diagnostica

Connect-EU groups contributors:
Connect-EU Agro-Food - Centre Tecnològic de Nutrició i Salut (CTNS)
Connect-EU Materials

With the support of: ACC1Ó Agència de Gestió d'Ajuts Universitaris i de Recerca; Generalitat de Catalunya Government of Catalonia

Bibliography

Documents

1. "A rough guide to the FP7 Work Programmes", March 2008. Ministry of Education and Research, Sweden.

2. Biocat report on the state of biotechnology, biomedicine and medical technology in Catalonia (2009).

3. "Current trends in nanobiosensor technology", Bellan et al, Wiley Interdisc. Rev. Nanomed. Nanobiotech., 2011.

4. "Concept for a European Infrastructure in Nanobiotechnology", Final Report, EURONANOBIO-FP7, 2009.

5. European Technology Platform on Smart Systems Integration (EPOSS) Strategic Research Agenda, 2009.

6. "Focus report: Nanotechnology and Therapeutic Delivery", ObservatoryNano, July 2010.

7. Green Paper on a Common Strategic Framework forEU Research and Innovation Funding.

8. "High-level Expert Group on Key Enabling Technologies", Final Report, European Commission, June 2011.

9. Improving Translation of Public Healthcare Nano-research in Europe (White Paper to the HORIZON 2020 FP for Research and Innovation), Nanomedicine European Technology Platform, 2011.

10. "Innovation Union-Europe 2020 Flagship Initiative", European Commission, October 2010.

11. "Nanotechnology in Europe", Dr Burton Lee, Innovarium/Stanford University, 2010.

12. "Preparing for our future: Developing a common strategy for key enabling technologies in the European Union", European Commission, September 2009.

13. Roadmaps in nanomedicine towards 2020, Joint European Commission /ETP Nanomedicine. Expert report 2009.

14. "Strategic research agenda – Nanotechnology". Netherlands Nano Initiative 2008.

15. Work Programme 2012 COOPERATION theme 1 HEALTH (European Commission C(2011)5068 of 19 July 2011).

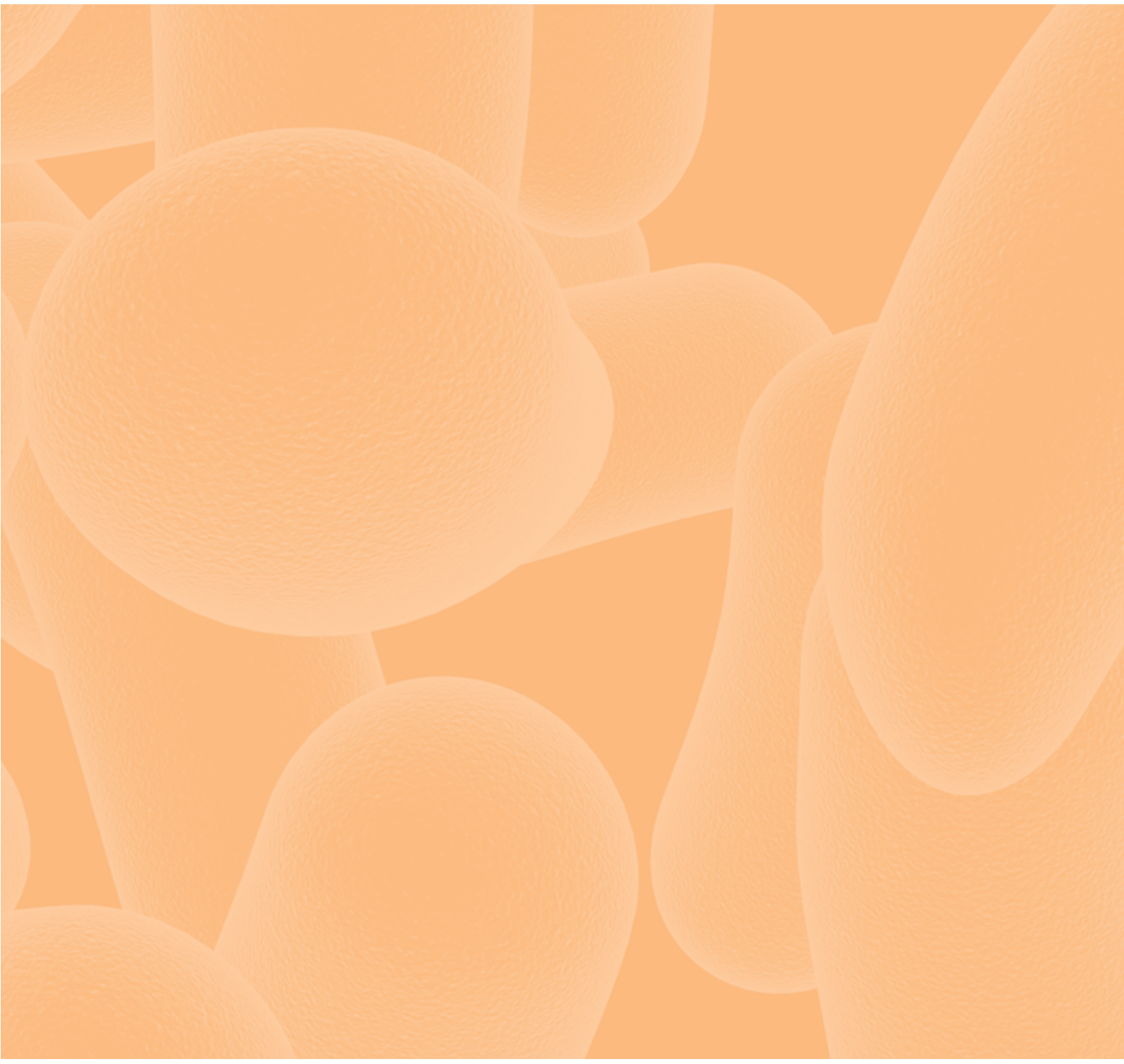
16. Working programme 2012 Draft (29/04/2011) COOPERATION. Food, Agriculture and fisheries, and biotechnology.

17. Working programme 2012 Draft COOPERATION. Nanosciences, Nanotechnologies, Materials and new production technologies – NMP.

Websites

- European Commission Europe 2020 Strategy, http://ec.europa.eu/europe2020/index_en.htm
- European Association of National Metrology Institutes, http://www.euramet.org
- European Research Council, http://erc.europa.eu
- BioNanoMed Catalunya, http://www.bionanomedcat.org
- Nanosafety Cluster, http://www.nanosafetycluster.eu
- Observatory Nano, http://www.observatory-nano.eu/project
- Community Research and Development Information Service, http://www.cordis.lu
- Project on Emerging Technologies, http://www.nanotechproject.org

Appendices



Appendix 1

FP7 Calls which have provided fundong for nanobiotechnology and nanomedicine topics in the programmes NMP, ICT, KBBE and HEALTH, with estimated figures of the budget allocated in each of them (2007-2010). In the case of the topics funded through the HEALTH programme, the calls are not exclusively addressing the nanobio-based applications. In the case of ICT, funding for exploratory research through FET programme has not been listed. Taking into account that NMP (>€200m), ICT (>€160m) and KBBE €30m) are nanobio-focused exclusive calls, the funding in the period 2007-2010 is for sure above €400m.

NMP	1.1 Nanosciences and converging sciences	1.2 Nanotechnologies and converging technologies	1.3 Health, safety and environmental impacts	1.4 Integration
2007	1.1-1 Nano-scale mechanisms of bio/non-bio interactions (approx €35million)	1.2-2 Analysis of the ethical, regulatory, social and economic environment of nanomedicine (€1m)	1.3-2 Risk assessment of engineered nanoparticles on health and the environment (€10m)	
2008	1.1-1 Converging sciences and technologies (nano, bio, info and/or cogni); (€40m) 1.1-3 Examining capacity building on nanobiotechnology (€1m)	1.2-2 Nanotechnologies for water treatment (€10m)		
2009	1.1-1 Nanobiotechnology: Applying life science principles as model for new nanotechnology-based mechanisms, processes, devices and/or systems (€35m approx)		1.3-2 Exposure scenarios to nanoparticles (€10m)	4.0-3 Development of nanotechnology-based systems for molecular diagnostics and imaging (€25m approx)
2010			1.3-1 Specific, easy-to-use portable devices for measurement and analysis (€20m)	4.0-1 Development of nanotechnology-based systems for detection, diagnosis and therapy for cancer (€20m)

HEALTH	1.2 Detection, diagnosis and monitoring	1.3 Suitability, safety and efficacy of therapies	2.2 Research on the brain and related diseases / 2.4 Translational research in major diseases
2007	1.2-1 Development of a hybrid imaging system* 1.2-2 Novel optical methodologies for detection, diagnosis and monitoring of disease or disease-related processes* 1.2-3 Novel targeted imaging probes** 1.2-4 *In vivo* image-guidance for cell therapy*	1.3-1 Novel alternative testing strategies for use in pharmaceutical discovery and development** 1.3-4 Alternative testing strategies for the assessment of the toxicological profile of nanoparticles used in medical diagnostics*	2.4.1-7 Improving targeted drug delivery to cancer cells for cancer therapeutics other than gene therapy* 2.4.3-9 Use of beta cell imaging in diabetes mellitus**
2009	1.2-1 Development of tools for sensitive and specific *in vitro* detection of proteins and their int. for diag/prog/monitoring purposes*		2.2.1-4 Understanding the blood brain barrier (BBB) to improve drug delivery to the brain**

** Average 3-4 funded projects, max €6m/project); ** average 2 funded projects; over €6m/project. NOTE: not all the projects are necessarily focused on nanobiotechnology*

KBBE*	
2007	2.3-04 Nano-devices for quality assurance, food safety and product properties 2.3-06 Network for facilitating the implementation of high-tech processing at industrial scale. 2.5-02 Converging technologies and their potential for the food area
2008	3.2-03 Nanobiotechnology based biosensors for optimized bioprocesses 2.3-01 Exploring the micro-structure of foods
2009	3.6-03 Nanobiotechnology: bio-interfaces for environmental applications 3.6-02 Nanobiotechnology: functionalised membranes 3.6-01 Nanobiotechnology: smart devices to study biomolecule dynamics in real time 2.4-01 Analytical tools for characterization of nano-particles in the food matrix

(*) One project funded per topic; €3m max/funding

ICT*	
2007	Challenge 3.6 “Micro/Nanosystems” (€75m) – sub-challenge: Micro/Nano-Bio-ICT Convergence, approx €35m Challenge 5.1 Call 1 Personal Health Systems (€75m)
2009	Challenge 5.1 Call 2 Personal Health Systems (€62m)

Appendix 2

Line: Fabrication, synthesis and functionalization of nanoobjects

Research Centre name:

Group:

Skills/Techniques:

a) Synthesis and production of nano-objects (nanoparticles, nanotubes, etc)

Type	Production scale	Comments
Liposomes		
Vesicles/Micelles		
Metallic NPs (specify type; properties)		
Polymeric NPs/polymers		
Nanotubes (Carbon/Other)		
Dendrimers		
Porous Si or other porous material		
Other (eg. nanocomposites)*		

Characterization Techniques	YES/NO
Electronic microscopies (TEM/SEM/e-beam lithography)	
Scanning probe microscopies (AFM/STM/LFM/CSAFM/MFM/ EFM/PFM/Nanolithography)	
Thermal Analysis (ATG/DSC)	
Magnetometry (SQUID/PPMS)	
X-Rays	
Spectroscopy (UV-Vis/IR/Fluorescence)	
Nanoquim Platform	
Particle size (DLS/Nanosight)	
Z-potential (Superficial Charge)	

b) Biomolecules synthesis

1.1 Biomolecules synthesis

Type	Production scale	Comments
Peptides		
Nucleic acids		
Proteins		
Policlonal antibodies		
Monoclonal antibodies		
Dendrimers		
Bioconjugate (please specify type)		
Other		

1.2 Purification and production methodologies and techniques

Technology	Comments
Bacteria-expression systems	
Eukaryote cell-expression systems	
Chemical synthesis	
Purification systems (specify)	
Other	

1.3 Characterization tools

a. NMR	
b. Mass spectrometry	
c. X-Rays	
d. Computational analysis	
e. Bioassays	
f. Other	

Functionalization:

Material to be functionalised:

- Au, Ag, other noble metal ❒
- SiO2/TaSi/ ❒
- Other metallic NPs (please specify) ❒
- Polymers(PLGA; PMMA...) ❒
- Other ❒

Functionalization type:

Method

- Physical (plasma, other; please specify) ❒
- Chemical ❒
- Biological
  - Antibodies ❒
  - Peptides ❒
  - Proteins ❒
  - Other ❒

Articles (3 max):

Patents (3 max):

FP7 projects related to above capacities:

Line: Techniques and skills in toxicology / toxicity

Research Centre name:

Group:

1.1 Toxicity techniques and skills adapted to the study of the fate of nano-engineered materials

1.2 *In vitro* analysis and studies

Assay	Observations
Citotoxicity	
Inmunotoxicity/Inmunogenicity	
Genotoxicity	
Reprotoxicity	
Oncogenesis	
Others (specify)*	

**Add new rows if necessary*

1.3 *In vivo* analysis and studies

Assay	Observations
Peritoneal barrier	
Inhalation barrier	
Dermal barrier	

1.4 Ecotoxicity analysis and studies

Assays	Observations
Terrestrial plants	
Waters	
Fishes	
Others	

1.5 Distribution analysis and studies

Assay	Observations
In vitro	
In vivo	
Internalization: Tracking, confocal microscopy, etc	

1.6 *In silico* studies of toxicity

Techniques	Observations
Data mining; automatic tools for knowledge mining	
Qualititative models for the prediction of nano-activity relationship	
QNAR: predictive quantitative nano-activity relationship models	

2. Development of assays to assess safety and efficacy of drugs (eg. adaptation to nanoconjugates evaluation)

2.1 *In vitro* assays

Assay	Observations
Cell viability	
Citotoxicity	
Internalization	
Study of toxic/therapeutic action mechanism	
Hemocompatibility analysis	
Other (specify techniques not listed)	

2.2 *In vivo*

Assay	Observations
Therapeutic efficacy in validated animal models with conventional monitoring and/or longitudinal (BLI, etc)	
Biodistribution: Molecular Imaging	
Biodistribution: pharmacokinetics, average life, urinary clearance	
Citotoxicity *in vivo* (necropsis, histopatology, etc)	
Other Inmunogenicity	

3 Available facilities/ equipment

Facilities/equipment	Notes/Comments (eg. capacity, model, type, etc)
Animal Facilities	
Other (specify)	

Articles (3 max):

Patents (3 max):

FP7 projects related to above capacities:

Line: Characterization at the nanoscale (nanobiophotonics techniques and others)

Research center:

Group:

Techniques and skills (adapted to the study of cells and macromolecules, or providing added value in these cases)

1.1 Development of "nanoscopy" techniques

Technique	Bio-applications/Examples
Single molecule detection techniques	
Nano-antennas	
Optical Tweezers	
Near-field optics (NSOM)	
Other (specify)*	

1.2 Development of *in vivo*/*in vitro* assays using these techniques

Assays	Comments

Articles (3 max):

Patents (3 max):

FP7 projects related to above capacities:

Line: Nanoelectronics, sensors and integration

Research center:

Group:

Techniques and skills

1. Capabilities to manufacture nanobiosensors

1.1 Sensor element: Bioengineering / Manufacturing

Manufacturing techniques	YES/NO	Comments
Supramolecular nanochemistry: Dip-pen litography		
Supramolecular nanochemistry: fluidic-enhanced molecular transfer operation		
Nano/micro imprint litography		
Nanowires/nanopores/etc fabrication techniques		
Synthesis and/or use of nanoscale materials as biomolecules tracers (eg. Gold NPs)		
Other		

1.2. Transduction method

Type of biosensor detection	YES/NO	Comment (biomarker detected, etc)
Electrochemistry		
Optical (SPR, interferometric, etc)		
Magnetic		
Other (eg. mechanical)		

2. Integration and other capabilities:

a. Nano/microfluidics (lab-on-a-chip)
b. Separation techniques for sample handling (eg. dielectrophoresis)
c. Other

Articles (3 max):

Patents (3 max):

FP7 projects related to above capacities:

GRUP
Connect-EU
Nanobio + Nanomed

With the support of:

ACC1Ó

Agència de Gestió d'Ajuts Universitaris i de Recerca

Generalitat de Catalunya