BR09

BIOCAT REPORT ON THE STATE
OF **BIOTECHNOLOGY**, **BIOMEDICINE**
AND **MEDICAL TECHNOLOGY**
IN CATALONIA

biocat
The BioRegion
of Catalonia

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Introduction

The importance of driving biotechnology as a countrywide strategy

Dr. Manel Balcells

President of the Biocat Executive Committee

Biotechnology can provide solutions to the needs related to human wellbeing in the future, which are linked to our planet's ability to continue to provide clean air and drinking water, productive land, diagnostic and treatment tools for common diseases, and energy for all human activity. Huge challenges lay ahead of us, to which biotechnology is already beginning to find solutions.

According to the PricewaterhouseCoopers report on investment in the United States in the third quarter of 2009, biotechnology (with 18.82% of investors) and medical technology (with 12.82%) are the first and fourth sectors, respectively, chosen by venture capitalists in this post-crisis era. The energy and information and communication technology sectors were second and third, respectively. 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.

Innovation as a strategy

Innovation is putting inventions on the market, making them productive, making them real solutions that generate economic profit.

As a strategy it is perfect: the whole country must commit to innovation. To do otherwise is not only to be left behind; it is to turn our back to the future.

We already know that on a European level this is clear. It was clear in 2000, at the Lisbon summit, where it was first established that the road to competitiveness lies in the knowledge economy; in 2002, at the Barcelona summit, which confirmed the inevitable need to invest in the knowledge economy in order to be competitive in the future; in 2006, when cluster policy was included in the list of basic priorities for Europe; and finally, in 2009, with the publication of a recovery plan for the European economy that stresses investment in innovation.

What do we have in Catalonia and what are we doing to foster it? The Biocat road map

The BioRegion of 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 see Barcelona being one of the key cities in the global biotech panorama in the next years. This is made clear at events like the BIO convention, in the United States, where Catalonia stood out (in 2009, 50% of Spanish participation was from Catalonia. Spain had the third largest participation, behind France and Germany and ahead of Canada). 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. In many ways, we are the leading biocluster model in Spain, as shown in the last two reports published by the Spanish biotech association Asebio.

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.

In order to foster what we have in Catalonia, we work in strategic and operational areas, providing solutions, establishing joint aims, acting as knowledge partners and signing specific collaboration agreements. It is not only a strategy to drive the sector: we establish the whole value chain, identify areas where it may be necessary and possible to act, and do this with everything from large-scale innovation service infrastructures to networking sessions, strategic plans for the sector, specific training programs or internationalization grants.

Biocat's actions to channel large-scale, countrywide projects are reflected, for example, in the creation of the Biopol consortium, negotiations to establish the Spanish headquarters of the Genome Sequencing Laboratory in Catalonia, and support from the National and Regional Governments to create an office to present Catalonia's bid to become a hub of the European Institute of Technology.

In order to consolidate the sector, Biocat has driven projects both on our own and in collaboration with other organizations. We have signed agreements with the Barcelona Chamber of Commerce, the Barcelona Medical Association, Barcelona Activa, ACC1Ó, ASERM (Spanish Rapid Manufacturing Association), CataloniaBio, Fenin, KimBCN, Asebio and Genoma España, among others. These agreements aim to promote entrepreneurship, coordinate internationalization efforts in the sector, draft strategic plans for the sector, design training programs and collaborate on improving and commercializing research.

In our international promotion activities, we work with the administration to make Barcelona and Catalonia a biomedical hub, putting our capital in the circuit of cities that hold the sector's key events, which can help our companies find partners and international funding, such as the Innovative Medicines Initiative (IMI) and the Interbio project of the SUDOE Interreg Program (Southwest Europe Area). Biocat is also a member of the Council of European Bioregions (CEBR) and has signed collaboration agreements with homologous groups in Quebec (Canada), USA, India and Australia.

Now we need a national innovation policy

Due to the economic crisis, despite recommendations from the European Commission in their economic recovery plan encouraging investment in innovation, significant cutbacks in this area are still taking place in Spain. According to the indicators, the crisis has affected the budget and in 2010 Spain will have fewer resources (3% overall decrease in R&D&i). This is bad news. In Catalonia, according to data available when this report was published, R&D&i budgets will not be changed.

Here at Biocat we ask the administration to encourage competitiveness, invest in the sectors of the future, keep innovation on the agenda, drive the increasing critical mass, foster growth opportunities, seek out strategic alliances and, above all, explore all available funding options. Our partners and, now, competitors are already investing not only in infrastructure but also in specific innovation projects, both public and private; listening to the leaders of top sectors when they ask for funding and reasonably priced land; facilitating access to talent in small companies and creating jobs for the next generation; providing training and support where it is needed.

Current snapshot

A true national innovation policy would contribute to strengthening the life sciences sector, which, as we have said from the beginning, can provide appropriate solutions to our future needs.

However, we must know our real abilities and what we can do to improve them. Who, in our area, has this snapshot? How should we position our sector compared to our competitors? What are the real weaknesses that slow down our growth and delay our success?

Biocat is publishing the first report on the state of biotechnology, biomedicine and medical technology in Catalonia. This is the first snapshot, still cropped a bit close. But it's the first, and we should be proud of it. Any mature sector takes a yearly self-portrait. Not as a self-congratulatory tool, but as a diagnostic one to show what needs to be promoted, changed and acted on. With this document we are showing what companies and research centers in the BioRegion do and the expertise with which they do it. This is an essential step in designing our own innovation policy.

Manel Balcells
President of the Biocat Executive Committee

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The strengths, weaknesses and challenges of a sector for the future

Dr. Montserrat Vendrell

CEO of Biocat

Since Biocat was created in 2006, one of our main objectives has been to consolidate the Catalan biocluster by identifying and raising awareness of active stakeholders in the BioRegion and fostering networking among them. It was, and still is, about creating a *dynamic ecosystem* where different elements complement each other and become more than just the sum of all the parts.

The Catalan biotech sector is still very young; most companies and research centers that make up the biocluster were created after 2000. However, the sector's potential to drive the Catalan economy is clear, if we can not only take advantage of its strengths but also detect its weaknesses and put in motion measures that address and rectify these weaknesses.

This first edition of the *Biocat Report* is a tool to help us move in this direction, because the first step in driving a sector like biotechnology and biomedicine is knowing its size and distinctive characteristics, the type of organizations it is made up of, their legal and financial structure, their specific activities and the needs these create, their economic impact, the type and number of employees, the type of research they carry out and the products this research leads to.

The *BR09. Biocat Report on the state of biotechnology, biomedicine and medical technology in Catalonia* has analyzed all these parameters for the BioRegion's companies and research centers using information from the Biocat Directory, a Biocat survey, and the cross-referencing and extrapolation of available sectorial data from Catalonia and Spain. This is a first approximation, starting from scratch, which will serve as a foundation to carry out later analyses of our evolution. We must also work in collaboration with other organizations to analyze more specific macroeconomic data for the sector in Catalonia. In any case, the data in this first report shows a dynamic, though still immature, sector; an extraordinary capacity for scientific research that has not yet found the way to market products and, therefore, lead industrial innovation and economic development; a sector that is too inward-looking and needs to work on internationalization first in Europe, then in the United States, the world's largest biotechnology market, and finally in developing countries like Singapore and China.

Publication of this report coincides with a moment of reflection in the international biotech sector. Although all economic indicators are still positive —the report entitled *Beyond Borders. Global biotechnology report 2009* (Ernst & Young) shows that the income of European biotech companies increased 13% in 2008 (or up to 17% for publicly traded companies)— venture capital investment in the European biotech sector has decreased 20% over the past year, mainly affecting small and less consolidated companies. This situation shows that we must pay attention to the growth of our companies, because their size and degree of consolidation may become a critical factor in the not-so-distant future.

Analysis of 2008 R&D investment by the top 100 European companies and the 100 largest companies in the rest of the world shows that, despite the economic crisis, the majority have made an effort to continue investment in this area, investing 6.9% more than in 2007. The EU Scoreboard study shows that the pharmaceutical and biotechnology sector —with 18.9% of the R&D investment in companies analyzed— invests more than any other sector, followed by ICT. Nevertheless, we can't forget that the same analysis shows slowing growth of investments (which had increased by 9% in 2007 and 10% in 2006). While North-American companies earmark 69% of their investment for R&D-intensive sectors (biotechnology, ICT, medical technologies), European companies only invest 35% of their funds in R&D&i.

The Catalan ecosystem

Over the past 20 years we have made a serious commitment to research, with investments to promote and consolidate research in our universities and, above all after 2000, to create research centers, science parks and technology platforms. Thanks to these efforts, Catalonia generates 2.5% of all scientific production in Europe and 0.87% of that in the world.

Catalonia is very important in the Spanish scientific research panorama, especially in the areas studied by the Biocat Report: biotechnology, biomedicine and medical technology. More than 70% of all genomics researchers in the country work in Catalan centers. Catalonia has nine biomedical research centers and 12 hospital research institutes, four of which —the Vall d'Hebron Hospital Research Institute (IR-HUVH), 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, through the Carlos III Health Institute. 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 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. And these are just a few examples.

Despite the indisputable overall improvement in research, which Catalonia has led in many fields, the Spanish industrial innovation sector is still among the last in Europe. In the latest Global Competitiveness Report 2009-2010, Spain is ranked 33rd in competitiveness —of the 133 countries analyzed—, with a score of 4.6 out of 7, and one of the weakest factors is innovation. Spain is 40th in this area despite being the eighth world economy. In Spain, the number of patent applications per inhabitant is only one third of the European average and, as our analysis in this report shows, the number of patents and new companies generated by our research centers —which are clear indicators of how scientific research becomes productive innovation— are very low (see section 8.3).

Therefore, we have a high quality developing 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.

The biotechnology sector has the potential to become a key part of this commitment to innovation that our economy so needs. First, we can look at what is happening in the rest of the world. Despite the aforementioned decrease in venture capital investment in the sector, global turnover in the sector in 2008 was 89,648 million dollars, 8.4% more than the previous year. European biotech companies earned 13,548 million euros, 1,800 million more than in 2007 (Beyond Borders 2009, Ernst & Young, 2009). This means that growth is slowing —in 2007 global earning in the sector increased more than 30%—, but the sector has weathered the crisis better than others and has been able to increase both the number of active companies (the Beyond Borders report identified a total of 1,836 companies in Europe in 2008 compared to 1,744 in 2007) and the number of products, particularly drugs. Only in Europe in 2008, there were more than 1,000 products in different clinical (I, II and III) or preclinical phases, although there was a big difference between countries, with the United Kingdom leading the ranking with nearly 250 products in different trial stages.

As explained in the introductory chapters and quantified in the analytical section of this first Biocat Report, red biotech, which is generating new therapies, drugs, diagnostic procedures and treatments that are key to 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 (see figures 7 and 44). 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 the pharmaceutical industry —which invested more than 1,000 million euros 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.

In the field of green biotech, we have a higher percentage of research centers than companies (32.5% of research centers carry out research in this area compared to only 17% of companies in the sector) (see figures 44 and 7, respectively). However, the importance of green biotech applications is clear: from improved animal or plant genetics to transformation and preservation of food, which directly effect economic activity in sectors like agrifood (the most important in Spain with production value of 80,000 million euros in 2008, accounting for 17% of the industrial GDP).

The same is true of white biotech, which applies bioprocesses or biomaterials in traditional industrial sectors in order to make them more profitable and sustainable. Furthermore, biofuel production is considered an alternative energy source that will gain importance in the years to come. And research has generated innovations to deal with important problems like contamination (bioremediation). Therefore, despite the fact that relatively few companies surveyed (17.6%) said they worked in industrial biotech —either as product or process suppliers— and this line of research is studied less in our research centers (27.5%), the potential number of users is huge —and so, therefore, is the market open to biotech companies (see figures 7 and 44).

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.

The ramifications and economic impact of our sector are, as illustrated in previous paragraphs, both important and difficult to define. This was one of the first challenges we had to face in creating this first report on the state of biotechnology, biomedicine and medical technology in Catalonia, particularly in condensing large figures on the sector. Therefore, using the Biocat Directory as our source, we can see that in Catalonia there are 65 biotechnology companies and 70 pharmaceutical companies —including the top five companies in the sector in Spain: Almirall, Esteve, Ferrer group, Lácer and Uriach, not to mention the Grífols group, known worldwide for its hemoderivatives.

According to the Genoma España report on the Relevance of the Spanish biotech sector in 2009, there is a total of 669 companies in the Spanish biotech sector —25% of which are in Catalonia—, while 47 of the 275 purely biotech companies in Spain are located in Catalonia (2008 data). This last group employs 4,240 workers directly, nearly half of which are researchers. As shown in the analytical part of this report, the majority of these companies in the BioRegion are very small, with less than 10 highly qualified employees that work almost exclusively on research tasks (see section 7.5). This model, which is often the result of a spin-off from a company (54% of companies surveyed stated that their origins are in the business sector), university or research center, brings us to one of the sector's weaknesses, which we will later discuss in further detail: the lack of business management know-how in many companies.

In addition to the strictly biotechnology and pharmaceutical companies, we find many others —more than one hundred are registered in the Biocat Directory— that provide services in the sector, from computer development for research to business consulting or training. Another hundred companies work in the medical technology field (in vitro diagnostics, medical devices, bioengineering, etc.).

The Biocat Directory currently registers 106 research centers and nearly 300 research groups in our sector, to which we must add, as explained in Chapter 6, a number of entities (hospitals, universities), facilities (supercomputing centers, synchrotron, etc.) and technical services that make Catalonia one of the leading European research hubs. The analysis carried out for this report 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. Their high level of excellence is, without a doubt, one of the sector's strengths.

The Catalan research system has received an important injection of public funds over the past years, as seen in the following chart showing that R&D&i investment in Catalonia doubled between 2001 and 2007.

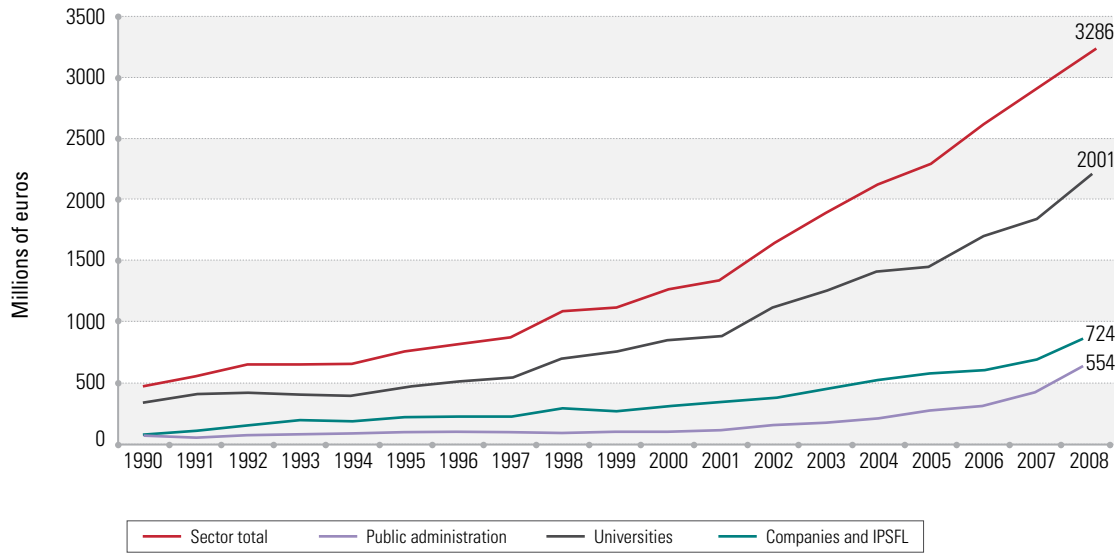
According to the latest analysis of public investment published by the CIRIT for the 2007 fiscal year, different departments of the Government of Catalonia invested a total of nearly 760 million euros in R&D&i, 56.36% of which (428 million) went to universities and research, 19.53% to healthcare (148 million euros) and 11.98% to industry (91 million).

Despite this improvement, we must be prudent in our evaluation of R&D investment in Catalonia, taking into account that the starting point for our country was very low.

Data recently published by the INE shows a 12.9% increase in R&D investment in Catalonia, putting this number at 1.61% of the GDP. Companies invested 60% of the total, while in the rest of the country the proportion is still 50:50. The average R&D investment in Spain was 1.35% of the GDP, having increased 10.2% from the previous year.

We must mention that other regions invest a higher percentage of their GDP than Catalonia, like Madrid (2.00%), the Basque Country (1.96%) and Navarra (1.92%).

Square I. **Evolution of R&D and Innovation Expenditure in Catalonia (in millions of euros)**



Source: *Statistics on R&D Activities for 2008* – Provisional results, National Statistics Institute (INE), Press release 18 November 2009 and *Actions funded by the Government of Catalonia in research, development and innovation.* 2007 budget year, CIRIT, 2008.

*IPSFL: Private not-for-profit institutions

If, on the other hand, we consider the number of patent applications as an indicator of the level of technology transfer (and therefore of economic development) that this R&D investment can generate, we see that, according to Eurostat, in 2005 Catalonia applied for 48,683 patents, behind the 67,652 applied for in Navarra and just ahead of the 44,071 in the Basque Country. In any case, this is far behind the number of patent applications generated by the most dynamic European regions.

All of these figures are global and it is difficult to know what part of this R&D investment is going directly to biotechnology and biomedical research and applications.

Addressing challenges

As shown in this first Biocat Report, we are facing an ecosystem made up of a relatively small number of companies that are very young and have high research potential. However they also have some important weaknesses: their small size —regarding both personnel and capital; the lack of specialized business management staff that also have good knowledge of the sector; and the difficulties they face in finding funding —particularly venture capital— to drive necessary growth.

On the other hand, we have a strong public research system, which has invested a large amount of resources —both economic and human— over the past years, but finds it difficult to put products derived from the ap-

plication of their research on the market. The necessary cultural change among researchers, better governing of research-focused institutions, an incentive system to stimulate innovation and regulation changes that facilitate the transfer process are just some of the issues we must keep in mind.

What are the most urgent challenges we face? In our opinion, those related to strengthening human capital in the sector, driving technology transfer, access to funding, and internationalization.

Human capital

In section 8.5 of this report we analyze the growth in university studies related to biotechnology, biomedicine and medical technology. 18% of degrees offered by Catalan universities (155 degrees) are connected to these fields, but the studies offered are still structured as isolated compartments, focusing on scientific excellence in a specific discipline with little regard to transversal skills and key abilities like intellectual property management, project management, communication, team management, entrepreneurship and innovation. Fortunately, there are starting to be more master's degrees focusing on managing innovative companies, but there is still much work to be done in fostering flexible training and finding a better balance of knowledge and market needs.

Nevertheless, the training of future Catalan biotech technicians and managers is just one aspect we must consider in this area. We also need measures that facilitate the incorporation of talent in biotech companies, allowing them to grow, consolidate and move into foreign markets. To do this, Biocat started up grant programs in the last semester of 2009 in conjunction with the Department of Economy and Finance to incorporate international experts and strategic consultants on company boards. The key to success lies in guaranteeing that this type of aid is stable and continues over time, without being effected by changing legislative mandates, so that companies can incorporate this human capital in their mid-term strategies.

Here at Biocat we have also started up training programs that focus on key issues like the strategic management of intellectual property and business development. However there is still room to expand the educational opportunities offered for those that lead the development of our sector. A region with a high level of knowledge —which must be made available on an international level— where scientists can take advantage of business opportunities and where experts in business management can receive training on specific aspects of the biotechnology and biomedical sector, a place where people with scientific, technological and business backgrounds can come together to develop the new profiles needed in knowledge-based companies. These challenges are part of Biocat's strategy for the coming years.

Driving technology transfer

The important growth in investment in scientific research we discussed previously will not drive our productive system nor encourage innovation in our companies if we are not able to create a dynamic and efficient technology transfer system.

Public research institutions in our country (universities, hospitals and research centers and institutes) must be the main motors of technological development in Catalonia. However, for this to be possible, the knowledge they generate must move beyond these organizations, mainly through the creation of spin-offs or the licensing of patents.

Today we are lacking in specialized entities that are aware of demand, able to identify the potential of research carried out, add value and bring it to market efficiently. On the other hand, we still need changes in the regula-

tory and legal framework to eliminate current barriers, particularly those related to hospital research. The draft of the Science and Technology Act made public by the Ministry of Science and Innovation in February 2009 put forth some measures to address this situation, like allowing public centers to authorize members of their team to work part-time in private entities or eliminating restrictions on contributing capital to companies related to their area of activity. However, at the end of 2009, the future of this act was still uncertain.

Funding

The international recession we are currently experiencing, with the stock markets at a stand-still and venture capital looking towards more developed companies, creates an uncertain future for companies just starting out.

The analysis Biocat carried out (section 7.4) indicates that only 10% of companies have received first-round funding (between 0.5 and 4 million euros) and scarcely 5% have benefitted from second-round funding (normally less than 10 million euros).

The youth and size of these companies, with inexperienced management teams, the lack of specialized venture capital funds that can open doors to international venture capital, business models that focus more on survival than value —less attractive for investors—, generate an inertia that is difficult to stop. These factors also make it difficult to find good-sized international companies for licensing or co-development deals.

Instruments like participative loans with schemes that adapt to the sector's characteristics, guarantee lines that allow access to credit and project-rights funds, can be dynamizing ingredients. Another element to keep in mind is the role family offices can play as a source of funding – responsible for 46% of all biotechnology transactions in Europe in 2008 – in search of refuge for their investments.

Looking to the future

If we take a step back and look at the scene painted in this report on the current state of biotechnology, biomedicine and medical technology in Catalonia, we see a growing sector that is full of potential at a critical point in its development that has coincided with a difficult and uncertain moment in the world economy.

This analysis also tells us that we have the potential to move forward: a leading position in research; a market that demands new products and more efficient solutions that adapt to the needs of the population and are more sustainable; a wide and dynamic business and industrial foundation... We lack, as mentioned above, new talent, a regulatory framework that better adapts to the sector, and appropriate funding instruments. We must drive internationalization —not just opening new markets for our products but also encouraging collaborative work to develop products jointly, because most of all we need international partners that will help us grow— and foster creativity.

Some of the solutions are easy, others quite complex, but we must make the right decisions and mobilize the necessary resources, starting now, so that a few years from now we can stop talking about a developing sector and start talking about a consolidated sector that has become a driving force for our economy.

Montserrat Vendrell
CEO of Biocat

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Figures and scope

This section aims to give the *Biocat Report* reader a quick overview of the impact of the biotechnology, biomedical and medical technology sector, both in the public and business arenas, set in a national and international context whenever possible.

Economic importance of Catalonia

- Economic activity in Catalonia in 2008 generated a GDP of 208,627 million euros (current).
- The Catalan GDP accounts for 19.92% of that of Spain as a whole (2008).

Square II. **Macroeconomic R&D investment data**

Spain

- R&D expenditure in 2008 totaled 14,701 million euros, up 10.2% from 2007, accounting for 1.35% of the GDP.
- R&D expenditure in the business sector increased by 8.3% from 2007, and by 13.8% in the public sector.
- R&D activities were mainly funded by the public administration (6,699 million euros or 45.6%) and the private sector (6,608 million euros or 45%).
- The 2009 budget for the Ministry of Science and Innovation (MICINN) was 5,280 million euros (50.9% for research and 47.7% for innovation). They are expected to reinforce non-financial assets, which will account for 60.8% of the total in 2010.
- The CDTI (Center for the Development of Industrial Technology) invested 1,067 million euros in research projects (CENIT, Interempresas, Neotec...), which is expected to increase by 20.2% to 30% in 2010, depending on the case.

Catalonia

- In Catalonia 3,286 million euros were 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 euros, up 9.5% from 2007); 16.8% from the public sector (554 million euros, up 39.2% from 2007) and 22.3% from the academic sector (724 million euros, up 6.9% from 2007).
- Catalonia participates in 9 of the 18 CENIT projects awarded as of November 2009, with important presence of both technology centers and businesses, for an additional 100 million euros in industrial R&D investment.

International

- The EU-27 invests 1.84% of its GDP in R&D: 54.5% in private investment, 34.2% in public investment and 11.3% in international investment (2007).
- The United States invests 2.61% of its GDP in R&D: 64.9% in private investment, 29.3% in public investment and 5.8% in international investment (2007).

(cont.) Square II. Macroeconomic R&D investment data

Human capital

- In Spain there is a total of 130,966 researchers, making up 6.5% of the working population (2008).
- Catalonia has 25,063 researchers, which is 7.6% of the working population. Of these, 41% work in the business sector (10,276); 16% in the public sector (4,010); and 42% in the academic sector (10,526), representing 24.4%, 19.2% and 18% of the Spanish total, respectively (2007).
- In Catalonia, 70% of all companies that carry out R&D tasks have an average of 104 workers, with less than 10 employees devoted to research. The panorama is quite different in the biotechnology and biomedical sector, with mainly SMEs and microcompanies where nearly 100% of workers concentrate on R&D tasks (see section 7.5).

Square III. Public R&D investment in the sector

Catalonia: biotechnology and biomedicine

According to information collected by Biocat in 2008 and 2009, the Catalan administration earmarked the following funds to biotechnology and biomedical research:

- The Department of Health earmarked 209 million euros (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 euros for research centers (2008). The budget for biotechnology-related CERCA centers was 220 million euros.
- ACC1Ó earmarked 6.7 million euros 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).
- The ICFH earmarked a total of 27 million euros in venture capital funds to be invested wholly or partially in the sector. As of September 2009, a total of 14.5 million euros from these funds had been invested.

Spain: biotechnology sector

- Subsidies for R&D projects, innovation and facilities in Spain was 507 million euros (projects 405 million, innovation 72 million and facilities 30 million).
- The joint total of subsidies and credits —direct and indirect— for the biotechnology sector was an estimated 1,300 million euros.
- The National administration, through the MICINN, earmarked 362 million euros (70%) and regional governments 115 million (22.5%). EU investment increased 18%, to 29 million euros (6% of the total).
- Catalonia received 105.7 million euros (24.9% of the total Spanish investment) in subsidies for R&D projects (2008), putting it at the top of the list, ahead of Madrid (21.9%) and Andalusia (16.44%).

(cont.) Square III. **Public R&D investment in the sector**

- 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 MICINN will earmark an estimated 259.7 million euros in 2010 for hiring personnel. Of this, the majority will go to research personnel training programs (FPI), 94 million euros, and to funding Torres Quevedo (65 million, up 17.8% from 2009).

Square IV. **Business investment and impact**

Pharmaceutical and biotechnology companies make up 18.9% of the R&D investment for innovative companies included in the European Commission's Scoreboard.

Pharmaceutical sector

- The pharmaceutical sector is ranked 10th in industrial turnover in Spain.
- Of all companies in Spain that carry out R&D, 40% are from the pharmaceutical sector, with a growth rate of 3.9% in 2007.
- The pharmaceutical sector was the only industrial sector to experience growth in 2009 (data from September), with a growth rate of 0.8%.
- Catalonia represents 49.5% of the productive capacity in Spain and 4.5% of the financial turnover.
- In Catalonia there are 145 pharmaceutical companies, 45% of the Spanish total.
- The most important Spanish-owned companies have Catalan shareholders: Almirall, Esteve, Ferrer Group, Lacer, Uriach and the Grífols Group.
- Catalonia has 2,306 R&D workers in the pharmaceutical sector (51.3% of the 4,521 in Spain), making up 3.6% of jobs in innovative companies in Catalonia.
- Catalan pharmaceutical companies invested 381 million euros in R&D in 2008 (up 9.6% from 2007). In Spain, investment in the pharmaceutical industry in 2008 totaled 1,001 million euros, which is 63.5% of the total R&D investment in industrial sectors.
- Almirall has 5.3% of the national market share by turnover, Esteve 3.2% and Ferrer Group 1.8% (2007). In 2008 Lacer's turnover was 127.8 million euros. The Grífols Group had a turnover of 689.6 million euros in the first half of 2009.
- Companies associated with the pharma industry (211 companies, 106 of which are Catalan) export 7,368 million euros, 70% to the EU and 9.2% to the USA (2008).

Biotechnology sector

- The direct, indirect and induced economic impact of the biotechnology sector is an estimated 8,189 million euros 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 euros (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.
- Research investment by biotech companies in Spain was estimated at 458 million euros, having increased 25% per year over the past decade. Companies invest 57% of the total (262 million euros).
- Turnover of biotechnology companies in Spain was estimated at 706 million euros for 2008, of which Catalonia contributed 22.7% (160.3 million euros). Annual growth over the past decade has been above 30%.
- Venture capital invested in biotechnology totaled 0.8% (25.4 million euros) 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 euros.
- The average investment is 1 million euros for companies with 20 workers (in the EU-15 the average is 6.7 million/company and in the USA, more than 15 million/company).

Medical technology sector

- The medical technology industry in Spain (1,700 companies employing 30,000 people) accounts for 8.3% of the total European market and generates annual turnover of 6,000 million euros.
- Catalonia accounts for 40% of the Spanish market, with a turnover of 1,200 million euros.
- Catalonia has at least 200 medical technology companies, with a high percentage of SMEs and a few large companies that drive the sector. In total, these generate 5,000 jobs for qualified personnel.
- 70% of demand in Catalonia is from the public healthcare system.
- The global market produces an estimated turnover of 187,000 million euros, 42% in the USA and 33% in Europe, with an annual growth rate of 5%.

Source: Elaborated by Biocat from reports and press releases listed in the bibliography.

Publications

- Catalan scientific publications make up 25.54% of the Spanish total, 2.5% of the European total and 0.87% of the total worldwide (2006).
- Catalonia generates 57% of biomedical publications in Spain (2006).
- In biosciences, Spain generates 3.2% of all scientific articles in the world and 8.5% of the European total (2008). This data situates us fifth among the EU-15.

Patents

- Spain occupies the 9th and 11th place, respectively, for patent applications and concessions in the EU-15, despite having doubled the number of patent applications in 2008 and 2007. In 2008, 200 applications were presented to the OEPM.
- More than half of biotechnology inventors in Spain publish on behalf of foreign institutions or companies.
- The ratio of biotechnology patents registered with the OEPM per researcher is 0.2.
- The number of licenses granted by public centers to companies was 74 in 2008 and 78 in 2007, and the associated economic return is still below 3 million euros per year.
- In Catalonia, according to data from seven public universities, more than 76 patents have been applied for and 22 licenses granted to companies in 2008 and the beginning of 2009.

Contracts with companies

- Contracts between companies and universities for biotechnology R&D projects numbered 1,724, which in 2008 meant an income of 61 million euros for universities in Spain, with an average of 30,000 euros/contract.
- Catalonia generated 453 contracts, valued at 17 million euros in 2008 (23.5% of the Spanish total); the cumulative total since 2000 is 2,479 contracts valued at 73 million euros.

Business creation

- From 2000 to 2008, universities in Spain promoted the creation of 76 spin-offs (estimation), which shows an average growth of 10-12 companies/year.
- In Catalonia, according to data from seven public universities, more than 24 companies were created in 2008 and the beginning of 2009.

BR09

BR09

Trends and impact of biotechnology: opportunities for Catalonia

1. Biotechnology: trends and answers in a key sector of the economy

John Burdon Sanderson Haldane (1892-1964), renowned British geneticist (and one of the founders of population genetics), believed that if something could be made by a microbe it wasn't necessary for humans to make it. With this thought, he gave us a glimpse of the concept of biotechnology as a tool for obtaining technical solutions. However, he probably never imagined that biotechnology would become what it is now: one of the driving forces behind the economy and a limitless source of technical improvements for human healthcare and wellbeing.

1.1 The biotech revolution

The 20th century saw the domestication and use of living beings that were previously unknown and species that hadn't been used before: bacteria, yeast, worms, insects, plants and vertebrates that could do almost anything. It also brought us descriptions of basic (genetic, molecular and cellular) mechanisms that make vital functions possible. We now know about biological mechanisms, which can be used both inside and outside of the original host**,** adapted to our needs, and combined to invent new capacities.

For nearly all of our existence, human beings have taken advantage of thousands of years of evolution to live better, although in a relatively passive way. First came plants to heal, animals to eat or yeast for bread and beer; then came microorganisms for antibiotics and vaccines. However we now understand the mechanisms behind them and know the molecular foundation of genetics, which allows us to create and not just use. We know how the immune system responds, which allows us to create new flu vaccines in less than six months; our knowledge of the biochemical and genetic base of both rare and common diseases is increasing. This profound understanding of nature and its basic mechanisms, and how they can be applied, is the root of biotechnology. In some cases, the ability to manipulate raises ethical issues: genetic selection of embryos; stem cells for therapeutic and reproductive use; genetically modified plants and animals are just three topics that are currently the focus of intense political and moral debate, which reveal the extent to which the profound knowledge and technological capabilities being developed in society are important beyond just economics. These examples, although extremely sensitive issues that should be treated with maximum rigor and respect, are just one slice of the wide range of possibilities biotechnology offers.

This first Biocat Report aims to put this revolution in context, with elements to help understand where we are, where we've come from and where we're going. We will also discuss the economic impact of biotechnology in advanced societies, and the situation of the sector in Catalonia.

1.2 The biotech industry

A unique sector

There isn't a definitive definition for the biotechnology industry or sector. According to the OECD (Organization for Economic Cooperation and Development), biotechnology introduces a new element to the production chain, living organisms, which is added to the traditional elements, liquid assets, fixed assets, infrastructure and human capital. Therefore, biotechnology, understood to be "the exploitation of biological processes to obtain technical solutions to be applied to new products and services", is really a transversal platform, and according to this criteria we could probably classify many companies as biotech companies, although this would not help us understand their econom-

ic leverage or the dynamics of this new sector. There aren't any pharmaceutical companies that don't use biotech tools to discover new drugs, but including these companies in the analysis of trends in the sector could skew the data. The influential publication *The Future of Biotech: The 2010 Guide to Emerging Markets and Technology 2009* (BioWorld, 2009), posed the question of how to identify a biotech company and came up with three possible characteristics based on three different criteria: scientific, cultural and structural:

- **Scientific criteria:** biotech companies develop or apply biological products as therapeutic, diagnostic, industrial or food agents and offer services based exclusively on molecular or cellular techniques.

- **Cultural criteria:** they are dynamic and agile decision-makers, operating in the biotech arena even if they don't necessarily generate biological products or services (a small chemical company, for example, that generates new molecules through traditional synthesis but has a biotech culture).

- **Structural criteria:** they tend to be small companies, normally less than 50 employees, are research-intensive, have received venture capital, and use some biological processes in their research or production tasks.

In any case, in the field where the biotechnology sector is most mature, biotech applied to healthcare, there is talk of a convergence between the pharmaceutical and biotech sectors. Large pharmaceutical companies add biological products to their pipelines, like antibodies and nucleic acids, and large biotech companies (like Amgen and Biogen-Idec) add chemically synthesized small-molecule products to their pipelines. In the field of biotech applied to healthcare, the cultural and organizational aspects are the clearest way to define a biotech company, although it is becoming more difficult to distinguish between a mature biotech company and a small pharmaceutical one.

Potential for growth

There is a general consensus that biotechnology can become a strategic sector for local economies. This sector has an expansive dynamic and its applications are still in the active growth phase (in healthcare applications the biotech sector is the main driver of the increased global turnover in pharmaceuticals; double-digit growth is expected in the bioenergy field over the next 10 to 20 years; there are always new applications, etc.). Nevertheless, one of the sector's disadvantages is its inertia. The value cycle is long, expensive and risky. However, with the appropriate incentives, the sector can grow and mature, showing a huge potential to transform productive models in a specific area. This has been the case in Cambridge (United Kingdom), Montreal (Quebec, Canada), Munich and Berlin (Germany), Copenhagen (Denmark), Turku (Finland) and all of Ireland, among others. In Catalonia, incentive mechanisms for the creation of new biotech companies have been in place since the end of the 1990s. In these ten years they have led to a business base that grows more than 20% per year (Asebio Report, 2008), and has generated nearly 2,000 jobs in the private sector, despite the fact that it is not yet a mature biotech sector.

The sector's potential can be seen in science parks, like the PCB (Barcelona Science Park) with more than 40 biotech companies. All of them started from scratch and nurture technology originally developed in academic environments. The first to locate to the PCB began operations in 2001, and nearly all of the companies that started there are still active, despite the fact that most Catalan biotech companies didn't exist before 2004.

Regarding employment, growth in the biotech sector generates new job opportunities: it is one of the few economic sectors that created new jobs in 2008, as shown in the pilot study carried out by CataloniaBio (*Functional structure, salary schemes and professional opportunities in the Catalan biotechnology sector 2009*). And the numbers are beginning to be noteworthy: five of Catalonia's pioneering companies (Advancell, Enantia, ERABiotech, Lipotec and Oryzon Genomics, which moved to Cornellà in September 2009 but still has laboratories at the PCB) currently employ up to 300 highly qualified workers.

New work opportunities generate a certain demand for training, due to the need for qualified technical personnel, in advanced vocational degrees and specialized bachelors degrees. As a result of this increased demand, the Autonomous University of Barcelona offered the first biotechnology degrees in 2004. Similar degrees are currently offered at the Universities of Vic, Pompeu Fabra and Lleida. Business schools are also focusing more on biotechnology, with

specific degrees offered at the Aliter International Business School and the IE Business School (both in Madrid).

The biotechnology sector, both in the public and private arenas, requires highly trained technical personnel to carry out research and support tasks. Specialists in molecular biology, nanotechnology, bioinformatics and cellular biology, among others, are needed. However, this leads to a paradox: the wide range of life sciences degrees offered generates a large number of university graduates that tend to seek out opportunities in the public sector, creating an excess of qualified personnel that could find a place in the private sector. And the biggest opportunities and weaknesses in the sector can be found in management. The sector's complexity makes it difficult to manage, and requires hybrid profiles (technical specialists that can carry out management tasks). There are opportunities in financing (venture capital funds need professionals that can evaluate new technology), in coordination (project management is essential to virtual business models), in industrial and intellectual property (it is impossible to draft or defend a biotech patent without significant technical knowledge) in marketing and communication (when selling expectations, communication is key), and in regulatory strategy. Finally, it is difficult to find qualified professionals to carry out business development and lead a biotech company beyond the initial start-up phase.

In short, growth of the biotech sector in Catalonia is generating new jobs for scientists and technicians in the life sciences field that go beyond merely applying technology. When the public sector can no longer absorb all the biomedical and biotechnology professionals, the private sector has a high enough potential for growth to absorb a good part of them, above all if they are able to integrate technical knowledge with transversal skills like negotiation and project management.

1.3 The colors of biotech

The theme of the BIO Convention (the most important event in the global biotech sector, organized each year by the American Biotechnology Industry Organization) in 2008 and 2009 was Healing, Feeding and Fueling the World. We are living a not-so-silent revolution, which is growing and taking over more sectors from healthcare to fine chemicals, from farming to oil refinery, from food to environmental recovery and textiles. The theme of the BIO Convention can be used to define its segments. Currently we talk about three colors: red for biotech applied to healthcare; green for biotech applied to agrifood; and white for industry-related applications. Some in the sector also use blue to define marine biotech, but we will not apply this criterion in the current report.

Red biotech or healthcare (biotech to heal)

This group is made up of therapeutic, diagnostic, animal health and biomedical research applications. It can also include biotech applied to developing functional food and neutraceutics.

Green biotech or agrifood (biotech to feed)

Although this is the most well known category because it includes transgenic crops (GM, or genetically modified, foods), in a larger sense it can include biotech applied to plague control (biocontrol), to improving soil quality (biofertilization), and even the agrifood industry (without a doubt society's first biotech industry, manufacturing bread, wine, yoghurt and beer are strictly biotechnology activities).

White biotech or industry (biotech to fuel)

This category includes all biotech applications linked to the chemical industry, to industrial processes for processing raw materials, to generating biological tissues, to generating fuel (biofuel), to biodetergency and bioremediation, which use biotechnology to decontaminate or prevent contamination, etc.

1.4 Red biotech

In fact, when we talk about the biotech sector we think of companies that carry out biomedical tasks, although this is not a real reflection of biotechnology and is due to our bias for this area as a result of its impact on public health. Biotech drugs first appeared with recombinant insulin in 1983, and now include more than 100 different molecules to treat over 200 different diseases, from arthritis to cancer, from highly prevalent diseases to rare ones like cystic fibrosis. Examples include insulin, growth hormones, coagulation factor IX, erythropoietin and its variants, interferon, etc. And those of the 21st century: monoclonal antibodies, Enbrel and human papilloma and cervical cancer vaccines.

In addition to this arsenal of new drugs, there have also been many spectacular advances in the diagnostic sector, where monoclonal antibodies, PCR (Polymerase Chain Reaction) and lower costs of DNA sequencing, in addition to increased sample and data processing capacity thanks to nanotechnology and bioinformatics, bring personalized medicine closer to reality. Before discussing figures on the economic impact of red biotechnology, we will first give a brief overview of the most important milestones in the history of biotechnology as a differentiated sector.

Square 1. **Genentech**

Modern biotechnology received its first big push in 1953, when James Watson and Francis Crick published a brief text in Nature (less than one thousand words) describing the structure of DNA and envisioning a mechanism to copy it. Watson and Crick, by deciphering the key mechanisms of life, opened the doors for possible commercial exploitation.

Nevertheless, 25 years would pass before biotechnology became an economic sector in its own right as well as an industry. October 1980 saw one of the most successful initial public offerings on the stock market up to that moment, from Genentech, a small company created by scientists from the University of California in San Francisco with support from a 27-year-old venture capital visionary from Silicon Valley. It wasn't coincidence that the huge expectation in the stock market created by Genentech was based on the discovery of Watson and Crick, in addition to 25 years of constant technological improvements. Basically, Genentech promised the possibility of creating new drugs based on our knowledge of how genes (written in DNA) codify protein synthesis (structural and functional building blocks of the cells), and on our technical ability to cut and paste pieces of DNA at will. Enough tools to manipulate genetic information in a controlled manner had been developed between 1953 and 1978, and we had learned to use bacteria to manufacture proteins. The first recombinant proteins (produced through genetic engineering) announced by Genentech were Somatostatin, which is still used as a therapeutic agent (in 1977), insulin (1978), growth hormone (1979) and interferon (1980). And the first commercial milestones included approval of recombinant insulin in 1982 (marketed by Lilly as Humulin) and the commercial launch of the growth hormone Protropin by Genentech in 1985.

The Genentech IPO wasn't only a technological milestone. Genentech also laid the foundations of the current biotech business model: hyping technology that can solve unresolved healthcare problems, transforming this hype into economic value so it can be bought and sold in a market similar to the futures market. With Genentech, and shortly after Amgen, the figure of the venture capitalist appeared, as well as the concept of technology transfer from public institutions to the private sector (in 1999, after a nine-year legal battle, Genentech had to pay the University of California in San Francisco (UCSF) 200 million dollars in recognition of their contribution to developing the technology the Genentech growth hormone was based on. And that wasn't all; Stanford and UCSF have earned hundreds of millions of dollars in royalties from the Boyer-Cohen patent since it was approved in 1980. This patent exploitation model for commercializing intellectual property is followed in many universities and research centers around the world. Genentech was also a pioneer in reinforcing the credibility of its message, establishing research, development and commercialization alliances with large pharmaceutical companies, like Lilly, to develop and market the first recombinant insulin.

Finally, another pioneering aspect of Genentech that is characteristic of the sector as we now know it is the transformation from scientists to company founders and managers.

Herbert Boyer, founder of Genentech, was vice-president until 1990, and later served on the Board of Directors. An article in Scrip in 2000 revealed that in that same year there were nine CEOs in American biotech companies that had begun their careers as scientists, at Genentech! It is not uncommon in the sector today to see people move from scientific to strategic management tasks (business development, project management or general management).

Important milestones

1953 Nature publishes article by Watson and Crick, proposing double helix structure of DNA and a mechanism to copy DNA information from one generation to the next.

1966 Genetic code deciphered, showing correspondence between nucleotide triplets and each of the 20 amino acids that make up proteins.

1972 Paul Berg and collaborators make first recombinant DNA molecule and publish their work in PNAS (Proceedings of the National Academy of Sciences).

1976 First monoclonal antibodies produced. Unlike genetic engineering, the procedure developed by Milstein and Kohler to obtain monoclonal antibodies wasn't patented.

1977
- Genentech announces first human protein for therapeutic use produced in bacteria through genetic engineering: Somatostatin.
- Walter Gilbert and Allan Maxam design a simple method of DNA sequencing, used extensively through the end of the 1980s.
- Sanger develops own DNA sequencing method.

1978 Genentech produces insulin (rights would be licensed to Lilly years later in a pharma/biotech collaboration model that is still used today).

1981
- First transgenic mice (carriers of genes from other living beings) obtained at the University of Ohio.
- Hoechst AG sets precedent in the industry, paying 70 million dollars to Massachusetts General Hospital for exclusive rights to patents generated there.

1982 FDA (Food and Drug Administration) approves first drug obtained through genetic engineering: bacteria-produced insulin.

1983 FDA approves first diagnostic test based on monoclonal antibody (to detect Chlamydia infections).

1984 Technique developed based on genetic printing, to identify people using their DNA. This technique began to be used in legal medicine in 1985.

1985
- Cetus launches PCR technology (Polymerase Chain Reaction), which generates thousands of millions of copies of DNA from just one molecule in a biological sample in only a few hours.
- First regulatory guidelines for human gene therapy experiments approved.

1986
- First therapeutic monoclonal antibody approved (for kidney transplant rejection), 11 years after first description of the technology.
- First automated fluorescent DNA sequencers appear, anticipating the possibility of sequencing complete genomes and laying the foundation for future human genome sequencing.
- FDA approves first vaccine using recombinant technology, for hepatitis B, developed by Chiron Corp. First recombinant product to treat cancer also approved: interferon.

1988 First patent for transgenic animal granted to Harvard scientists (Philip Leder and Timothy Stewart) for a mouse with elevated tendency to develop breast cancer.

1989 National Center for Human Genome Research created with the aim of completing human genome sequencing by 2005 and initial budget of 3,000 million dollars. One year later, the Human Genome Project, an international initiative with a budget of 13,000 million dollars, was officially launched.

1990 First clinical trial of gene therapy: patient Ashanti da Silva, then a four-year-old child with a gene mutation

that caused a deficiency of an enzyme that is key to the immune system, began to receive periodic injections of cells from her own blood to which the normal gene had been transferred.

1993
- Recombinant interferon beta approved to treat multiple sclerosis.
- Kary Mullis receives Nobel Prize in Chemistry for invention of PCR.
- Biotechnology Industry Organization (BIO) created, which currently has 45 state-level organizations in the USA.
- First connection between gene and breast cancer discovered, followed by explosion of connections between genes and diseases. This led to the creation of a new generation of biotech companies (genomics) that specialize in researching this type of connections and patenting new genes: Human Genome Sciences, Incyte, Pharmagene, Decode Genetics, Millenium.
- First drug approved in 30 years to treat cystic fibrosis, a recombinant version of the dNase enzyme.

1995 First complete sequence of a living organism obtained (previously only virus had been sequenced, including HIV): the bacteria Haemophilus influenza.

1996 Sequencing of first eukaryote: the yeast Saccharomyces cerevisiae.

1997
- Dolly the sheep cloned at the Roslin Institute in Scotland. First monoclonal antibody with anti-cancer activity approved, for patients with non-Hodgkin's lymphoma.

1998
- Monoclonal antibody to treat Crohn's disease approved.
- First animal genome sequencing completed: flatworm Caenorhabditis elegans, often used as a model in experiments.
- RNA interference discovered, leading to high-impact technology. Scientists that discovered the technology, Craig Mello and Andrew Fire, were awarded the Nobel Prize in Physiology or Medicine in 2006.

2000
- Celera, headed by Craig Venter, with collaboration from the academic arena, publishes sequencing of 180 mb of genome from Drosophila melanogaster, the longest sequence up to that moment and confirmation of Venter's controversial shotgun method.
- Joint announcement of first draft of human genome sequencing, by Human Genome Sequencing (16 institutions in France, Germany, Japan, China, United Kingdom and United States) and Celera, at a joint ceremony at the White House.

2001 Publication of two drafts of the human genome: in Nature (15 February) and Celera in Science (16 February).

Square 2. Targeted gene therapy: the long road

In 2009, nineteen years after the first clinical trials, there was only one commercial treatment, in China (approved in 2003), for head and neck cancer*. In 2005, analysts said that the potential market for gene therapy products could reach 5,000 million dollars in 2011. However, looking at the developments underway in 2009, it is hard to believe this prediction will come true. Despite the great potential, biology is stubborn and in addition to the risk involved in using viral vectors to administer DNA we must also mention that it has been shown that random insertion of DNA into cell genomes can cause cancer. It isn't crazy to say that gene therapy, after spending more than 5,000 million euros on some 1,800 clinical trials since 1990, is one of the therapies with the greatest unfulfilled potential in the brief history of biotechnology as a business.

However, there are some 200 biotech companies that carry out gene therapy research and venture capital funds are interested in investing in this research. Developing non-integrative vectors (that can express genes without being part of the main genome), the practical demonstration that it is possible to develop DNA-based vaccines and improve vehiculization systems for drugs in the field of nanomedicine partly explain why gene therapy is still an area of interest for developing new drugs. This area is made up of some 250 active clinical trials funded by the industry, according to the NIH register (National Institutes of Health) in the USA, but initial expectations have been lowered and will possibly be surpassed by the curative possibilities offered by stem cell therapies.

* Incluye los cánceres de laringe, conducto nasal y nariz, cavidad oral, faringe y glándulas salivares.

2002 Promising data on the first cervical cancer vaccine, based on inhibiting human papilloma virus. Only in 2009 would vaccines become a commercial reality (Gardasil, from Merck, and Cervarix, from Glaxo)

2003/ 2009

The list of milestones in this period is so long and the acceleration seen in different areas connected to biotech over the past years has been so fast that it is difficult to highlight specific dates. We could even say that we lack the necessary perspective to do so. In fact, some speak of new or contemporary biotechnology when referring to fields that have achieved spectacular breakthroughs. Nonetheless, following are some particularly important events:

- Tests for cellular reprogramming, a mechanism that creates stem cells from the sperm cells of a number of patients.
- Micromatrix technique, which shows expression and translation profiles of nucleic acids (and is the base of diagnostic chips associated with personalized medicine).
- Stem cell cultures for many different applications, including cloning animals for production or pets, regenerative medicine or cell therapy.
- Other spectacular breakthroughs have been made in molecular diagnostics, with the development of markers, or in genome sequencing, with faster and more affordable techniques, or in the application of genetic engineering to plants, insects and animals to obtain drugs (biopharming). We could also add to this list the new promises in gene therapy, which have led to a revitalization of the technique, or the efforts of synthetic biology to develop "a la carte" life forms with industrial or therapeutic applications. We hope that a few years from now all of these can be used to generate important breakthroughs, but for now we have decided to discuss only a small selection in the section entitled "Tools: five technologies for the future".

Square 3. **Theranostics and targeted therapy**

The positive results obtained around 1998 with the new monoclonal antibody (trastuzumab) opened up what is known as theranostics, or therapy associated to an existing diagnostic condition that is part of the treatment. The antibody blocks estrogen receptors that, when present, indicate a type of breast tumor. This association between antibody and receptor was a breakthrough in separating patients according to personalized criteria and thus increasing possibilities of successful treatment. At that moment, the term theranostics was coined to express this association. In 2009 the development of new drugs associated to a patient's molecular diagnosis is considered one of the industry's new paradigms.

Square 4. **Transfer RNA (RNAi)**

Seven years after this technology was discovered (Breakthrough of the year in 2002 and Nobel Prize in 2006), it is commonly used as a tool in research laboratories. In 2009 there were many companies (some 200 in the world and 20 in Spain) that based their business model on applying RNA interference (among them Silentis, from the Zeltia group, which announced approval to start clinical trials with their first therapeutic product based on this molecule in July 2009). There are products in clinical phase II, essentially for local application (the first indications were connected to macular degeneration, with direct injection into the eyeball). The first product for systemic administration, by Quark Pharmaceuticals, is aimed at reducing complications associated with kidney transplants and is in phase I/II trials.

At the end of 2006, Merck paid 1,100 million dollars for partial rights to develop the products of one of the companies with the most solid intellectual property, siRNA Therapeutics (in reference to small interfering RNA). It is important to point out that this company, one of the pioneers in developing therapeutic applications for RNAi, had to reinvent itself, as it began its history in 1992 under the name Ribozyme Pharmaceuticals, based on the discovery that RNA could have catalytic activity. This discovery –deserving of a Nobel Prize– never reached fruition, even after an investment of 200 million dollars. However, the work done and the methodological parallelisms between ribosome technology and RNA interference allowed the company to attract 48 million dollars in 2003 and become siRNA Therapeutics.

Economic impact

This field of biotechnology stands out for its therapeutic applications. In 2000 Ernst&Young (*Convergence: The Biotechnology Industry Report*, 2000) was one of the first to speak about the convergence of biotechnology and pharmaceutical companies. After that year, biotechnology became a true driving force behind growth in the pharmaceutical industry (see square 5).

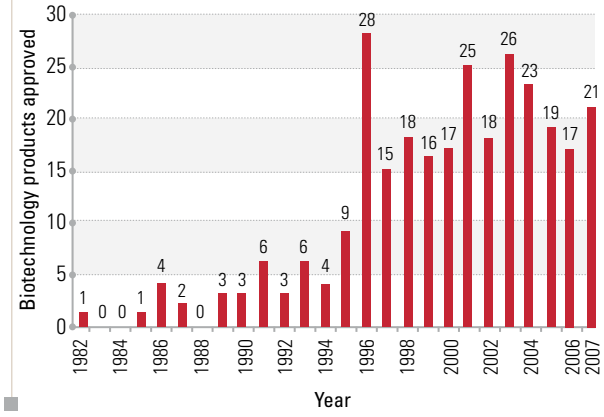
One result of this is that, while the drug industry grew around 5% over the past years, sales attributed to biotechnology-based drugs have grown over 10%. Therefore, the influence of biotechnology on new drugs is becoming more relevant, which is made clear by analyzing the historical evolution of biotechnology drug approval: during the 1980s there were five; in the 1990s, 103; from 2000-2008, 283 new drugs were registered. And, more importantly, 35% of drugs currently in development are based on biotechnology (figure 1).

In 2008 nearly 15% of the global pharmaceutical turnover, 780,000 million dollars, corresponded to biotechnology drugs, with five purely biotech products selling over 5,000 million dollars per year (see table 3). It is estimated that by 2015 more than half of all new drugs will be biotechnology-based.

Furthermore, according to the Burrill Report 2008 (*The Billion-Plus Blockbusters: The Top 25 Biotech Drugs, BioWorld®*, 2009) on sector trends, 75% of all products approved for new indications were biotechnology-based in 2006 and 2007. Biotechnology, thus, is having a significant effect on the drug chain, both in sales and annual growth, as well as in the generation of new products and as a vector for discovering drugs to treat diseases that previously had none.

We must point out, however, that if we take into consideration the aggregate data for the industry, regarding publicly traded companies, the sector is not yet generating profit. The good news is that, despite the crisis, it is very close to achieving this goal. According to data from Ernst&Young, in 2007 aggregate losses totaled 3,100 million dollars, while in 2008 this figure was only 1,400 million (*Beyond Borders, Ernst & Young*, 2009). According to the 2009 edition of another important report on the sector, the Burrill report (*Biotech 2009: Lifesciences, Navigating the Sea Change*, Burrill & Co., 2009) (which only takes into account

Figure 1. **Biotechnology products approved between 1982 and 2007**



Square 5. **Craig Venter and the frontier**

2001 Prince of Asturias award-winner Craig Venter was the first person to sequence the whole genome of an organism (Hemophilus influenza in 1995). He was the driving force behind human genome sequencing projects and their commercial applications through the company Celera Genomics. He also created the first totally synthetic virus, in 2005. In 2007 he announced that he had all the necessary components that make up a viable organism, and he demonstrated it in 2008 when he synthesized the bacterial chromosome with the highest capacity for self-replication (Mycoplasma genitalium). In August of 2009 he announced that he had successfully transferred a bacterium's genotype to transform it into another, with different and new functions. This opened the door to "a la carte" microbial design, mainly in order to generate cleaner energy, eliminate industrial contamination and reduce CO2 levels in the atmosphere. His latest company, Synthetic Genomics, leads the field of commercial applications of synthetic biology, mainly to obtain microorganisms for generating new biofuels, stabilizing atmospheric CO2 levels and bioremediation.

Table 1. **Top-selling biotechnology products**

Commercial name	Technical name	Indications	Company	Total sales in 2008 (millions of dollars)
Enbrel	Etanercept	Arthritis	Amgen-Takeda-Wyeth	6.378
Rituxan/ Mabthera	Rituximab	B lymphocyte cancers, rheumatoid arthritis	Roche-Genentech	5.449
Avastin	Bevacizumab	Glaucoma and different types of cancer	Roche-Genentech	5.207
Herceptin	Trastuzumab	Breast cancer	Roche-Genentech	5.092
Neupogen/Neulasta	Filgrastim/Pegfilgrastim	Neutropenia	Amgen	4.659
Humira	Adalimumab	Psoriasis, arthritis, Crohn's	Abbot Laboratories	4.521

Source: *MedTrack, 2009 and Beyond Borders,* Ernst & Young, 2009.

Table 2. **Macroeconomic data on red biotech in 2008**

Area	Number of companies	Employees	Turnover (millions of dollars)	R&D expenditure (millions of dollars)	Financing (stock market or increase of capital) (millions of dollars)
USA + Canada	2.112	141.930	68.168	25.973	13.476 (22.451 en 2007)
USA	1.836	47.720	16.515	5.171	2.595 (7.494 en 2007)
Asia - Pacific	769	15.280	4.965	601	Sin datos
Total	4.717	200.760	89.648	31.745	<20.000
Total 2007	4.414	204.930	84.782	31.806	>30.000

Source: *Beyond Borders: Global biotechnology report,* Ernst&Young, 2009.

a selection of companies traded in the United States), the sector generated profit for the first time in 2008, around 3,500 million dollars. And, if the sector doesn't break even in 2009 it will be due to a growing trend for biotech companies that generate profit to disappear in the statistics, because they are acquired by pharmaceutical companies. The clearest case of this is Genentech: when the acquisition by Roche is complete it will no longer be included in worldwide biotechnology statistics.

Business models

In a value chain with such a long cycle and with so many technical uncertainties, like with red biotechnology, various niches can be occupied by companies using different business models. Forgetting fully integrated companies for the moment, which can assimilate perfectly to the pharmaceutical industry (large biotech companies like Genentech, Genzyme, Biogen-Idec, Amgen and CLS), and cover the entire value chain, the classification that best explains the biotechnology universe is based on the technology companies offer. Specialists talk about product-based companies, platform-based companies and research (CRO: Contract Research Organization) or manufacturing (CMO: Contract Manufacturing Organization) service companies.

Product-based companies

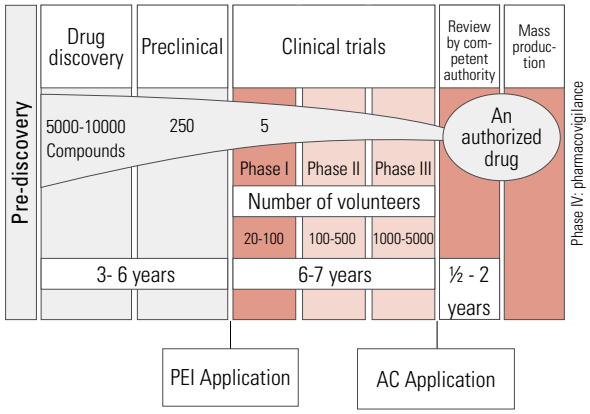
The vast majority of these companies don't really have any products on the market. Their value is based on ex-

Table 3. **Top 4 biotechnology companies by profit**

Company	Turnover (2007)	Employees	Drugs for sale	Drugs in development	Market value (millions of dollars)
Amgen	14.700	17.450	19	77	52.500
Genentech	12.177	11.174	41	107	87.140
Genzyme	4.268	10.000	24	50	17.760
Biogen-Idec	3.922	4.300	9	47	11.880

Source: *Medtrack*, updated in October 2008

Figure 2. **The R&D process: Long and complex**



PEI (Producto en fase de investigación clínica)
AC (Autorización de Comercialización)

Source: *Profile*, Pharmaceutical Research and Manufacturers of America, 2009

pectation of success of one or a number of molecules currently in development. Normally they created the molecules they develop and try to advance their development until they obtain proof of clinical concept, meaning until they show that the molecules have some level of effectiveness in patients. The end-client for these companies isn't the patient or the prescribing doctor, because few of them commercialize the drugs on their own. Their possible end-clients include specialized venture capitalists, the capital market, large biotechnology companies and the pharmaceutical industry, which bases 30 to 50% of its pipeline on products acquired in the initial phases from the biotechnology industry. Over the lifespan of product-based companies, we can observe a move towards advanced phases of development, close to market, and even a commitment to commercializing their own products in niche markets (a good example is Pharmamar, which commercializes Yondelis, a drug for soft-tissue sarcoma, which a fairly uncommon indication that can be served with limited commercial effort, and to which they licensed the rights for ovarian cancer, a much larger market, to Johnson&Johnson).

Technology platforms

These are companies created around a potentially disruptive technology (meaning that it allows us to do things that were previously impossible or significantly improve what can be done), and offer their platform transversally for molecules from other companies (some examples in Catalonia include Aromics, Arquebio, Leitat and Omnia Molecular, among others). Normally, they need some time to mature before showing that their technology works and exploiting its potential through limited agreements that include a feasibility phase and, later, an execution phase, which is associated to a license. These companies tend to evolve into product-based companies (given that in the long run they develop their own pipeline) or are absorbed by the industry after a first exploratory phase that serves to validate the utility of the technology. Drug delivery companies, when based on patented technology, tend to use this business

model instead of a service-based model (in Catalonia, Activery Biotech, Cocali, Endor Nanotechnologies and GP Pharm from the Lipotec group, among others), although there are strictly service-oriented drug delivery companies.

Service companies

These companies specialize in a specific niche in the value chain. They are CROs (in Catalonia, Infociència, Intelligent Pharma, IUCT, Kymos Pharma Sciences, Recerca Clínica), or CMOs (BCN Peptides, Bioglane, BioIngenium, Enantia) that specialize in chemical synthesis or biological products. There are even some CBDOs: Contract Business Development Organizations) (Trifermed), where large international companies can develop a drug from the preclinical through the final phases (Covance, Huntington and Quintiles), or that are clearly positioned before phase I (Aptuit). The panorama of service companies connected to red biotech is very wide. So much so that it has led to a new paradigm of a virtual company (see section 1.6.). Companies with few people and enough money can carry out the full drug development cycle, from discovery (licensing the rights from a university) through industrial production (using a CMO specialized in chemical or biological development, which is necessary to move from pharmaceutical formula to commercial scale), clinical development (working with preclinical CROs for safety and toxicology tests and with clinical CROs to complete development) and approval (using CROs specialized in regulatory management).

We must also mention that specialized venture capital does not normally invest in service companies, as they believe their growth potential is limited, except in exceptional cases (Sofinnova, one of the most important operators, invested in CEREP, an in vitro pharmacology service provider that is traded on the French stock market). In immature markets (like the Catalan market in regards to biotechnology investment), the trend is just the opposite. It is easier to obtain initial or seed financing with proposals that use a mixed business model, combining a product-based model with a service- or technology-based one. The money, however, doesn't come from large, international, specialized venture capitalists, but from government funds or other private alternatives. The economic crisis is reinforcing this trend, because many proposals to create value in the long run have had limited access to capital since the beginning of 2008. And, according to Steven Burrill in his latest report, this situation will not change until the end of 2010.

New paradigms

An entrepreneur that wants to convince an investor to support the development of a new technology must use a series of pioneering concepts with an economic perspective of the future market that allow the investor to see the business model that will be used to carry out development. And all of this in the long term, as investors specializing in biotechnology look at the long-term and invest in projects that will be profitable in some ten years. To make a selection of these pioneering market concepts we must first discuss the future trends regarding application and business models. This report has made the following selection:

Targeted therapy

We understand the mechanisms of different pathologies better and better, which allows us to design strategies to target only diseased cells and not those that are healthy. Oncology is a good example, with 70 products in development that could clearly be classified as targeted therapy. We assume that this strategy will lead to safer drugs, with fewer side effects, that are possibly more effective.

Personalized medicine

This will be the Holy Grail of healthcare biotechnology over the next few years. Steven Burrill, one of the most important opinion-makers in the industry, uses a graphic image to explain personalized medicine in the future: an individual goes into a shopping center to buy a diagnostic kit, where they deposit a drop of saliva and then send the results to a virtual pharmacist, who will prescribe a drug or not depending on the results, not only to treat a symptom but also to prevent future diseases.

Beyond these futuristic projections, personalized medicine is already a technical and business reality (see square 5). Genetic or protein profiles help predict a patient's response to a specific treatment; some biomarkers indicate the need for specific medicines and in some cases help predict the probabilities of developing certain diseases.

It is becoming more and more important to associate the development of new drugs with specific biomarkers or diagnostic systems that allow us to predict individual effectiveness or toxicity of a drug (associations known as companion diagnostics or response biomarkers). In more prevalent diseases, patients are divided into subpopulations, depending on their risk of developing the disease and their capacity to respond to treatment. Doctors can decide –and are already deciding in some cases– if it is necessary to medicate the patient and with which drug, depending on their genetic profile and the presence of certain biomarkers in their blood, saliva or urine.

Companies devoted to personalized medicine attract investors, even in relatively slow financial times, like the current recession. Some previsions indicate that by 2016 the response biomarkers market will be worth 150 million dollars, with some 150 companies actively developing diagnostics that can segment patients in order to receive specific therapies (*Pitfalls Undermine Promise of Theranostics*, Genetic Engineering & Biotechnology News, 2008).

According to Peter Winter (executive at Burrill&Co) in his consultancy's latest report (*The Next Big Thing*, Winter, P., The Burrill Report, 2009), these companies are *the next big thing*. So much so that they predict these companies will radically transform the public healthcare market. According to Winter, 500 million dollars were invested around the world in companies that are developing new diagnostic tests for personalized medicine in 2008, and this report points to emerging companies like Crescendo Bioscience, Pathwork Diagnostics, Precision Therapeutics and Neuroptix. Apart from these companies, Winter affirms a growing interest in companies that use pharmacogenomics (a combination of pharmacology and genetic tests) and gives Herceptin and Vectibix as examples (see square 6).

In Catalonia there is intensive activity in this area, with companies like Oryzon (both the company itself and its consortium Oncnosis with the Ferrer Group) and Gendiag, plus others that are just being started like Transbiomed, which are committed to discovering and developing new diagnostic tests for personalized medicine. Other Spanish companies include Progenika and TCd Pharma, emerging examples from the Basque Country and Madrid, respectively. Additionally, the intensive research activity on behalf of the public research institution is noteworthy, as it means an increased number of patents that back up the predictive or prognostic capabilities of cellular, gene and blood markers.

Square 6. Markers and associated therapies

The association of a treatment and a personalized diagnosis is beginning to be a clinical, regulatory and commercial reality. The trend was started by Roche to associate a test to detect a receptor with a treatment using a specific antibody for this receptor, applied to breast cancer (HER-2 and trastuzumab, with the commercial name Herceptin). Additionally, diagnosis of the k-ras oncogene is a clinical criterion for administering the drug Erbitux, marketed by Merck-Serono (and developed by biotech company ImClone) for colorectal cancer. Likewise, Amgen received accelerated approval for their monoclonal antibody Vectibix (panitumumab) to treat metastatic colon cancer, thanks to patient segmentation according to the expression of the receptor for epidermal growth factor (EGF). And in July 2009, AstraZeneca announced an agreement with Manchester DxS to commercialize a diagnostic kit (TheraScreen EGF29) that can identify patients with microcytic lung cancer that are candidates to receive their drug Iressa (Gefinitib).

Nichebusters and biosimilars

Advances in our knowledge regarding response biomarkers, the possibility of personalized treatment and expiration of patents on second-generation biotechnology products will drive the growth of two types of products. On one hand, highly effective and innovative niche products (drugs associated with molecular diagnostic markers for less prevalent diseases that can be subdivided into smaller patient samples). And, on the other, biosimilar products, also wrongly called biological generics, given that the biological synthesis process creates complex molecules that, generally, are slightly different from the original. For this reason, regulatory agencies require complementary safety and effectiveness studies for biosimilars that are not required of generics created through chemical synthesis. However, there is without a doubt an important potential market for these products after many original biological drugs go off patent (when the patent

expires) over the next few years. According to the article *Biotech set to dominate drug industry growth* (EP Vantage, 2009), by 2014 there will be at lest ten biotechnology products with sales above 5,000 million euros, and by 2020 these products will be off patent.

The virtual company

If we analyze historical data on investment in biotechnology, related to the total return on investment, it is clear that the main driving force in the industry, for the moment, is the commercialized final product.

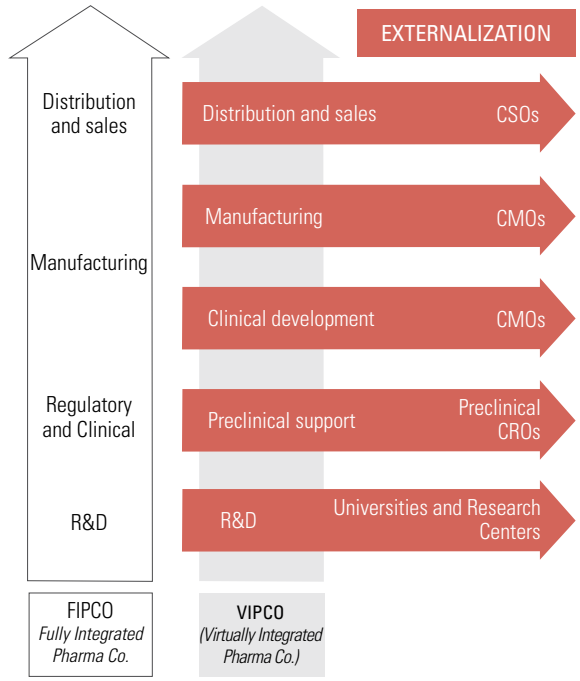
With a fragmented value chain like we find in the drug industry, with technical and commercial risks, and with long development cycles, so far the traditional motor of the industry has been a growing expectation of creating value. The closer a development is to the clinical phases, and the more advanced and closer to market, the more value it accumulates. Investors participate not only with the idea of collecting dividends on future sales of a final product, but also in hopes of multiplying their investment through a total or partial buyout of the company, an IPO, or a licensing agreement with a large pharmaceutical company. In this context, the trend in the sector has always been to specialize in the science that the company's value is based on, and the rest of the necessary skills are acquired through externalization. Taken to the extreme, this model ends up generating virtual companies, where a few individuals with resources and transversal vision of the industry are able to manage all the elements of the value chain, from discovery (licensing technology from the academic arena) through commercialization (through commercialization agreements with pharmaceutical companies or contracting an ad hoc sales force).

The economic crisis of 2008, during which survival of companies in the sector has depended on conserving their war chest until investment picks up again, has accentuated the downward trend described, since emerging companies tend to minimize fixed expenditure and focus on variable expenditure. Looking at costs, the most effective way to access improved skills is by externalizing.

Simply, it is becoming more complicated and inefficient to integrate. The traditional model of fully integrated companies (the so-called FIPCO), which cover the whole value-creation cycle from discovery through development and commercialization, has evolved towards a network model. Companies establish collaborations of varying intensities (from service providers to co-development partners), in order to seek out synergies depending on their project and stage of development. This model favors companies that operate on contract (the aforementioned CROs, CMOs, CBDOs).

The biotechnology sector has taken this model to the extreme so that, right now, only a limited number of companies are growing towards full integration: they either move towards the right-hand side of the value chain (market), or work as project accelerators through to proof of concept and then pass the baton off to a larger company.

Figure 3. **Business models**



Source: *Biotech 2009: Life Sciences, Navigating the Sea Change*, Burrill & Company, 2009.

Biotechnology as an applicable tool

Biotech-pharma convergence

Ernst&Young, in their 2000 report, was the first to discuss the concept of convergence between the biotechnology and pharmaceutical industries (*Convergence: The Biotechnology Industry Report*, Ernst&Young 2000). The pharmaceutical industry sees biotechnology as an opportunity to feed their increasingly limited pipeline. On the other hand, the recession that began in 2007 has had a notable effect on the biotechnology sector, which was used to a model of growth based on expectations of future value. The markets have severely punished this formula and have practically halved the value of most small and medium companies. This has made biotechnology companies with attractive pipelines worth significantly less than what their value would have been two years ago. Therefore, pharmaceutical companies are very interested in acquiring these companies, particularly those with products in advanced development stages.

Clear symptoms of convergence of the pharmaceutical and biotechnology industries include Schering-Plough's take-over of Organon Biosciences (for 14,400 million dollars); AstraZeneca's take-over of Medimmune (15,600 million dollars), the merger of Merck and Serono (14,000 million dollars) –all three in 2007-, the take-over of biotechnology company Millenium by Japanese multinational pharmaceutical company Takeda, for 9,000 million dollars, that of ImClone by Eli Lilly (6,500 million dollars), both in 2008, and the aforementioned take-over of Genentech by Roche for 50,000 million dollars in 2009.

The multinational pharmaceutical companies' huge interest in biotechnology products also shows in the multimillion-dollar licensing agreements, like those signed in 2006 between GSK and the small Danish biotech company Genmab for a monoclonal antibody to treat leukemia and lymphoma and that signed by Bms and Imclone for another antibody to treat cancer, both valued at more than 2,000 million dollars.

Among the most noteworthy operations of 2008 that show the pharmaceutical industry's growing interest in products created by biotechnology companies, we must mention that Takeda purchased 12 products from Amgen for an advance of 300 million dollars, and up to 1,200 million more. Takeda also acquired a portfolio of RNAi products in the discovery phase from Alnylam for a total of up to 1,000 million dollars, and an advance of 100 million dollars. Cephalon acquired the rights to a product from Immupharma to treat lupus –still in phase II–, for a total of 500 million euros (15 million euros up front). Genzyme participated in two interesting operations (an inverse example of biotech/pharma integration, as they acted more like a large pharmaceutical company): acquiring two stem-cell-based products from Osyris Therapeutics, in phase III, for nearly 1,200 million dollars with an advance of 75 million, and the development and commercialization rights outside the United States for Mopeserten from Isis (an injectable drug in phase III based on antisense RNA used to reduce cholesterol levels in patients with a family history of high cholesterol) for up to 1,750 million dollars with an advance of more than 300 million, including shares in the company.

Additionally, over the past three years we have seen a clear trend of traditional pharmaceutical companies to exploit the creativity of the biotech sector. Some clear symptoms that the pharmaceutical industry recognizes the biotech sector's ability to innovate and adapt to the new needs that they cannot meet include: Pfizer creating a bioincubator in San Diego, which devotes 10 million dollars per year to mature eight to ten start-ups while maintaining first-option rights to projects they develop; Lilly announcing that they will earmark 560 million dollars for biotechnology acquisitions; and Merck-Serono creating a venture capital fund valued at 40 million dollars to invest in new biotech companies.

This trend is influenced by both the technological capacity and the organizational aspects that make companies with a biotechnology culture more profitable when generating innovative products. This way, and in conjunction with the economic crisis, it is clear that the industry model is focusing more and more on small, innovative companies that pass their developments off to large companies that can invest, develop and commercialize them. The biotechnology industry discovers and validates, while the pharmaceutical industry develops, positions, creates a market and commercializes.

Diagnostic Applications

Everything from pregnancy tests to HIV tests are biotechnology products, as are the sophisticated DNA chips that allow us to read important genes to find out if a person will

suffer a mutation or if they are at risk for cardiovascular disease. Biotechnology is also the base of agents that are essential to image diagnostics (image biomarkers).

The in vitro diagnostics market is valued at some 50,000 million dollars, practically one-fifteenth the total value of the pharmaceutical market. However, development expenses and technical difficulties are much lower, and the margin, higher. This market has a double-digit growth rate, which is expected to reach 100,000 million dollars by 2016. The personalization of medicine will give diagnostic applications a growing economic dimension, and some experts, like Steven Burrill, dare to say that in the future there will be more added value in diagnostics than in pharmaceuticals, since the latter will be subject to and a consequence of the former (see square 6).

In fact, for the biotechnology industry, the nearly obligatory strategy for obtaining new therapies includes analyzing the possibilities of developing a diagnostic system, alongside the drug, to anticipate response and segment patients, during both the development and commercialization phases. The FDA recommends parallel development of response biomarkers and patient segmentation criteria, according to the presence or absence of specific mutations, or the over-expression of key receptors. In the case of Erbitux and Vectribix (see square 5) the initial indications have been restricted for patients that don't express a key mutation of the k-ras gene, which sets an interesting precedent as they based their decision on a retrospective analysis of clinical data.

The area of in vitro diagnostics with the most activity in the biotechnology sector is molecular diagnostics. This includes all technology based on detecting variants of genes or their expression patterns, which can be used to diagnose or predict a patient's risk of developing a disease, their possible evolution and response to treatment, regarding both effectiveness and possible side effects. The main obstacle in applying this technology in normal clinical practice is its high cost and technological complexity. Nevertheless, given historical trends toward lower prices and simplified technology, it is inevitable that it will end up in normal practical use. It is interesting to contrast the cost of sequencing the first individual human genome, nearly 500 million euros in 2003, to the cost of sequencing the entire genome of Dr. James Watson (co-discoverer of DNA), 750,000 euros five years later. Knome currently offers individualized sequencing services for 350,000 dollars, and in August of 2009 Helicos Biosciences announced that they had sequenced their founder's genome (the third genome of a named individual, after Craig Venter and James Watson), for 36,000 euros and four weeks of work by three people (with an error every 20,000 bases sequenced). Following this trend, some predict that in two or three years prices will drop to 1,000 dollars, with a margin of error of one per 100,000 bases, which would allow for routine use of this technology in clinical practice. The efforts of private investors have been significant in this process, funding companies that can quickly sequence large quantities of genomes. For example, the 85 million dollars invested in Pacific Biosciences or the 45 invested in Complete Genomics in August 2009 (the latter aims to sequence 10,000 human genomes in 2010, at less than 5,000 dollars each).

All of these technological advances have necessarily been linked to clinical validation and evaluation of the relevant associations, as well as their evaluation from a pharmacoeconomic and ethical point of view. It is not very useful (and ethically complex) to offer a diagnostic test if the result doesn't allow doctors to take a clinical decision. However, one of the pioneering companies in studying associations in genetic profiles and predisposition to disease, deCODE genetics, offers the public the opportunity to do a full genome screening (which is different from a complete sequencing, because it is based on detecting one million genetic variations) for less than 1,000 dollars (in fact, they are offering a special *launch price* of 195 dollars). The product, deCODEme, informs users (not just patients) of their risk of contracting up to 42 different diseases. This trend will continue to increase, since the technology is becoming less limiting and the information, more openly available.

In the diagnostic field in Catalonia there is intensive activity to develop new products based on molecular diagnostics, and a long business tradition (Biokit is the most significant representative of innovation in the diagnostic market, with a noteworthy biotech component). Gendiag launched their first product in summer 2009, the first DNA chip (CardioIncode) to detect cardiovascular risk. However, before 2005, Lácer had already developed Lipoxip, a chip that measures more than 200 DNA variants to diagnose family history of high cholesterol (which is currently commercialized by the Basque company Progenika). We must also mention Oryzon's work to discover and validate new prognostic and predictive markers for neurological and oncologic diseases.

Functional foods and nutraceutics

The application of biotechnology to food has already had a significant impact on the economy. The market for yoghurts that help raise the body's defenses and milks that improve cardiovascular health, to mention just two well-known examples of functional foods (those that claim to have positive indirect effects on health), will be worth an estimated 100,000 million dollars in the near future, while the nutraceutics (active ingredients that are not categorized as drugs but commercialized with curative properties) market is already valued at more than 200,000 million dollars. Both markets are experiencing double-digit growth and high social demand, although this trend is changing with the new regulations requiring phase I clinical trials (safety) be carried out on all functional food products.

Tools: five technologies for the future

There is a general consensus that biotechnology advances will change the near future of medical practice and the value chain for drug development. The tools that will allow this to happen are too many to name, and new ones will undoubtedly appear over the next few years. This first report has collected current opinions and reflections from experts like Daniel Levine (editor of *The Journal of Life Sciences* and columnist on biotechnology in a number of economic journals) and Steven Burrill, who we mentioned previously. However, regardless of the source, they all coincide in predicting a convergence of different disciplines. As an example, we mention the synergies between the growing processing capacity of computer systems, the advances in molecular diagnostics thanks to new DNA ultrasequencing tools, and the huge capacity for miniaturization that nanotechnology contributes. As a result, there is a general consensus that medicine in the future will adapt treatments to patients, preventing and curing diseases instead of just treating the symptoms.

The contribution of ultrasequencing to molecular diagnostics

Sequencing of complete individual genomes isn't a technical problem, but an economic one. The barrier of 1,000 dollars per genome, which would allow any individual to establish their genetic profile, has been broken indirectly thanks to breakthroughs in our knowledge of significant mutations in a large number of genes, which allows us to do a more or less exhaustive screening for relevant mutations throughout the genome.

In August of 2009 it was announced that an individual's complete genome had been sequenced for 36,000 euros in four weeks of work, and predicted that it would be possible to break the magic barrier of 1,000 dollars per genome in two years. The next step is to integrate genetic analysis in pharmacologic treatments and exhaustive population association studies.

In general, pharmacogenetics (which associates a response to treatment with the way a cell or tissue expresses a specific gene) and pharmacogenomics (which associates individual response to drugs with an individual's genome sequencing or that of a tumor cell) will allow us to define, for a large number of diseases, the most appropriate treatment for the patient. And not only because a specific genetic profile has a higher predisposition to a disease or is an indicator of an unfavorable diagnosis, but also because the way the body processes drugs depends mainly on the genetic profile of each individual. Therefore, with a molecular diagnosis based on the study of the expression or sequencing of specific genes, we can predict the patient's risk of developing certain diseases, diagnose or determine their evolution, predict their response to a specific drug and facilitate the development of new molecules designed for specific genetic profiles. All in all, the definitive implantation of personalized medicine will depend on the balance of diagnostic cost and the improvement to effective use of drug resources it represents (pharmacoeconomics). If we take into account, however, the trend towards exponentially lower prices and the constant increase of results that associate drug response and predisposition to disease with genetic profiles, it is easy to predict that molecular diagnostics based on DNA sequencing and associated with a medical decision will be a clinical and commercial reality very soon.

Stem cells

Stem cells are the base of regenerative medicine, allowing us to cure disease by restoring lost functions to the body. Some stem cells are from embryos and some are from adults. Embryonic stem cells currently have better differ-

entiation capacity (pluripotent), while those from adult tissue have a more limited capacity for differentiation (multipotent). For example, they can be stem cells for neuronal, muscle, cartilage, or tumor tissue.

Stem cells derived from bone marrow are most commonly used in clinical trials (in some cases phase III) and non-clinical trials (for implantology or bone fractures). Adipose tissue is also a good source of adult stem cells. Their therapeutic applications are already fairly advanced because significant commercial activity has been detected, acquiring licenses and company valuation. In 2008, Cellerix, a company in the Genetrix group, received 25 million euros in international funding for their drug (Ontaril) in phase-III trials, which treats fistulae produced by Crohn's disease. Genzyme reached an agreement with Osiris Therapeutics, giving them access to two phase-III drugs for up to 1,250 million dollars (depending on the different milestones met). And, more recently, Novartis acquired the rights to autologue stem cell technology (from the patient's own cells) from Opexa (University of Chicago) for 3 million dollars and the promise of up to 50 million dollars in milestone payments (not counting royalties for each product and manufacturing rights, which Opexa still holds).

Data from the NIH (National Institutes of Health) put the number of clinical trials for cell therapies at 2,157 at the end of 2008, compared to 3,647 for diabetes, 1,507 for arthritis, 1,611 for asthma and 10,011 for cardiovascular diseases, which are the most prevalent.

Nonetheless, despite the doubts and commercial uncertainties that surround this technology, there is intensive research activity. For the moment, the technology and knowledge only allow for autologous application, using the patient's own cells like a self-transplant. But it seems that we will be able to use stem cells for heterologous applications in the future, just as we currently do (and have done for the past 40 years) with bone marrow and umbilical-cord cells. This is why it is important to develop induced pluripotent cells, described for the first time in humans in 2007, which open the door to deriving stable cell lines that can be used therapeutically in patients other than the donor, without the ethical complications that arise from embryonic stem cells.

2009 also marked a milestone in possible therapeutic uses for embryonic stem cells, with the FDA's (United States Food and Drug Administration) approval of the first clinical trial using these cells, by American company Geron Pharmaceuticals. The new drug will repair spinal cord injuries through direct injection of cultivated embryonic stem cells that are partially differentiated into oligodendrocytes. Geron claims to have enough cells to cover therapeutic demand over the next 20 years. However, despite their initial approval, in August 2009 the FDA delayed the start of the trial after analyzing data on escalation, which once again shows the difficult road ahead for treatments based on disruptive technology.

Finally, in the field of stem cell research, there is also a large commercial and therapeutic interest in creating individual stem cell banks (these already exist for cells taken from umbilical cords and adipose tissue), with huge therapeutic potential that would guarantee that the donor's future needs be covered, as well as the needs of their family members. Despite the fact that related legislation is still being adapted to the technical realities of this technology, discrepancies in the laws of different countries lead to the commercial possibility of offering stem-cell storage in one country and creating a stem-cell bank in another.

Therapy based on nucleic acids: beyond gene therapy

Traditionally, drugs interact with the proteins that cause a disease or its symptoms (known in the industry as therapeutic targets). However, advances in our understanding of the structure and dynamics of the genome have led to different strategies based on the use of genetic material as a therapeutic tool. Direct injection of DNA codified for a specific protein was a first step, although it was not very successful from a commercial point of view. But now all eyes are on RNA. Products based on antisense RNA have already been approved for local administration and products based on RNA interference are in phase II and III trials for local administration and I and II for systemic administration. The most relevant aspect, from an economic point of view, is the intensive activity in licensing, investment, mergers and acquisitions this field produces. Merck's take-over of siRNA for 1,000 million dollars in 2007 is just one example.

To the list of therapeutic nucleic acids (DNA, RNA interference, antisense DNA and RNA) we must add a new one: microRNA. The presence or absence of these small segments of RNA can be related to cancer, viral infections,

metabolic alterations or inflammatory disease, and there is commercial interest and activity working to develop biomarkers based on these molecules. The potential of this treatment is huge because these elements can regulate individual genes as well as important gene networks, like those that cause cancer or inflammation, in addition to its therapeutic and diagnostic potential.

Nanobiotechnology and nanomedicine

The spectacular advances over the past years in nanotechnology, the development of new materials and, particularly, their use to administer and functionalize drugs (introduce a functional group), has led to their convergence with biotechnology, particularly in the fields of diagnostics and controlled administration of drugs. According to the European Nanotechnology Platform, by reducing materials to a nanometric scale we take advantage of their new or improved, physical, chemical and biological properties. In pharmacology, scale is reduced to 1 μm, although the regulatory definition of a nanotechnology material states that its diameter must be less than 100 nm (0,1 μm).

The combination of nanotechnology and biological products is expected to generate innovative new products, particularly in three areas of consensus: regenerative medicine, controlled dosage of drugs, and diagnostics. In fact, nanotechnology allows us to move closer to the Ehrlich's magic bullets (The Nobel Prize in Physiology or Medicine 1908, The Nobel Foundation) both passively (below 200 nm retention of nanoparticles in highly vascularized growing tumor tissue is non-specific, due to the so-called EPR (enhanced permeation and retention) effect), and actively, thanks to the possibility of adding specific recognition elements.

There is a wide range of technological diversity: solid lipids, polymerics, micelles, dendrimers**,** liposomes, gold and magnetized nanoparticles. All of these can be "functionalized", for example, by adding an antibody that recognizes a specific receptor in a cancerous cell. Dendrimers, for example, are branched structures that can carry multiple functional arms that considerably increase their recognition and therapeutic action capabilities. In some cases, they can act as contrast agents (for example, magnetic nanoparticles) and can be used for both diagnostic and therapeutic applications. Furthermore, the development of new materials could lead to biosensors that could detect changes in a specific cell or tissue.

In any case, the 100 nm barrier is complex: it is a scale on which interaction with cell structures is highly favorable (the scale on which cell receptors and many macromolecules "talk"; that which viruses and antibodies use, etc.), and it is therefore also a scale on which we can find unexpected toxicity. In fact, there are specific regulatory guidelines designed to prove the safety of products smaller than 100 nm, which are particularly relevant when designing nanomedicines based on new materials. The European Commission is also making a significant effort to define the margins of safety for products that combine nanotechnology and biotechnology (for example, the Nanotest program under the 7th Framework Program).

Synthetic biology

Good proof that synthetic biology, which focuses on how to build artificial biological systems with new functions that don't exist in nature, is already a commercial reality is Exxon-Mobil's (the most important oil company in the United States) 300-million-dollar investment in Synthetics Genomics for research on algae as a source of biofuel. Synthetic biology research is very active and takes genetic engineering to the extreme, with a totally controlled concept that is more common in engineering than in biology. In the near future, this will most likely begin to generate intense ethical debate on the consequences and limits that should be put on synthetic biology's ability to manipulate. However, it is clear that there are many possible applications for this technology. According to the technology watchdog report by the Genoma España Foundation for 2006 (*Synthetic Biology*), although in the short and middle term applications with be mostly industrial (environment, industrial processes and new materials), 5 or 10 years from now the contributions will be more significant in the field of bioenergy, and in 10 years we will begin to see the first biomedical applications.

For the moment, the most immediate use of this technology is in the industrial sector, for bioremediation, biofuel and biodetergency, although there are also therapeutic projects on the horizon (designing and creating bacteria that can produce drugs and introduce them inside an organism).

1.5. Green biotech or agrifood: beyond Genetically Modified food

There are 23 countries in the world in which biotech agriculture dominates, including the United States, Canada, Mexico, Brazil, Argentina, Australia, China, India and South Africa. These countries plant a total of 120 million hectares (soybeans making up 50%), which is a surface area equivalent to that of Spain and France combined.

The cultivated land in these countries, which have integrated transgenic crops into their economies, is growing at rate of 12% per year. Crops with global impact, like soybeans, cotton or corn, are on their way to becoming predominantly transgenic, driven by their clearly superior profit margin. Europe is near the bottom of the world ranking regarding economic impact of transgenic plants in agriculture. Basically, only one type of corn is grown in all the European Union, and the total cultivated area is 100,000 hectares.

Nonetheless, the applications for green biotech are not limited to transgenic crops for human consumption. Using biotechnology to control plagues is an industrial reality (biocontrol). Biotechnology can also be used to favor the systematic reproduction of vegetable species (biofertilization). The global market for transgenic seeds is valued at approximately 8,000 million dollars, according to data from the 2009 Burrill Report (*Biotech 2009: Life Sciences: Navigating the Sea Change*).

Table 4. **Main transgenic crops approved for commercialization in 2008**

Area	Crop	Authorized application
Argentina	Herbicide and insect-resistant corn	Planting, human and animal consumption
Australia	Improved-quality corn, herbicide-resistant rice, herbicide-resistant soybeans	Human and animal consumption
Brazil	Three varieties of corn resistant to different herbicides.	Planting
Burkina Faso	Cotton	Planting
Canada	Herbicide-resistant and improved-quality corn	Planting, human and animal consumption
European Union*	Two types of soybean resistant to different herbicides	Human and animal consumption
Japan	Three varieties of insect- and herbicide-resistant corn	Planting, human and animal consumption
USA	Herbicide-resistant corn and soybeans	Planting, human and animal consumption

Source: *Biotech 2009: Life Sciences Navigating the Sea Change*, Burrill & Co, 2009.
* Regulations distinguish between authorization to plant, process and use crops as a raw material in products for human and/or animal consumption.

1.6. White biotech or industry: towards bioenergy

The ability to produce fuel like ethanol or diesel using biotechnology has a clear economic impact: a spectacular increase in the price of soybeans and corn. In the United States, 35% of all corn harvested in 2007 was used to produce bioethanol.

The controversy created by the possible effects on the agrifood industry of producing biofuel is leading us to search for other alternatives. For example, since 2008 Ceres, a company in California, has been selling plants that are not fit for human consumption but have qualities that make them very attractive to the bioenergy industry. Biotechnology also allows us to recycle glycerin from oil refineries to make biodiesel, which opens up the possibility of producing relatively clean, organic fuel.

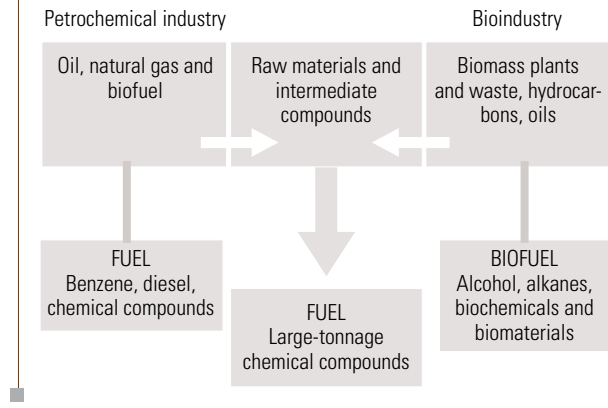
All in all, biotechnology applied to energy has a traditional component. In fact, we could say it was Ford, at the beginning of the past century, that decided the automobile industry would be fueled by gas and not ethanol. However, even at that time, we had the technology to produce ethanol from plants. Brazil has led worldwide production of bioethanol from sugar cane since the 1970s and all fuel in this country currently has at least 25% ethanol from biotechnological sources. Brazil is currently the top sugarcane producer in the world, with 500 million tons, and exported 1.2 million tons of ethanol to the United States in 2008. Before 2006, Brazil was the top producer of ethanol but was surpassed by the United States in that year, with 24,000 million liters compared to 20,000 million liters produced in Brazil. Some countries, like Zimbabwe, use ethanol as the base for all of their fuels. Controversy surrounding the impact on the environment (mainly due to deforestation) and the food supply (higher grain prices and farmland substitution) has given modern biotechnology a clear role in the search for alternatives and improvements. Two examples from 2009: BASF announced an agreement signed with Brazilian company CTC (specializing in sugarcane) to launch a transgenic variety of this plant that produces 25% more and is more drought-resistant (a clear effort to reduce the crop's impact), and, as we discussed before, ExxonMobil, the most important oil company in the world, announced in July 2009 that they will invest a total of 600 million dollars to develop technology to obtain biofuel from algae (300 million of which will go to Craig Venter's company, Synthetic Genomics).

Investors are interested in this line of research, with significant transactions in 2008 like the Qteros company of Massachusetts, which received 25 million euros in funding to develop microorganisms that can transform cellulose into biofuel (one factor that limits the commercial viability of biofuel is the current cost of processing cellulose to obtain ethanol).

2007 and 2008 were particularly favorable for capital risk investment in bioenergy projects, and although it is still an unproven sector from an investment point of view, in 2008 private funding contributed 750 million euros to projects connected to biofuel production. Additionally, 2,300 patents were applied for in the United States in 2000, while in 2008 the total number of applications was 30,000. In addition to bioenergy, industrial applications also give us biodegradable plastics and other biomaterials (*Biofuels Report: Economics for a Driven Market*, Bioworld®, 2008).

In the same way that biotechnology is converging with the pharmaceutical industry, process biotechnology is also

Figure 4. **Emerging industry of biorefineries**



converging with the chemical industry. By 2015 an estimated 25% of all processes in the industry will be biotech-related. According to professionals in the sector, "fermenters are already present in chemical plants".

In fact, biotechnology is causing an important paradigm change in the chemical industry, shown in the diagram below, proposed by Steven Burrill in his 2008 report.

Biotechnology is also helping invent new words for industrial activities: bioremediation (using biotech tools to decontaminate deteriorated environments) and biodetergency (which uses biotech solutions to clean equipment and surfaces). It will also impact important traditional sectors, like the textile sector. A good example is the BioTex project, a strategic research agenda agreed upon by Euratex (European Association of Textile Manufacturers) and Europa-Bio (European Association for Bioindustries), with the aim of increasing the impact of biotechnology on the future of the European textile sector, creating a long-term cooperative framework between textile manufacturers and producers of new biological products in order to obtain textile products for global use, like fibers and composites, functional materials that respond to the users' needs, enzymes and microorganisms that can be integrated into the textile production process, biopolymers, etc. with special emphasis on functional fabric, catalyzing enzymes and new polymeric materials.

1.7. Biotech as a model for regional development: the cluster theory

A sectorial cluster of any type implies an association of institutions based on common and complementary interests. Due to their proximity, both geographic and in the nature of their activities, members enjoy different types of benefits (common location, proximity to large industrial areas, access to technology and equipment, externalization of processes and services, access to human capital and suppliers, possibility of sharing best practices and knowledge, pressure to improve execution due to proximity to competition, etc). In short, the trend towards cluster creation is advantageous because of the tangible economic benefits it creates.

In accordance with strategic EU documents regarding biotechnology, the road map to keep up with the United States and Asia starts with strengthening our scientific capacity, transforming this into value through training, and fostering entrepreneurialism. However Europe does have additional difficulties, compared to the United States, due to the fragmentation of R&D funding and the lower level of territorial cooperation.

As a way to improve, Europe has decided that it must drive networking in knowledge-development hubs, focusing on bioregions and biotechnology communities that provide open access to knowledge, strengthen links between universities and business, and promote a culture that protects results and encourages cooperation in the area. Furthermore, according to the OCDE, the existence of clusters in a region is an indicator of innovation (*Innovation Clusters*, European Commission, 2007).

The biotechnology and biomedicine sector includes activities that range from life sciences research to product commercialization and the application of processes to improve healthcare and quality of life, in a value chain that includes research centers of excellence, universities, science and technology parks, traditional hospitals and research foundations, support organizations, large-scale research facilities, technology platforms, the traditional pharmaceutical industry, the emerging biotechnology industry, the medical technology industry and service providers and product suppliers.

There are many different stakeholders in the Catalan biotechnology community, as well as in the national community, that act in these areas. Biocat is the organization that drives and promotes biotechnology and coordinates the Catalan biocluster, both in the private and public sectors; CataloniaBIO is the association of Catalan biotechnology companies; pharmaceutical companies belong to this association, as well as the Farmaindustria association,

which operates on a national level. Asebio is the association of Spanish biotechnology companies and operates in coordination with Genoma España, which is part of the Ministry of Science and Innovation and coordinates biotechnology on a national level. However, as in Catalonia, other bioregions have been created and consolidated in Spain: in the Basque Country, Madrid, Valencia, Andalusia and the Balearic Islands, in chronological order (with the Bioregion of Catalonia second after BioBasque). In each community, the regional governments, city councils, universities, hospitals, etc., have their own development agencies and bodies (in Catalonia, ACC1Ó and Barcelona Activa), valorization, technology transfer and entrepreneurship organizations (like the OTRI, valorization structures for research in hospitals and universities, technology springboards, etc.).

Although not everyone agrees that clusters have to be geographic or virtual (Steve Burrill believes that the clusters of the future will be defined by themes, diseases, markets or industrial segments), there is a clear trend towards clustering around the world, and the relevance of this trend should not be minimized. What's more, we are already moving into megaclustering, which is the use of critical mass to drive megaregions. The closest to home is the Pyrenees/Mediterranean Euroregion, a geographic framework to drive regional cooperation and association that the BioRegion of Catalonia participates in.

In short, the aim is to create an environment that is conducive to optimizing interaction among all cluster participants, making it more efficient and effective. This means we must follow cluster policies to create innovative ecosystems that favor the knowledge economy.

We have seen, thus, that the scientific revolution that began just over a century ago on a microscopic level has become a global economic and productive revolution, which is influencing key issues like personal wellbeing and the future of our society. New therapies and drugs than can be adapted to a specific patient; new energy sources that are cleaner and more sustainable; new industrial processes that are more efficient and environmentally friendly...

We are looking at a sector that is very new and hard to define, that is found in advanced research (with cutting-edge scientific tools like genome sequencing, stem-cell research and nanotechnology) and from which experts expect a huge potential for growth and generation of wealth.

In this first introductory article we have analyzed the state of the art and the future perspectives of red biotech, which, as seen in the data and analysis included in this first Biocat Report, carries the most weight in Catalonia. In the following articles we will look more closely at green biotech (agrifood and environment), white biotech or industry, and the subsector of medical technology. This will complete the panorama that has shown to be full of opportunities, which we must take advantage of, and challenges, which we must know how to face, for the benefit of science, the economy and, most of all, the wellbeing of people in our country.

2. Biotech applied to agriculture and food in Catalonia

Dr. Pere Puigdomènech
Director of the Center for Research in Agrigenomics (CRAG), CSIC-IRTA-UAB

If we seriously consider the OECD's classical definition of biotechnology: "The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services" (Statistical Definition of Biotechnology. (OCDE), 2005) then biotechnology applied to plants and animals would be the oldest type of biotechnology and one of the keys to human society. And this is due to the fact that plants and animals, which are living organisms, directly or indirectly contribute essential goods to our lives, like food. And in order to reach the high level of food production we need, we have had to apply both science and technology.

We currently use a more restricted definition of biotechnology, which includes molecular and industrial approaches that were developed in the 20th century. In any case, the biotechnology applications we use in agriculture and agrifood are often more important than medical applications.

The importance of biotechnology applied to agrifood proves the fact that plants and animals provide our food, but that isn't all. We also produce fiber, construction materials, medicines and cosmetics from plants and animals. And we can't forget that plants have provided us with fuel for centuries, an issue that is on the table once again. We produce food directly from plants and animals, which we also use to produce food for our animals. The fibers we use for clothing are traditionally plant-based, like cotton or linen, or animal-based, like wool or silk. Plants are traditional sources of drugs and cosmetics. And we know that until little over a century ago wood and charcoal fueled our transportation, building and heating. All of this can sometimes sound like a thing of the past, but it will probably also be the future of our society.

Biotechnology and plants

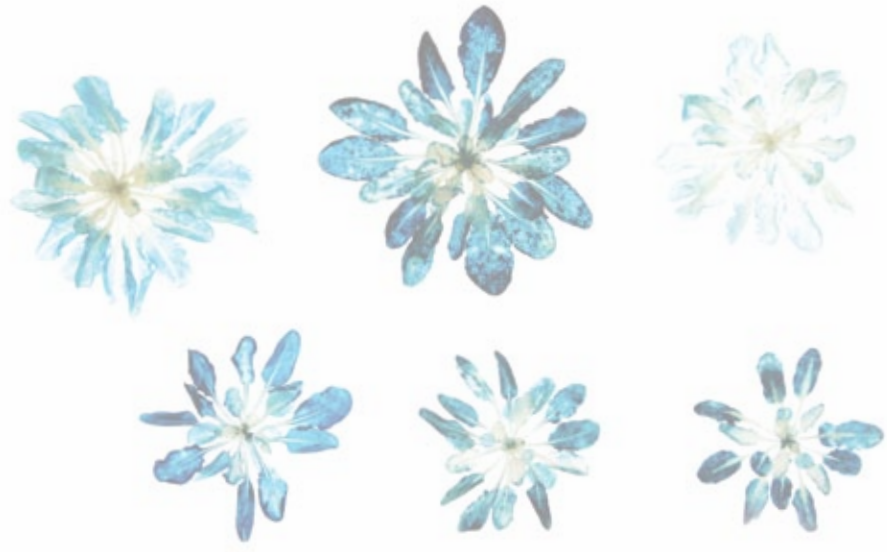
Biotechnology applied to vegetables essentially aims to produce plants that are more effectively cultivated or that provide better quality fruit. Domestication of plants carried out in the Neolithic age is the very foundation of our society. Over the last century, we have significantly improved plant yield through the systematic application of genetics, which has allowed us to avoid the Malthusian prediction that we would not be able to produce enough food for the growing population. None of the crops that make up our basic food supply have not been through intensive genetic selection. During the last third of the past century, biotechnology began to be used in force in this type of application, through a number of methods.

Important crops, above all those that produce ornamental plants and fruit, are obtained from cuttings or fragments of young plants. Starting in the 1950s, this technology became more sophisticated and moved into in vitro cultivation. This system allows us to save a culture of undefined cells from a plant indefinitely. We have methods that allow us to use these cultures to generate whole plants, giving us a limitless source of identical plants. Micropropagation of plants was first developed in Catalonia at the Institute of Agro-Food Research and Technology (IRTA) and has been used, above all, by companies in the ornamental plant sector.

In vitro cultivation is also the foundation for plant transformation. It is well known that some 40,000 hectares of genetically modified corn are planted in Catalonia. This is one of the few genetic modifications that has been approved by the European Union and is developed by the Monsanto Corporation. There are many varieties of plants that use this genetic modification under license in Catalonia. Transformation techniques are an important tool for molecular genetic research in plants and as such it is used in academic laboratories like the Center for Research in Agrigenomics (CRAG) driven by the CSIC and the IRTA, and the Universities of Lleida and Barcelona.

We have also taken advantage of genetic transformation to obtain plants that produce substances of interest, i.e. for pharmaceutical or veterinarian applications. These methods are studied in research projects at the University of Lleida and the CRAG. The latter produced a spin-off, ERA Biotech, currently located in the University of Barcelona Science Park, that applies protein production methods for use in pharmaceuticals to plant and animal cells.

Genetic modification is not the only application of molecular techniques in plants. Genetic improvement is a discipline that was developed before genetic modification appeared, and applies the laws of genetics in order to obtain strains that are adapted to the needs of agricultural production. Molecular techniques are allowing us to understand genetic characteristics that are essential to production, like plague and insect resistance. One important aid to genetic improvement is the use of molecular markers based on DNA, which can be developed by indentifying the gene or genes related to the characteristic or the fragments of DNA that accompany the gene in question. Using these markers allows us to substantially speed up the improvement process. Marker-assisted improvements have been developed by the IRTA, now the CRAG, and are used by research groups at the Polytechnic University of Catalonia, the University of Lleida and the IRTA in Lleida, as well as by a number of seed producers, like Semillas Fitó.



Biotechnology in animals

The application of biotechnology in animals has different characteristics. We also apply genetic improvement methods in animals and, in fact, current farm species like cows, pigs and chickens have been and are genetically improved. Similar to what we saw with plants, these programs tend to aim for animals that are more resistant to illness, take better advantage of their feed, or produce better quality milk, meat or eggs. On the other hand, it is also possible to obtain genetically modified animals with the same aims, but above all to obtain samples to study human diseases and produce therapeutic substances.

Biotechnology tools can also be applied in research to create vaccines to protect farm animals and pets from different types of diseases. Regarding this objective, we should mention that there are many companies in Catalonia that are leaders in Europe, like Hipra or Fort Dodge. Regarding animal health, it is also important to mention the work being done at the Animal Health Research Center (CRESA), created by the UAB and IRTA, which uses molecular technology to identify and characterize different types of pathogens that affect animal species.

The production of genetically modified animals for use in biomedical research is probably one of the most important applications of this technology. There are millions of animals in research centers, above all mice. Catalonia is home to most of the animal facilities for hospitals and biomedical research institutes. The Center for Animal Biotechnology and Gene Therapy (CBATEG), located at the UAB, produces transgenic mice for biomedical research. The United States, on the other hand, has approved the first product for clinical use produced from a transgenic animal. It is a hormone produced from the milk of transgenic goats. Similar experiments with cows and sheep are being carried out around the world. There is also research that uses other transgenic animals, mainly pigs, for transplants and therefore their immune systems must be modified so the transplanted elements are not rejected.

These applications focus mainly on clinical use. It has also been shown that it is possible to create genetically modified animals with a faster growth rate. A type of salmon with these characteristics has even been approved in Canada. The same has been shown possible with trout and tilapia, but neither of these animals is currently being produced.

Just as we saw with plants, there is a growing use of biotechnology to genetically improve animal species. The use of molecular markers to accelerate this improvement has increased spectacularly over the past years. Sequencing has already been done for the main species of farm animals or will be finished in the next few months and collections of genetic variations are being obtained to create a genotype for the species most commonly used in genetic improvements. There are groups at the CRAG (UAB) and IRTA-UdL that actively work in this direction, which will help improve and control species used for human consumption. There are also applications of cellular biology, like in vitro fertilization, division of embryos and nuclear transfer cloning, that are being applied to the most valuable species, like cows and pigs. There are research groups here in Catalonia, at the UAB for example, that are working on these processes.

Marine species are also the focus of active biotechnology research. Systematic overfishing and the resulting depletion of our natural marine resources have led to systems that cultivate fish in captivity. This way, aquaculture has become the source of a growing number of fish for human consumption. Research focuses on physiology and genomics of fish being used for human consumption or those that could be used in the future, in order to know more about their resistance to disease and the quality of the product or to improve the species. Research in this field in Catalonia is carried out by the UAB, the CSIC's Institute of Marine Science and the IRTA, at their center in Sant Carles de la Ràpita.

Biotechnology of microorganisms used in food

In addition to agriculture, the use of microorganisms in food is one of the oldest applications of biotechnology. We use yeast for different types of fermentation, bacteria and fungus to transform various foods, and we aim to eliminate some bacteria and fungus in the food we eat because they are pathogens or produce toxins. These uses have so far been applied empirically, but modern biotechnology techniques allow us to control the presence of microorganisms at different moments in the food process precisely.

Fermentation using yeast is essential to processes that are of great economic importance in Catalonia, like making wine, beer and bread. These processes are highly controlled and the strains of yeast used in each case are well defined and part of the quality conditions of the final product. To this end, technology has been developed to identify these strains, using molecular technology, and to improve some of their characteristics. There are groups at the University of Rovira i Virgili and the CSIC participating in this type of research in collaboration with some of the top wine, beer and champagne producers.

The meat processing industry is also very strong in Catalonia. Their preservation and processing methods, like curing meat and making sausages, also require strict controls in order to have the appropriate bacteria in each case. The IRTA in Monells and the University of Girona have established collaborations with industrial groups on projects using molecular technology. These centers, and many Catalan universities, have developed methods to analyze food quality or safety components in these products.

Perspectives for the future

Producing food from plants and farm animals has allowed countries in the developed world to reach an acceptable level of sustenance, regarding both quantity and safety. This has been possible because, for centuries, we have applied the best knowledge available at every moment, and it would be a mistake to think that the future will be any different. Global production levels could probably feed the current human population, but serious inequalities around the world show that many important challenges still lie ahead. We must end the situation suffered by large minorities that still don't have access to enough food, while our agricultural and agrifood industry works to meet demand for an ever more plentiful, safe and healthy food supply. And we must do this in a globalized environment facing agricultural practices that need to be revised, because some are detrimental to the environment, and climate changes that will probably significantly affect our food production capacity. Therefore, continued application of the best knowledge available to food production, as we have done since the birth of agriculture, will most likely be a necessity.

This need becomes an opportunity, when seen from the view of the technology currently available or in development. Modern biology has given way to molecular and cellular methodology with enormous potential. These methodologies allow us to understand the basics of how biological organisms behave, and the ones we use for human consumption are no exception. We have tools to maintain and increase our ability to produce safe and healthy food sustainably. These tools come from cellular biology and molecular biology and now genomics, which are the foundation of new biotechnology.

The agrifood industry has the largest turnover and employs the most people of any industry in Catalonia, Spain or Europe. In Catalonia we have a scientific and industrial foundation that will allow for interesting developments over the next few years, thanks to the scientific level of our research groups and the technology of our industries, which put modern biotechnology tools to use in line with international standards. So far, within the possibilities of our scientific and industrial structure, scientific activity, industrial use of modern tools and collaboration between the business and scientific sectors has been noteworthy. We hope to create the necessary conditions to allow this activity to increase in the future.

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3. Industrial biotechnology: business opportunities in Catalonia

Dr. Josep Castells i Boliart
President of the University Institute of Science and Technology (IUCT)

White or industrial biotechnology (IB) can be defined as the "group of companies that manufacture chemical substances, equipment or consumer goods industrially using biotechnology tools."

This definition has a wide enough scope to include companies from traditional industrial sectors (chemicals, plastics, fine chemicals, textiles, shoemaking and consumer chemical production, like detergents, fuel, food, metal and distribution, etc.) and generally does not include biotechnology companies. This is due to the fact that industrial biotechnology is clearly a tool and not an end in itself. Nor can it be considered a sector because the use of biotechnology tools is the only element that this group of companies has in common. Normally the fact that they use these tools sets them apart from other companies in their sector, because thanks to these tools they can develop and market products and processes that incorporate intrinsic innovation factors, which allows them to be more competitive than their more traditional competitors.

Recently, IB has been used as a technological innovation factor in traditional and mature sectors, which have serious problems staying competitive with developing countries. By incorporating this technological innovation, companies create new products and processes that can be patented, improved regarding economic and environmental efficiency, and therefore become more competitive and dominate a larger part of the market.

Specifically, some solutions that biotechnology has contributed to improving processes or industrial processes are as follows:

- Using renewable raw materials and, therefore, reducing oil dependency.
- Taking advantage of agricultural, forest and industrial waste, which can be reused.
- Reducing the use of organic, inflammable or hazardous reactives, materials and solvents.
- Reducing waste production and generation of by-products (hazardous)
- Lowering energy consumption and substituting fossil fuel with biological sources and, as a result, reducing the greenhouse gasses emitted into the atmosphere.
- Reducing manufacturing costs and improving profit margin
- Increasing quality of biotechnology processes, saving on storage and liquid treatment costs and eliminating the need for environmental measures established by law.

Companies that use industrial biotechnology make up a subsector, whose activity and products are strictly biotech related, called IB suppliers.

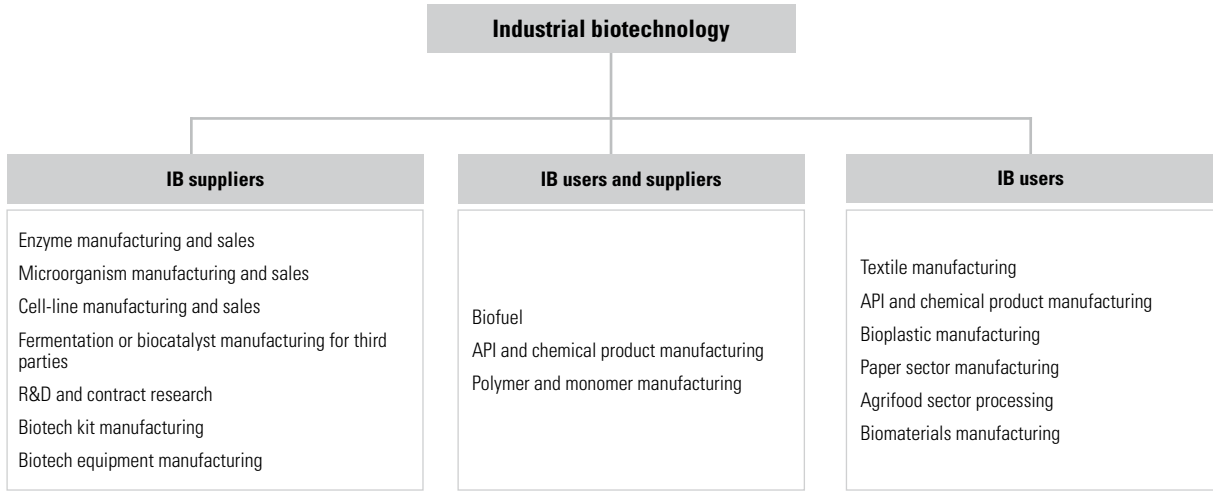
Materials and applications

IB has such a wide range of applications that it is difficult to visualize in an organized structure. IB has high potential both in traditional and developing sectors. The following are a few of the most important examples

a) Chemical products and raw materials

Nowadays it is possible to produce inexpensive, renewable raw materials through fermentation (molasses, bagasses, starch, etc.), which previously had to be extracted or chemically synthesized. Well-known examples in the agri-food sector include vitamin C, glutamic acid and citric acid. There are also a number of products that can be synthe-

Square 7. **Classification of companies in the industrial biotechnology area (IB)**



Source: created by the author. * use renewable raw materials

sized using microorganisms, and their use is being studied to replace petrochemical synthesis on an industrial scale, like succinic acid and adipic acid (a precursor of nylon).

b) Fine and specialized chemical products

These compounds, specialized and often complex, require many steps and large amounts of energy to synthesize. Biocatalysis (catalysis using biological agents, including enzymes or living microorganisms that carry out the conversion steps), on the other hand, often takes place near room temperature. This allows us to develop much more efficient and sustainable processes from both an economic and environmental point of view. Some examples include maleic acid (used for ink synthesis), benzaldehyde (use to manufacture plastics), some APIs (active pharmaceutical ingredient) with high added value, compounds like aspartame (sweetener), eritorbic acid (antioxidant) and amino acids like lysine (nutritional additive in animal feed).

c) Enzymes

Enzymes have become one of the main products of industrial biotechnology and there are companies that are exclusively devoted to manufacturing and marketing them. Thanks to these enzymes, biochemical reactions that require high temperatures, excess substrate or complex dissolvents can be carried out specifically and selectively at room temperature, in aqueous solutions that are normally non-toxic.

Enzymes began to be used industrially in the 1980s, when they were introduced as whiteners and degreasing agents in detergents. This reduced the amount of artificial surfactants, which are very bad for the environment. Today there are 150 additional enzymes in commercial use, applied in all industrial sectors. In the agrifood industry, pectin is used to eliminate pulp from fruit juice, transaminases as compacting agents in meat processing, amiyases to improve bread dough, and galactosidases to obtain lactose-free dairy products. In the textile sector we find examples like cellulases –which substitute stonewashing–, lacasses and catalases for whitening, pectinases for treating cotton and proteases for leather treatment. In the paper sector lacasses and xylanases are used for whitening.

Industries involved in obtaining and purifying enzymes develop genetically modified microorganisms that produce and excrete enzymes at high production rates, which significantly lowers production costs. At the same time, the application of modern biochemical engineering techniques has allowed us to design enzymes to meet our needs, which are more active than those occurring naturally, or that can degrade new substrates or generate new non-natural products.

d) Biofuel

Biofuel, along with enzymes, is one of the stars of industrial biotechnology. Biofuel is fuel for internal combustion engines made with biological or renewable (mainly vegetable) raw materials. First-generation biofuel: there are currently two types of biofuel on the market: bioethanol (for gas engines) and biodiesel (for diesel engines). One disadvantage of these types of first-generation biofuel is that they are created from seed crops. To manufacture them, therefore, fertilizers, pesticides and agricultural machinery are needed, creating greenhouse gasses and reducing the net savings compared to traditional fuel.

Second-generation biofuels: these are made from biodegradable agricultural, forest or industrial waste. The main advantage of this type of fuel is that is uses biomass, minimizing the competition for raw materials with food producers. The most cutting-edge projects even propose using urban waste as a source of carbon. This would decrease emissions by more than 90%. Second-generation bioethanol will be used on an industrial scale by 2012. Bioethanol will be obtained from lignocellulosic material, using a combination of optimized enzymes and genetically modified microorganisms. Second-generation biofuel is obtained from alternative carbon sources, like glycerin (byproduct of the current biodiesel industry) or different types of biomass. In order to avoid using methanol, new sources of non-edible oils are employed (microalgae or Jatropha).

There are other biofuels that are not used in the automotive industry, like biogas (gasified hydrocarbons from decomposing organic materials) or biomass from various sources that, when ground and dried, are an excellent fuel source for homes and industry.

e) Biomaterials

Biomaterials, synthesized from biological material or using methods based on biological systems, are possibly the newest products in industrial biotechnology. They are also those with the most potential for research and experimentation.

These materials can be used for a number of applications (from construction to toy-manufacturing industries) as a substitute for plastics and other oil-based materials, maintaining and often improving their characteristics and features. The most highly developed biomaterials so far are polymers produced from microorganisms, plants or plant derivatives, as an alternative to plastic.

Bioplastics have similar properties to traditional plastics but are totally biodegradable, decomposed easily by bacteria in the soil and water, and generate up to 80% less toxic gas emissions during manufacturing. There are bioplastics on the market made from biological polymers, cornstarch and synthetic polyhydroxybutyrate from glucose. Another approximation is synthesizing monomers using genetically modified bacteria like hydroxypropionic acid and polylactic acid, used in automobile or container manufacturing.

Some cases of commercial success in manufacturing polymers include: NatureWorks, worldwide leader in biodegradable plastics like polylactic acid (PLA) (used for thermal sealing, labels, wrapping, etc.); Novamont Bioplàstic, producers of mater-Bi, obtained from corn, wheat and potato starch (used in foams, hygiene products, ecological toys and tires), and BASF Ecoflx®, based on PLAs and corn and potato starch. There are many applications for bioplastics: Nestlé Resin, used in chocolate packaging trays; Mitsubishi and Sony use them in the shells of their walkmen; Motorola uses them in a cover for their mobile phones; Pioneer, Sony and Sanyo have used them to create storage discs; and Fujitsu, Hewlett-Packard and NET, computer shells.

There are other biomaterials, like silk-based fibers from spiders (one of the strongest, most flexible and lightest known to man), which are already being used in the laboratories of more than one biotech company. There are transgenic silk worms that produce silk of similar quality and even goats that produce this silk protein in their milk.

Economic impact of industrial biotechnology

The impact of industrial biotechnology on many industrial sectors is growing and is expected to increase further in the future.

In 2002, production of chemical compounds derived from biotechnology already totaled 2.7 tons. By 2005, the value of this market was 50,000 million euros, the equivalent of 7% of all production, and is expected to be more than 80,000 million (10% of production) in 2010.

The production of bioplastics, despite being an immature sector, has not been left behind. 10,000 tons of acrylamide are currently manufactured each year using enzymatic catalysts instead of chemical catalysts, 28,800 tons of polylactic acid and some 90,000 tons of polymers from 1,3-Propanediol. The productive capacity of bioplastics has seen spectacular growth over the past years. In 1990 only an insignificant amount of bioplastics were produced; in 1995, nearly 15,000 mt/year; in 2000 some 50,000 mt/year, and in 2002 some 260,000 mt/year. Production stabilized in 2005 at around 280,000 mt/year, which jumped spectacularly with the increase in oil prices over the 2006-2008 period to 510,000 mt/year, and is expected to reach 875,000 mt/year in 2010.

The gross added value for enzyme production totaled 685 million euros in 2005, only in the European Union, which is the worldwide leader with 80% of all production.

Regarding biofuel, the bioethanol market – which made up most of the market– was valued at 14,000 million euros in 2005. After 2005, biodiesel began to gain importance and in 2008 Spain consumed nearly 600,000 mt of this product. Estimated consumption for 2010 is 2 million tons. The European Union has predicted that biofuel will account for 10% of all fuel used by 2020, which could be upwards of 4 million mt/year.

Despite its economic potential, manufacturing biofuel and bioplastics is still more expensive than their petrochemical alternatives. Progress in science and technology will contribute new solutions to existing technical problems, in addition to discovering new industrial applications for biological processes. However the degree to which this occurs depends on a serious commitment to R&D.

Situation and business impact of IB in Catalonia compared to Spain

The Catalan academic arena is well positioned and provides enough trained professionals to cover the needs of the Catalan business fabric and absorb any predictable future growth. There are a number of universities that offer degrees in biotechnology (with good marks), biochemistry, chemistry and biology, which are essential to having a base of well-trained professionals; as well as a number of scientific masters degrees offered by both universities and specialization centers, that produce highly qualified professionals.

Additionally, there are advanced and basic vocational training degrees in pharmaceutical chemistry and healthcare that meet the current demands of the sector. However, if the expected growth becomes a reality in the Catalan biotechnology business fabric, these will probably be insufficient.

Regarding basic research developed both at private and public universities and at research centers like the CSIC, we have an extraordinary quality that must be maintained. However, we must establish mechanisms to transfer this knowledge to society, which can only be achieved through companies than transform these ideas into industrial products and processes.

We will analyze, therefore, the state of business in Catalonia and its future perspectives. To do this, we must first consider the exponential influence of a mature, strong, multisectorial industrial base; having a hub of supply companies for the biotechnology industry creates synergies and generates opportunities for companies that employ IB, driving industrial development in the area. Catalonia is the most industrialized area in the country and, therefore, meets the necessary conditions for IB development.

Another factor is the level of penetration and relevance of IB suppliers. In this regard, Catalonia is in a good position but could improve.

Catalan companies that supply industrial biotechnology

The most innovative Catalan companies with the highest projected growth in this area make up 15% of ASEBIO members in the industrial biotechnology and biofuel categories (44 total in Spain). We must add to these another dozen companies that are very active in IB but do not belong to this association. Following is a list of these companies and their area of expertise:

- Fermentation or industrial biocatalysis (Laboratorios Calier, Sandoz, Purac and Biolbérica) and enzyme and microorganism manufacturing (Biocon, Biocontrol Technologies)
- Biosynthesis processes (Arquebio, Bioingenium and IUCT). The UAB has a pilot plant that will be able to do scale projects for companies. Other renowned university groups also work in this field (UAB, UB, CSIC, UdL, UVic and URL) and some of their spin-offs, like Bioglane.
- Manufacturing and development of kits, reactives and cellular reactives, and biotechnology materials (Biokit, Roche, Advancell, Biosystems, Microbial and Proglutamic).
- Manufacturing biotechnology equipment (Grifols Engineering, Telstar Projects and Hexascreen)
- Manufacturing renewable raw materials for biofuel or other industrial products (Agrasys, Era Biotech and IUCT).
- Manufacturing biodiesel. Catalonia currently has three small/medium plants: Stocks del Vallès (manufactures biodiesel from recycled vegetable oil and animal fat); Bionet Europa (uses more than 60% recycled cooking oil), Ceferino Martínez Transport Company (uses biodiesel from their own plant). These Catalan plants have been able to stay competitive and maintain production levels in Spain over the past three years of crisis in this sector, which has been due to the increased import of double-subsidized American biodiesel.

Finally, we must mention that we have found the first internationally patented second-generation biodiesel, developed by the IUCT.

Companies that use biotechnology

It is difficult to give an exhaustive view, due to the fact that they are distributed over a number of sectors and in many cases do not advertise their use of IB because they see this as industrial secret.

The agrifood, textile, leather and shoemaking sectors make intensive use of IB (particularly enzymes and microorganisms for fermentation processes). Consumer chemical companies are starting to introduce products like detergents and stain removers that use enzymes, and bioremediation products for contaminated containers. The chemical sector is beginning to use industrial biotechnology to improve synthesis processes and efficiency (particularly in fine chemical companies) and is also investing in the development of new products or product lines based on IB.

In Catalonia we currently have human resources prepared to meet IB needs, with appropriate quality training programs at vocational education and university levels. However, if the biotechnology sector grows, we will need to increase the number of professionals with the necessary technical training.

R&D developed in universities, research centers and institutes is of high quality but there is not enough transfer of knowledge to industrial products that can go to market. The innovative capability of Catalan companies is clearly limited and insufficient to absorb the high volume of knowledge developed and transform it into new products and new industrial processes.

In order to solve this problem, we must encourage the creation of spin-offs to grow the industrial biotechnology subsector. However, for this to be feasible, we need venture capital companies that specialize in biotechnology, which are totally non-existent today. IB venture capital investment in Catalonia was virtually null over the past three years. And it not only needs to grow but also to incorporate new rounds of funding: seed, growth, expansion and initial public offering.

In Catalonia we have a good base of IB supply companies, and this area has the highest concentration of traditional industry in the country. These two factors are crucial to the development of companies that use IB. Therefore, we can expect a strong growth of this type of company in the medium-term. In order for this growth to be as large as possible, it needs the clear support on behalf of the administrations for innovative processes developed in these companies and access of mature companies to venture capital, so that traditional companies can introduce industrial biotechnology into their processes with guarantees for success.

4. Challenges and tools for growth in the medical technology sector in Catalonia

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Life sciences and medical technology are considered two of the most important sectors for the future. Scientific research (R&D) is becoming more and more important to driving the economy. It is key, thus, that we discuss how to drive our medical technology sector and foster innovation collectively, while at the same time encouraging entrepreneurship among professionals in the medical and healthcare fields.

It is not an exaggeration to say that Barcelona is one of the European capitals of life sciences and medical technology research. The coordinated efforts of the Administration and a number of institutions are contributing to create a positive climate for the creation and development of new products and services in this sector. Over the next years, there will be many new opportunities and we must make the effort to support entrepreneuring doctors and researchers, while defending their rights in this process. This is the only way to get the ball rolling.

A diverse and fairly fragmented sector, from a business point of view, is grouped under the heading of medical technology, but it has great potential for growth. However, we cannot forget the important number of multidisciplinary research groups and technology centers that provide research and, in some cases, services for companies. In this environment we find, by type of company, many subsectors such as in vitro diagnostics companies (which identify new markers and manufacture diagnosis kits), image diagnostics companies, telemedicine companies that have strong links to the ICT field, companies that design and produce medical devices and, finally, contract manufacturing companies, which are often from traditional industrial sectors and develop and/or manufacture components for healthcare technology products.

This article focuses mainly on medical device companies, although we consider an all-encompassing definition of medical devices including any device that is used —on its own or in combination with other devices— to diagnose diseases, for therapeutic processes or for palliative uses that affect human health. These devices, and therefore the production processes and companies behind them— are so diverse that they range from catheter manufacturing through laser scanners for tomography.

Medical technology and, above all, medical devices make up an attractive alternative market. A number of different key factors influence this: demand from the public health sector; quality and multidisciplinary research often carried out in the hospital itself, as well as in research centers and companies that generate innovation and, therefore, high economic value; and, finally, a shorter time to market than drugs (3-5 years for a medical device compared to 12 years on average for a new drug). As a result, this sector is attractive to investors, as they can see faster returns on their investment and profit in this market that will grow an estimated 10% over the next five years (*An Introduction to Medical Technology Industry*, EUCOMED, 2009).

Lines of innovation in medical devices

The success or failure of a new medical device depends on many factors, although there is no doubt that the most important of these are design and technological innovation. We will begin, therefore, with a quick summary of the general innovation trends in R&D&i in our area in order to better understand where the sector is headed.

a) Microprocessors

Microprocessors have changed medicine. They are currently used in all types of medical devices, both those that are implanted in patients and those used in therapeutic instruments or tools. Microprocessors add value to products because they provide increased functions, a higher degree of automation and smaller size.

In our area, we can see that an increasing number of medical devices even include decision-making algorithms that allow the device to respond to the patient's changing clinical conditions. This ability to analyze and respond is surprisingly fast and precise, often more so than analysis and response provided by highly trained doctors. Thus, in many cases, the device (for example, a pacemaker that can analyze heartbeat and apply itself as needed) provides functionality that specialists on their own cannot offer.

The most important aspect of this trend is that there are devices that not only allow us to improve processes (quantitative functional improvements), but also to do things that in the past were impossible (qualitative functional improvements).

b) Convergence with information technology

Information technology contributes new methods of transmitting information to processors. These new methods also lead to qualitative changes and allow for therapies and follow-ups that were previously impossible. For each of us, health is our most valued possession, and few things are more important than controlling our health with medical devices that we can connect, for example, to our mobile phone to monitor blood sugar level or blood pressure and add this data automatically to our medical record, or devices that warn us of allergens in the area, for those with asthma or allergies. The possibilities are practically endless.

This convergence allows us to develop a new field of medical devices, designed to treat chronic illness (wireless disease management programs), a field that is beginning to create a good number of start-ups and about which we will hear a lot over the next few years.

c) Breakthroughs in materials

Catalonia has a network of top technology centers, universities and research centers that study materials. Breakthroughs in the development of nanomaterials, polymers, plastics, coatings, new metal alloys and other materials being researched have led to rapid progress in the sector. It is not enough for the device's design to be effective; the materials used to manufacture it must be constantly improved in order to interact more efficiently and appropriately with the microenvironment of the human body.

Breakthroughs in plastics, for example, have allowed ever-smaller catheters to be developed, which can reach parts of the human anatomy that were previously inaccessible. Their new mechanical characteristics allow them to bend and take on temporary shapes, which has improved their effectiveness enormously. The effectiveness and versatility of many medical instruments depend to a large degree on the materials they are made of.

d) Convergence of medical devices and drugs

Another of the most interesting trends in the sector is the combination of the therapeutic capacity of drugs and the functions of medical devices. This combination makes the devices more effective and makes it possible, for example, to apply drugs locally to the affected areas in higher doses, thereby reducing side effects. It also improves the durability of medical implants, which are covered in substances that facilitate their integration with the human body.

This convergence is moving forward at a good rhythm and needs new resources, capacity and knowledge in start-ups that want to be competitive in this sector. Therefore, it is becoming more common to see alliances between small, innovative companies and biopharmaceutical companies to design, develop, get authorization and market new products.

Tools for growth in the sector

Although market forces tend to favor the consolidation of the sector in a few large companies (created through successive mergers and acquisitions), we are currently seeing new start-ups dedicated to medical technology each year.

Of all the new ideas I hear about from healthcare professionals, a significant number are related to designing or patenting a new medical device. And many have great potential. The five keys for growth that we discuss with new start-ups are:

- clinical needs that are not currently met
- aging population
- qualitative technological advances
- more efficient channels of information and contact
- consolidation as motivation for new start-ups

a) Clinical needs that are not currently met

One of the pillars of growth in this sector is the possibility of using new technology, materials and products to meet needs identified by healthcare workers. The ability to meet existing needs is an essential requirement when evaluating the viability of a new start-up.

The magic of the sector is that, at times, a new million-euro market can appear out of nowhere, where demand was previously zero, thanks to a new technology or material.

Consider, for example, the endoscope. This new technology has led to innumerable start-ups devoted to products in this field, where there was previously no activity at all. In this way, new breakthroughs in medicine will lead to new opportunities for healthcare professionals that are able to detect these new needs.

b) Aging population

The population is aging and the percentage of people over 50 is increasing rapidly. There are not only more people above this age, but these people wish to remain active, stay in shape and be more mobile than previous generations.

The older population consumes more medical products than young people and they want to stay healthy now more than ever. The combination of these two trends can potentially have a positive effect on design and production of the best medical devices.

c) Qualitative technological advances

Technology is advancing at an ever-faster rate. This technology increases both safety and efficiency and, as a result, there are more doctors and healthcare workers that use medical devices in their professional work in order to improve results. In many cases, these same professionals design and develop new devices and even start up companies to produce the devices and introduce innovation in the sector. This circle is a great boost to growth in the sector.

d) More efficient channels of information and contact

Year after year, communication channels to disseminate information about innovations in medical technology to healthcare professionals, who are the natural prescribers, and hospital managers, who are the main buyers, are improving. This improvement is influenced, on one hand, by the growing maturity of the sector, which allows for stable relationships between doctors and companies.

Given that healthcare professionals are key to a device's viability, firstly, and later its profitability, it is natural that one priority of medical technology companies is to strengthen their relationship with this group. This investment focuses mainly on three areas: funding clinical programs in clinical centers, training and promoting sales. The relevance of this factor to the development and growth of any start-up is clear if we consider that once they have established a relationship with a hospital or medical professional, new products can flow through this communication channel and lead to future sales. For a start-up, establishing these communication and distribution channels is like belonging to a private club: it is expensive but once they are in, it guarantees a constant flow of income. Therefore, one of the most important strategic decisions for companies in this sector is to open up their own distribution channels. Failure to do so can be the difference between success and failure.

e) Consolidation as motivation for new start-ups

The existence of large companies competing in the sector and their tendency to buy innovation, or grow through the acquisition of small, innovative start-ups, can be a good incentive for new companies in the medtech sector. It is fairly common, at some point in a start-up's history, for an entrepreneur to license or sell a new medical device (or even the company that holds the patent) to one of these leaders in the sector. This is a highly profitable option for many entrepreneurs —and for those who have invested in the company. Furthermore, many of these large companies may be interested in licensing one of these ideas.

Why would a large company be interested in our medical device? With an innovative new product, large companies can cover at least three of their needs.

Square 8. **Economic impact of the medical technology sector**

Global market

- Turnover: 187 billion €
- 20,000 companies around the world
- Annual growth rate: 5%

United States

- Domination of the North-American market (42% of the global market)
- Highly concentrated: 10 companies control 90% of the turnover
- Large number of companies with income less than 3.3 million €
- R&D investment: 11%
- Total sales: 98 billion €

Europe

- 33% of the global market (2nd after USA)
- Total sales: 63.6 billion €
- 435,000 jobs
- 11,000 companies (80% SMEs)
- 6.8% of total healthcare expenditure (=0.55% of the GDP)
- R&D expenditure: up to 3.8 billion €
- Major exporters: Germany, Ireland, France and the United Kingdom

Spain

- 8.3% of the European market
- 1,700 companies
- 6,000 million € in turnover
- 1,500 million € in exports and 3,700 million € in imports
- 30,000 jobs

Catalonia

- 40% of the Spanish market
- 200 companies
- 5,000 jobs
- 1,200 million € in turnover
- Multinational companies
- 90% of the sector located in the Barcelona Metropolitan Area
- 70% of demand from the public healthcare system

Source: created by Biocat from data in An *Introduction to the Medical Technology Industry,* EUCOMED, 2009 and the *Fenin Annual Report,* FENIN, 2008.

Firstly, the need to continue growing. Large companies must continue to grow constantly in order to offer the best return on investment. By acquiring small companies with innovative products, they can meet this objective and open new, previously unexplored, markets.

Large companies are also motivated by their need for excellent distribution channels. Over time, large medtech companies have developed good access to the sector that allows them to be more profitable by adding new products to their catalog. If large companies have better market access, it is often start-ups that have the best and most innovative products, making collaboration beneficial to both parties.

Finally, large companies need to increase their scope in different fields. This can happen in three dimensions: geography (exporting to more countries), product (incorporating new devices in their catalog) and clients (covering needs that were not previously met). By buying or licensing a healthcare product created by a small start-up, they can extend their presence in one or more of these dimensions.

For the entrepreneur, the advantages of this type of agreement with a large company are clear. By licensing a product or selling their start-up to a large company, entrepreneurs gain access to improved distribution channels, increasing the geographic scope of the company and minimizing the risk of market changes that particularly affect a company with only one product (as often happens in start-ups).

The medical technology sector in Catalonia has extraordinary potential and not realizing and taking advantage of this potential could be detrimental to our country. Everyone working in this sector must make an effort to reduce the gap between ideas and execution, between healthcare professionals and inventors, and between the concept that the medical profession is essentially treatment-based and the new vision of doctors as innovation leaders in the medical technology sector.

Over the next years there will be many new opportunities and we must all make an effort to support entrepreneuring doctors and researchers, while protecting their rights in this process.

For the first time, Catalonia is in a strong position in the biotechnology and healthcare innovation field. We all have to work together to make the most of this opportunity and help position our country as a European benchmark. To do this we need the dedication and driving force of everyone related to the sector.

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Analysis of companies and research centers

5. Introduction to the results

The aim of this analysis is to provide as accurate a look as possible at the state of the art in the biotechnology, biomedicine and medical technology sector in Catalonia, taking into account the diversity of entities and organizations that make it up.

This first report will lay the foundation for future editions to analyze evolution and trends using indicators that will allow us to indentify weaknesses and, therefore, define strategies to solve these problems.

The public research system in the biotechnology, biomedicine and medical technology sector in Catalonia is complex and wide reaching. It is made up of a large number of centers, research groups, hospitals and other interrelated entities. Given this complexity, Biocat has chosen to give an overview of the public R&D&i system by evaluating research centers and discussing the rest of the entities in the system and their specific importance in the following section, as well as including a joint analysis of university research groups in Chapter 8.

For this reason, the section presenting the results has been designed using an evaluation of BioRegion members structured as follows:

- Types of organizations in the BioRegion of Catalonia
- Analysis of companies
- Analysis of research centers
- Conclusions

Another point we must clarify before moving on to the analysis itself is the subsectors of activity, which distinguishes between red biotech (medical and healthcare applications), green biotech (agrifood and environment), white biotech (industry) and medical technology according to the criteria laid out in the introduction on the colors of biotech. These subsectors of activity have been defined according to the criteria explained in the following table (Table 5).

Table 5. **Classification of subsectors of activity**

Red Biotech	• Drug discovery/development • Diagnosis • Therapeutic products • Drug manufacturing • Animal health
Green Biotech	• Agroindustry • Agrifood industry • Environment • Aquiculture
White Biotech	• Biomaterials • Bioprocesses • Fine chemicals • Biofuel • Bioremediation
Medical Technology	• In vitro diagnostics • Image diagnostics • Medical devices • Electromedicine

In order to draft the section on the results of the Biocat Report, we have used two main sources of data: the Biocat Directory and the survey filled out by a significant number of members of the BioRegion of Catalonia. In some areas, the Catalan government has provided additional data, the source of which is explicitly noted in each case.

The survey this study is based on was sent out in June 2009 to 368 entities (mainly companies, research centers and institutes, and technology centers). 58.32% of these

entities filled out the survey, which can be broken down as follows:

- **Companies:**
  - Surveys sent: 320
  - Surveys received: 108
  - Participation: 33%

- **Research centers, hospital research institutes and technology centers:**
  - Surveys sent: 48
  - Surveys received: 40
  - Participation: 83%

This level of participation has led to an analysis that, in some cases, is more qualitative than quantitative.

In this section we would like to thank all those that participated, the effort they put into this report and point out the dedication with which data was treated as a whole.

In future editions of the report we expect to send this survey to all members of the BioRegion in coordination with other entities of the Catalan Administration. We also hope that the analytical potential of this report drives collaboration of all entities and that participation increases substantially in order to obtain reliable indicators with which we can establish solid collective policies.

6. Types of organizations in the BioRegion

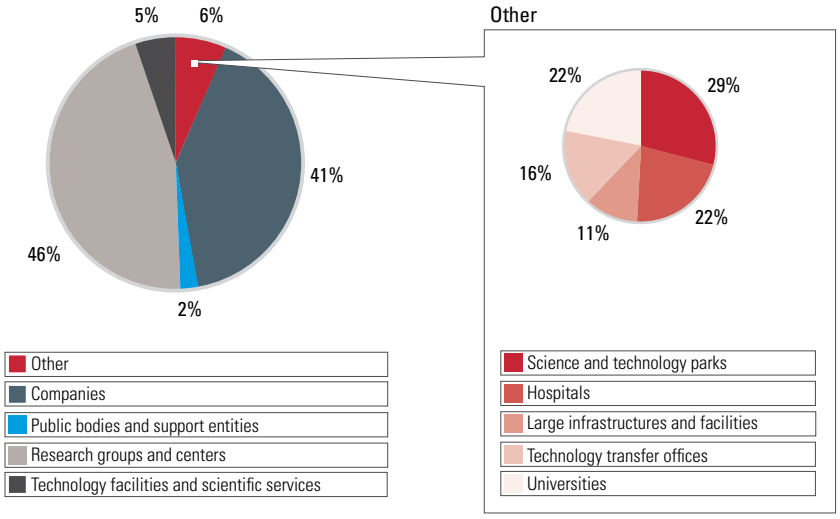
In this chapter we aim to provide detailed information on the different types of organizations that make up what is colloquially known as the sector, using data from the Biocat Directory. We will look at representatives from the triple helix —companies, research centers and institutes, and support and governmental organizations— that make up the BioRegion of Catalonia.

Analysis of the Biocat Directory shows (figure 5) an important number of companies, specifically 358 (41% of all registered in the Directory), that carry out both research and development of biotechnology products, support services or activities related to the sector. Those devoted to research can be broken down into the following groups:

- 65 biotechnology companies
- 70 pharmaceutical companies
- 60 medical technology companies
- 27 fine chemical companies

To a slightly higher degree, the public entities that carry out R&D&i in Catalonia represent 57% of all organizations in the sector. This percentage corresponds to the sum of research centers and groups (399 registered in the

Figure 5. **Types of organizations in the BioRegion**



Source: *Biocat Directory*. Sample size: 874 registers from the *Biocat Directory* (September 2009)

Directory of the BioRegion, 46% of all entities), technology facilities and scientific services, and a group of entities shown in figure 5 under the heading "other", which is made up of the following:

- 17 science and technology parks
- 12 hospitals
- 12 universities
- 6 large infrastructures

We must point out that the Biocat Directory only includes hospitals that carry out research activity and not those whose activity is only healthcare related, which explains their limited number.

Entities that provide non-business related support (technology transfer offices [TTO] and public bodies) make up slightly more than 2% of the sample.

It is important to remember, for comparison, the size of some mature clusters mentioned in the introduction, like the ERBI (Cambridge, United Kingdom), which has 370 members including pharmaceutical, biotechnology and medical technology entities; the Medicon Valley Association (Copenhagen, Denmark), which includes 473 companies, 10 universities and 33 hospitals; and in Germany, the Munich BioTec Region (Biom), which is made up of 160 companies, 3 Max Planch Institutes, 4 universities and 2 hospitals, and the BioTOP in Berlin, with 300 companies, 5 universities and 20 research centers; and the GIP Genopole, which has the largest concentration of biotechnology companies in France, with 69 companies, 20 academic research laboratories and 19 shared infrastructures, according to data from their respective web pages.

In this section we must highlight that the entities grouped under the heading "other" are essential to a knowledge-based sector and represent an important volume of research carried out in the BioRegion. We will therefore discuss the most relevant aspects of these organizations.

For a biocluster, both universities and hospitals are essential agents, contributing knowledge, research projects and qualified human capital.

The function of universities is three-fold: education, research and innovation, understood to be technology transfer. In Catalonia there are seven public and three private universities that carry out these three activities in the life sciences arena. The oldest is the University of Barcelona, founded in the 15th century, with six campuses connected to technology transfer. These campuses work collaboratively with the Bosch i Gimpera Foundation, which has some 15,000 research projects and contracts. The newest of these institutions is the Pompeu Fabra University, created in 1990. As an example of their implication in top-notch European research, the group of Catalan universities is among the top entities with regard to participation in the European Union's 7th Framework Program, heading 13 projects in the first year of this program (Catalan Inter-University Council, March 2008). This report does not aim to provide an exhaustive study of the particularities of each of these universities, but it does analyze, in section 8.5, the number of students and degrees at each university in order to give an overview of the future generations of professionals that will grow the sector.

Regarding Catalan hospitals, their implication in clinical research in collaboration with the industry is a key factor in Catalonia. According to data from 2008 collected in the BEST Project (Farmaindustria, 2009), Catalan hospitals participate in more than 1,800 trials of the nearly 7,000 carried out in all of Spain. These are mainly phase III trials (58%), followed by phase II (24%) and only around 4% are phase I. According to the aforementioned report, clinical research in Catalonia has a statistical weight that is clearly above what we would expect from its population size, with a patient recruitment rate above the national average and recruitment and documentation time below the national average. All this without mentioning the growing interest of Catalan hospitals in basic and translational research, recognized by the Carlos III Institute in 2009, which accredited four Catalan centers (Vall d'Hebron University Hospital Research Institute, Bellvitge Biomedical Research Institute, Health Sciences Research Institute of the Germans Trias i Pujol and the August Pi i Sunyer Biomedical Research Institute), out of a total of five in the whole country, as leaders in bridging the gap between basic and clinical research, in accordance with the Act on National Healthcare System Cohesion and Quality (16/2003 28 May).

According to data from the Catalan Healthcare Institute (ICS) in 2007 (available on their webpage), the network of

centers that carries out research activity has a total human capital of 2,372 professionals, who have generated 1,793 publications —with a global impact factor of 6.189 and an average impact factor of 3.45— 696 research projects and 56 million euros in funding. The most important scientific areas at the ICS research centers are neuroscience, infectious diseases and transplants, inflammatory diseases, chronic and degenerative diseases, epigenetics, cancer biology, epidemiology and public health, among others.

Another key element in the biocluster is the existence of science and technology parks. This type of entity is vital as a liaison between organizations that generate knowledge and start-ups, offering highly specialized technical/scientific services, business incubation spaces and technology transfer offices (TTOs).

In Catalonia there are nine science and technology parks focusing on the life sciences sector (figure 6), mostly located in the Barcelona Metropolitan Area. The oldest, founded in 1997 although it did not start functioning until 2001, is the Barcelona Science Park (PCB). Afterwards, additional parks have been created with different focuses: the Barcelona Biomedical Research Park (PRBB), which concentrates more on basic research, and the UAB Research Park (PRUAB), founded in 2005. However, this type of infrastructure is also being created around the universities of Lleida (Lleida Agrifood Science and Technology Park, PCiTAL), Girona (University of Girona Science and Technology Park) and Tarragona (Tarragona Science and Technology Park and Tecnoparc –Camp Technology Park in Reus) because of their ability to attract applied research centers and business incubation spaces. These parks are members of XPCAT (Network of Science and Technology Parks of Catalonia).

Catalonia has all the necessary types of organizations to lead biotechnology, biomedicine and medical technology in Europe

Finally, we must discuss large facilities, which serve as hubs for companies, top-notch science groups and human capital. In Catalonia, the Government recognizes nine large-scale facilities, eight of which work in this sector to some degree. They are as follows:

- MareNostrum
- Supercomputing Center of Catalonia
- International Center for Numerical Methods in Engineering (CIMNE)
- BM16 Beamline (ESRF)
- Alba Synchrotron Light Laboratory (CELLS)
- Nuclear Magnetic Resonance Laboratory
- Molecular Genetics Laboratory – Center for Genomic Regulation
- White Room - National Center for Microelectronics

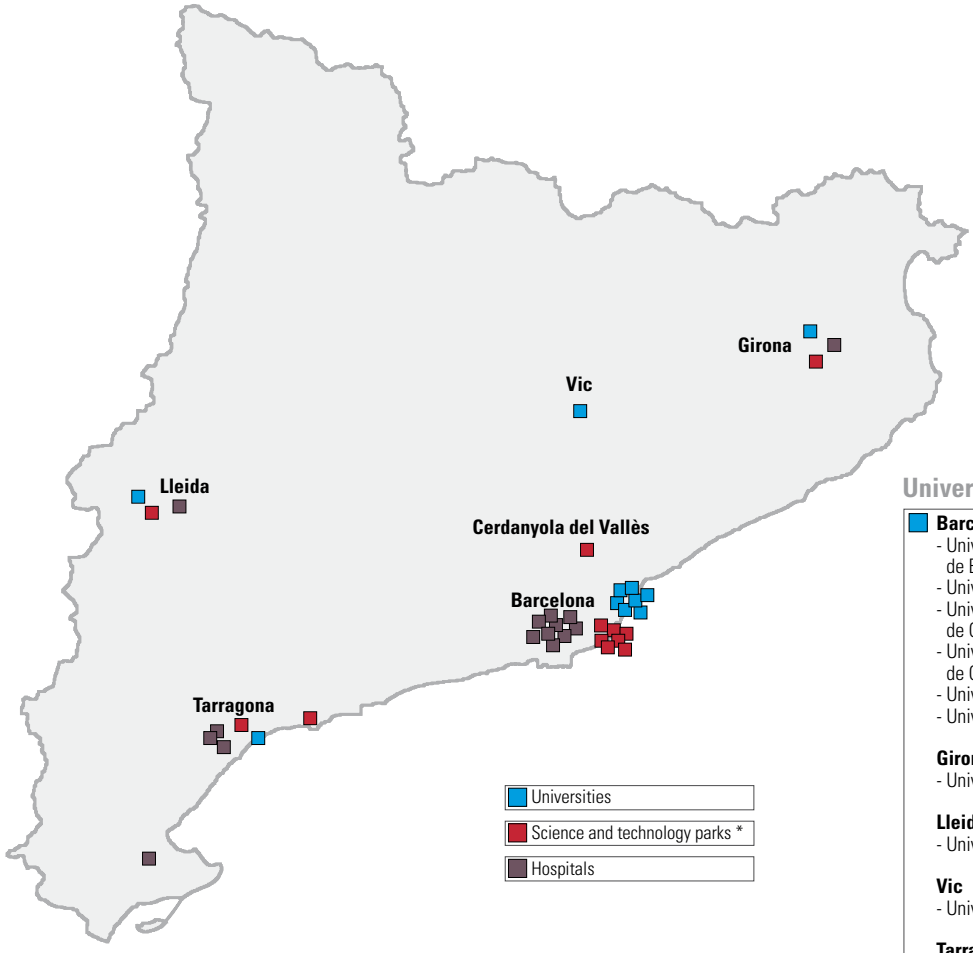
Recently, the World Intellectual Property Organization (WIPO) published an interview with the heads of the CERN Large Hadron Collider (LHC) (CERN and Innovation, 2008), in which they evaluated the impact of the construction of this facility, to which we must add the new businesses and knowledge generated. Thus, 630 companies participated in the construction process. When asked about the project's impact on the company: 30% said they had developed new products, 17% had opened new markets and 14% had created new business areas.

Here in Catalonia, the MareNostrum located at the Barcelona Supercomputing Center (BSC), has lead to 1,200 projects carried out in 4 years, 26% of which were in life sciences fields, including joint research projects with the IRB (Barcelona Institute of Biomedical Research). According the their annual report, the BSC has gone from 200 to 320 professional employees in 2008, mainly due to collaborators and foreign researchers and the increase in research projects. Their 2008 budget was 23.9 million euros, of which 9.2 million were from competitive projects (23 projects funded by the EU, 30 with industry and 30 national projects).

And as an example currently in construction, we have the Alba synchrotron, in the UAB area, which will begin functioning in 2010 and occupy 22,870 m2. In the surrounding area one million square meters have been set aside for a scientific research park, which will coexist with spaces for other productive uses, residential spaces and facilities.

In absolute numbers of types of organizations, it is clear that Catalonia is in a good position within Europe. Another issue is the level of maturity that has been reached in the BioRegion, which is implied in the analysis of activity of the organizations that make it up, as we will see in the following sections.

Figure 6. **Geographic distribution of universities, hospitals, science parks and technology parks in Catalonia*/****



Universities

Barcelona
- Universitat Autònoma de Barcelona (UAB)
- Universitat de Barcelona (UB)
- Universitat Internacional de Catalunya (UIC)
- Universitat Politècnica de Catalunya (UPC)
- Universitat Pompeu Fabra (UPF)
- Universitat Ramon Llull (URL)

Girona
- Universitat de Girona (UdG)

Lleida
- Universitat de Lleida (UdL)

Vic
- Universitat de Vic (UVIC)

Tarragona
- Universitat Rovira i Virgili (URV)

Science and technology parks *

Barcelona
- Parc Científic de Barcelona
- Parc de Recerca Biomèdica de Barcelona
- Parc Tecnològic de Barcelona Nord
- Parc de Recerca i Innovació UPC
- Parc de Recerca UPF
- Biopol
- 22@Barcelona

Girona
- Parc Científic i Tecnològic de la UdG

Lleida
- Parc Científic i Tecnològic Agroalimentari de Lleida (PCiTAL)

Tarragona
- Parc Científic i Tecnològic de Tarragona
- Parc Tencnològic del Camp-Tecnoparc

Cerdanyola del Vallès
- Parc Tecnològic del Vallès
- Parc de Recerca UAB

Hospitals **

Lleida
- Hospital Universitari Arnau de Vilanova de Lleida

Tarragona
- Hospital Sant Joan de Reus
- Hospital Universitari Joan XXIII de Tarragona
- Hospital Verge de la Cinta de Tortosa

Girona
- Hospital Universitari Doctor Josep Trueta de Girona

Barcelona (Province)
- Hospital Sant Joan de Deu (Esplugues)
- Hospital Universitari de Bellvitge (Hospitalet)
- Hospital Universitari Germans Trias i Pujol de Badalona
- Corporació Sanitària Parc Taulí

(City)
- Hospital Clínic i Provincial de Barcelona
- Hospital de la Santa Creu i Sant Pau
- Hospital Universitari de la Vall d'Hebrón
- Hospital del Mar

* that carry out activities in the biotechnology, biomedicine and medical technology sector
** Hospitals with noteworthy research activity

7. Analysis of companies

The data included in this section comes from a survey Biocat sent to companies (June 2009) except in specific cases, in which the origin is noted.

Number of companies invited to participate: **320**
Surveys completed: **108**
Participation: **33%**

This level of participation leads us to be cautious in some of our conclusions, however it does allow us to carry out a valuable first analysis of what is happening in the BioRegion of Catalonia.

7.1 Overview

As a starting point for this analysis, we will look at the subsectors of activity (colors of biotech) in which the companies work, their age, their origin and geographic distribution and who promotes them. Additionally, we will examine the existence and typology of support companies.

One characteristic we must take into account when interpreting the results is that many companies carry out more than one activity, which is characteristic of the sector, and led to multiple responses to some questions.

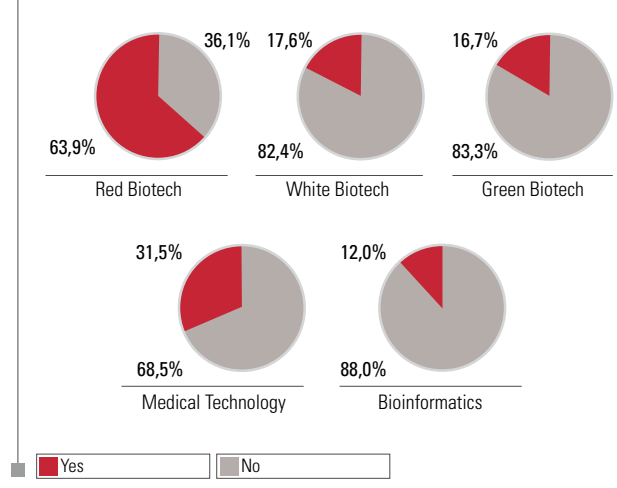
Subsectors of activity

In studying the subsectors of activity, we can see (figure 7) that the large majority of Catalan companies surveyed carry out activities related to the healthcare sector, either red biotech (64%) or medical technology (32%). This number is due, in part, to the Catalan and Spanish administrations' strong commitment to biomedicine over the past 10 years, which has driven research in centers and institutions from which the youngest companies have been created.

We must also stress the relative importance of bioinformatics (13%), which is at nearly the same level as green and white biotechnology. The impact of bioinformatics is mainly found in simulation techniques, gene predictions, protein modeling, creation of large storage databases, treatment of genome sequences, etc. As we mentioned in the first chapter, in order to be competitive the bioinformatics sector must become one of the growing niches of activity.

Regarding the weight of white or industrial biotech shown in the study (18%), we must say that the results do not reflect the reality of the region due to the bias of the sample surveyed. The survey focused on companies that make up the BioRegion and did not include companies that belong to other industrial sectors and, therefore, as indicated in the introduction by Dr. Castells, employ biotechnology in their processes or biotech products as a raw material. However, if we consider the weight of some activities

Figure 7. **Subsectors of activity in companies**



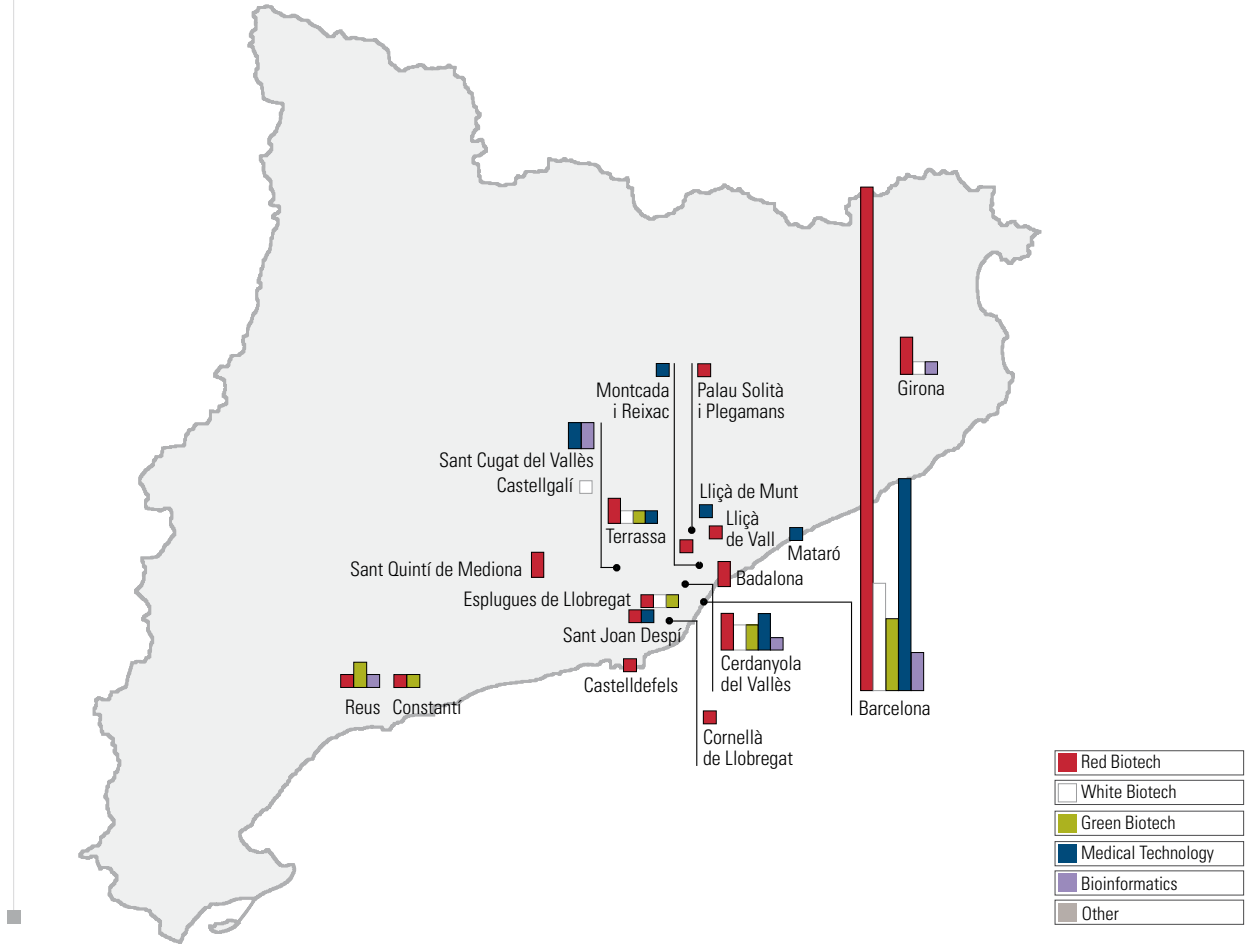
(bioprocesses, kits, API manufacturing, etc.) carried out in companies that were included in the survey, it is clear that industrial biotech is a subsector with high economic potential, as discussed in section 7.2.

The companies surveyed that fall under the category of green biotech mainly work in agrobiotechnology. These companies mainly focus on improving plant and seed genetics and plague control, although those that work on genetic improvement often carry out other biomedical activities.

Regarding geographic distribution (figure 8), the majority of companies, regardless of the subsector, are located in the Barcelona metropolitan area. This confirms that the city is a hub of progress and business, as established in the *European Cities Monitor* report (Cushman and Wakefield, 2008).

Companies in the BioRegion mainly carry out biomedical research

Figure 8. **Geographic distribution of companies in the BioRegion by subsector of activity**



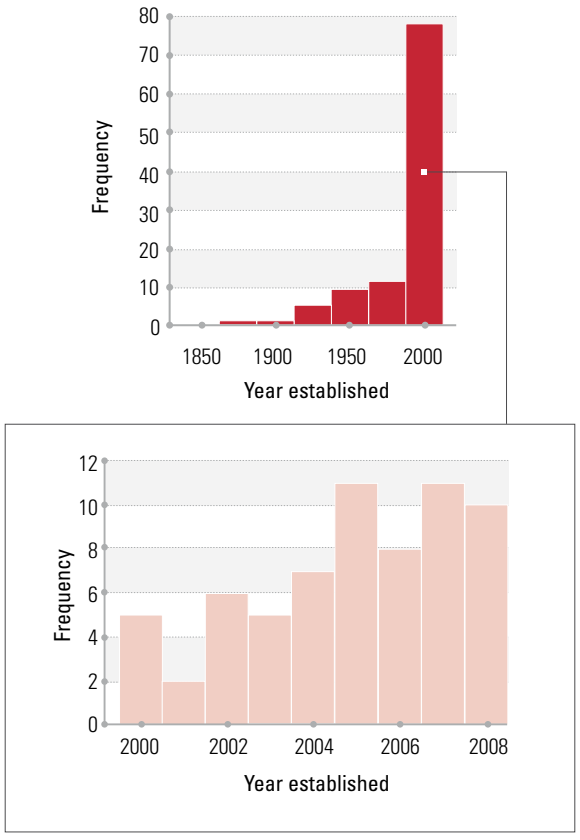
Year companies were created

In line with industrial evolution in Catalonia, the first companies appeared at the end of the 19th century, mainly those devoted to chemicals (figure 9).

However the boom of Catalan-based pharmaceutical companies didn't occur until the 1950s, along with the appearance of the first multinational subsidiaries and clinical research centers in Catalonia.

Regarding medical technology companies, their activity also started some 40-50 years ago, while what we now consider white or industrial biotech started in the 1980s.

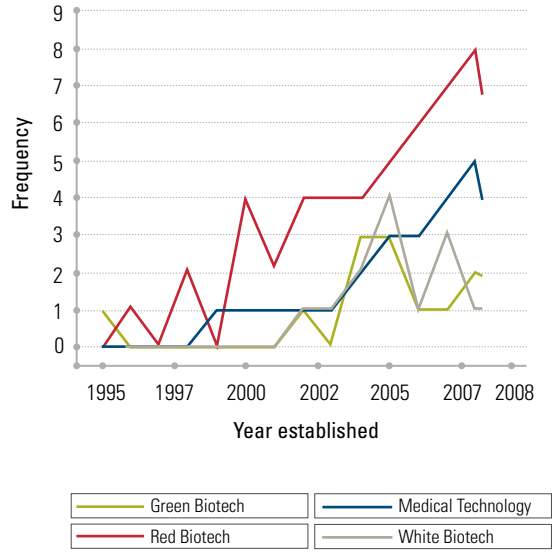
Figure 9. **Year of establishment for companies in the BioRegion of Catalonia**



From 2000 (figure 10), there was an important increase in the creation of new companies in the sector, mainly in green biotech. More than 50% of companies in this subsector were established sometime in the past nine years and after 2005 we see an important increase in white biotech and a significant number of new medical technology companies.

There are three main factors behind this boom starting in 2000. In the period between 2002 and 2004, the work of CIDEM (now ACC1Ó) was key, creating specific grants for start-ups and dynamizing technology springboards and the IT Network. On the other hand, the Barcelona Science Park opened in 2001, with its business incubator, offering a favorable business environment for the creation and growth of biotech companies, as reflected in the increase experienced in the 2004-2008 period. Finally, a wave of support reached the sector in this period, which had begun years earlier in Europe, with the creation of various science parks, which in many areas served as hubs around which to create a cluster. Some examples of this

Figure 10. **Year of establishment for companies by subsector of activity**



phenomenon include Heidelberg (1985), the Cambridge Science Park (1970), which is the oldest in the United Kingdom, and the Genopole Biopark (1998) in France, a more recent example.

This growth continued in 2006 and 2007. Catalonia was the most dynamic region in Spain regarding new biotech companies, with a rate of 10 new companies per year, according to Asebio reports.

Company origins

Regarding the origins of these companies, we can see that approximately half (54%) were created by the business sector, mainly as spin-outs of pharmaceutical companies (figure 11).

The other half of these companies was created by the public research arena, mainly universities (18%). When we compare the origin of the companies with the year of foundation, we see that 25% of this last group was created sometime around 2004. This reflects the results of policies put into action by universities to this effect, by creating support infrastructures (technology transfer offices), start-up promotion programs, and innovation fostering.

We must point out that there are still few companies created out of hospital or medical research institutes (5%), which we started to see only in 2005. The legal barriers (incompatible regulations in Act 7/2007 of the Basic Statute of Public Employees), lack of regulatory framework for innovation, incompatibilities between academic and support tasks, and the small impact of patents and licenses on professional careers are just some of the causes for this low percentage.

Companies that are created out of technology centers (2%) are also scarce and founded in 2003, with no new companies in the biomedical field in the last years according to the sample analyzed.

If we compare the information on the origin of the companies with their subsector of activity (figure 12), we can

54% of start-ups are business spin-outs

Figure 11. **Origin of companies by type of promoter**

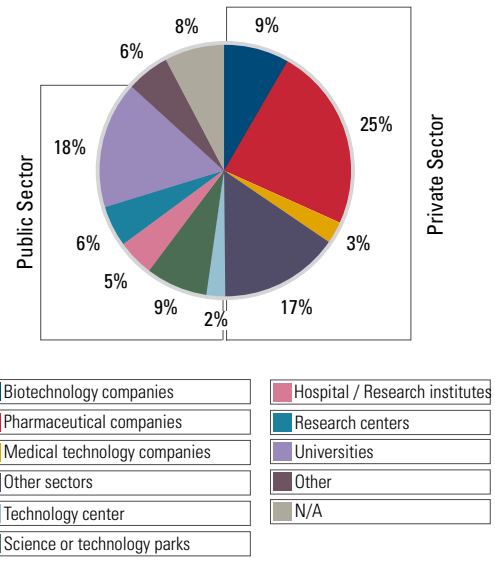
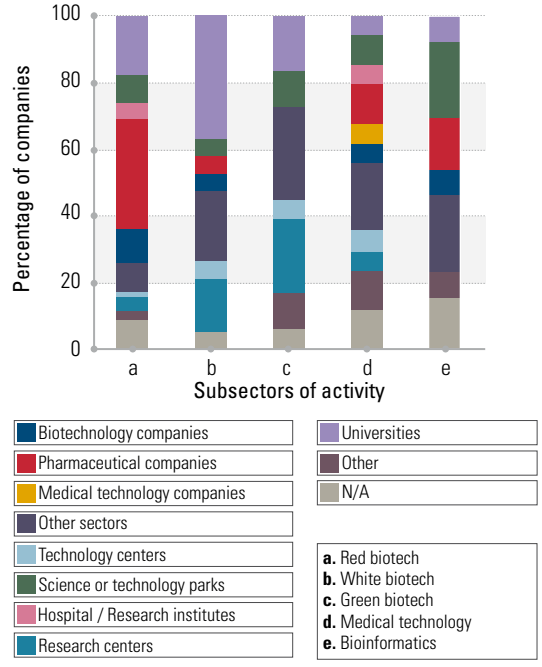


Figure 12. **Origin of companies by subsector**



see that the majority of red biotech companies were created out of a pharmaceutical company or a university, which again shows the limited participation of hospitals. On the other hand, medical technology companies also originate in the business sector. However, most of the companies come from other traditional industrial sectors that see the biomedical sector as a potential for new business, as noted in Chapter 4.

White biotech companies, however, are mainly promoted by universities, with those focusing on bioprocessing and bioinformatics coming mainly out of science parks.

Number of promoters

One characteristic that these companies share is a low number of promoters (figure 13).

They are mainly started up by 1 to 4 people. The training and position of these people within the company will be discussed in section 7.5.

Support or sector-related companies

In the BioRegion, in addition to the companies analyzed so far, there is also a group of support companies, which were not specifically addressed in the survey or for which the survey only related to their main area of activity and not the services they offer. These activities are carried out by nearly 50% of the companies registered in the Biocat Directory.

These companies are mainly technical suppliers and consultancies (figure 14). The analysis also shows that there are few venture capital companies that invest in the biomedical field and few specialized business development companies, which demonstrates the trends discussed in the introduction and the need to increase the number of biomedical management professionals and specialized analysts.

Below is a table showing some venture capital companies that invest in the sector in Catalonia, according to the investment phase they focus on.

Figure 13. **Number of promoters per company in the BioRegion**

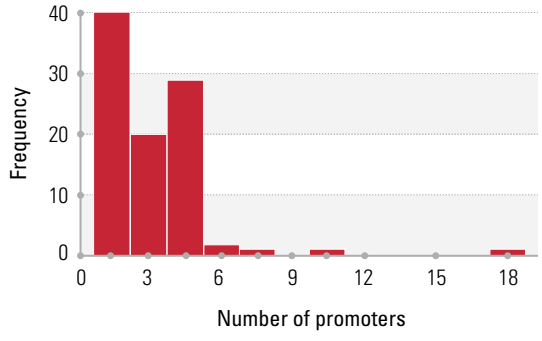
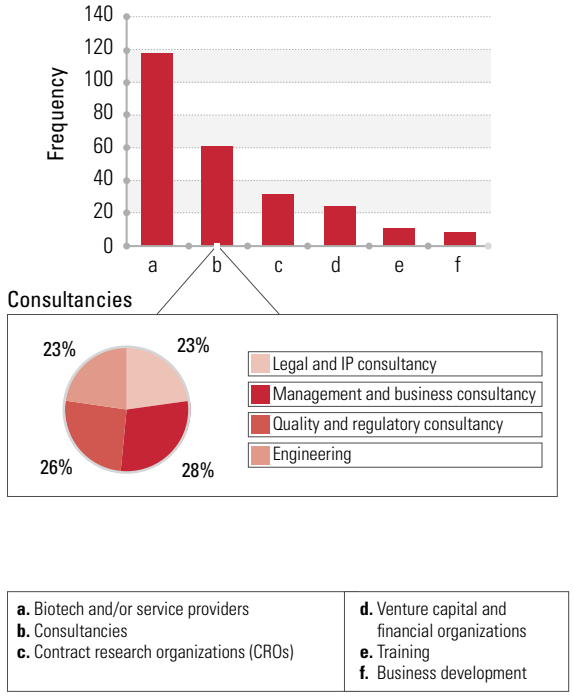


Figure 14. **Sector support companies**



a. Biotech and/or service providers
b. Consultancies
c. Contract research organizations (CROs)
d. Venture capital and financial organizations
e. Training
f. Business development

Square 9. **Selection of venture capital funds in the BioRegion that invest in the sector**

a. BA*: 50,000 € to 400,000 € **b.** Seed: 300,000 € to 700,000 € **c.** Round 1: de 1,500,000 € to 4,000,000 €	**d.** Round 2: de 10,000,000 € to 20,000,000 € **e.** Round 3: Aprox. 30,000,000 €

Source: Metasbio and Biocat. *Business Angels.

In short

We have observed a predominance of companies (biotechnology, pharmaceutical and medical technology) that focus on biomedicine. Most of these have been created very recently and have a small number of promoters. They mainly come out of business environments and universities and they are nearly all located in the Barcelona metropolitan area. A support subsector does exist but there are still few specialized venture capital and business development companies, which is in line with the sector's youth. We have found a notable growth in the companies' interest in bioinformatics.

7.2 Main areas of activity

In order to define the sector's commercial model, regarding the companies we have analyzed, we evaluated their main activities in the sector, the areas of the value chain they focus on, whether this activity is carried out internally or subcontracted, the business model they use, and their priorities for the future.

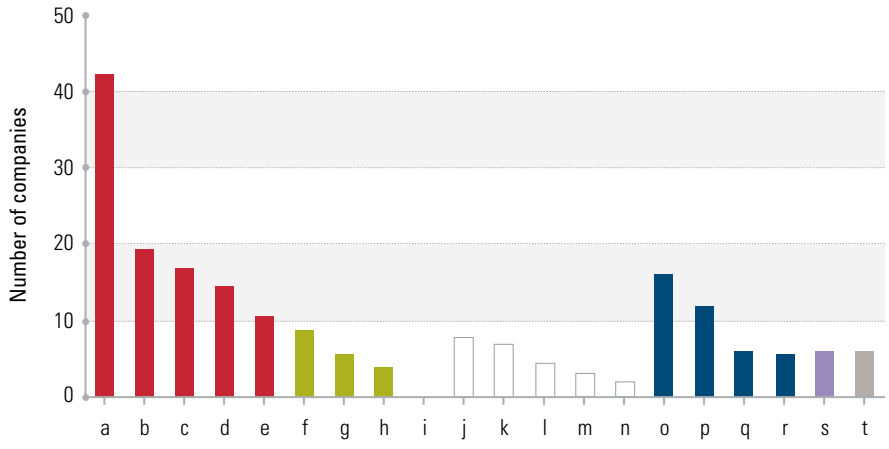
Main activity

As seen in the following charts (figures 15 and 16), activity in the sector focuses on red biotech. In this subsector, 41% of companies surveyed carry out drug research and development. In medical technology, the most common activity among the companies surveyed is manufacturing medical devices (17%).

In white biotech, generating and optimizing bioprocesses accounts for 8% of the total activity and is carried out mainly by small biotech firms. We should point out the lack of semi-industrial production under the GMP (Good Manufacturing Practices) standards for the application of these bioprocesses to drug development, which is essential in the clinical phase.

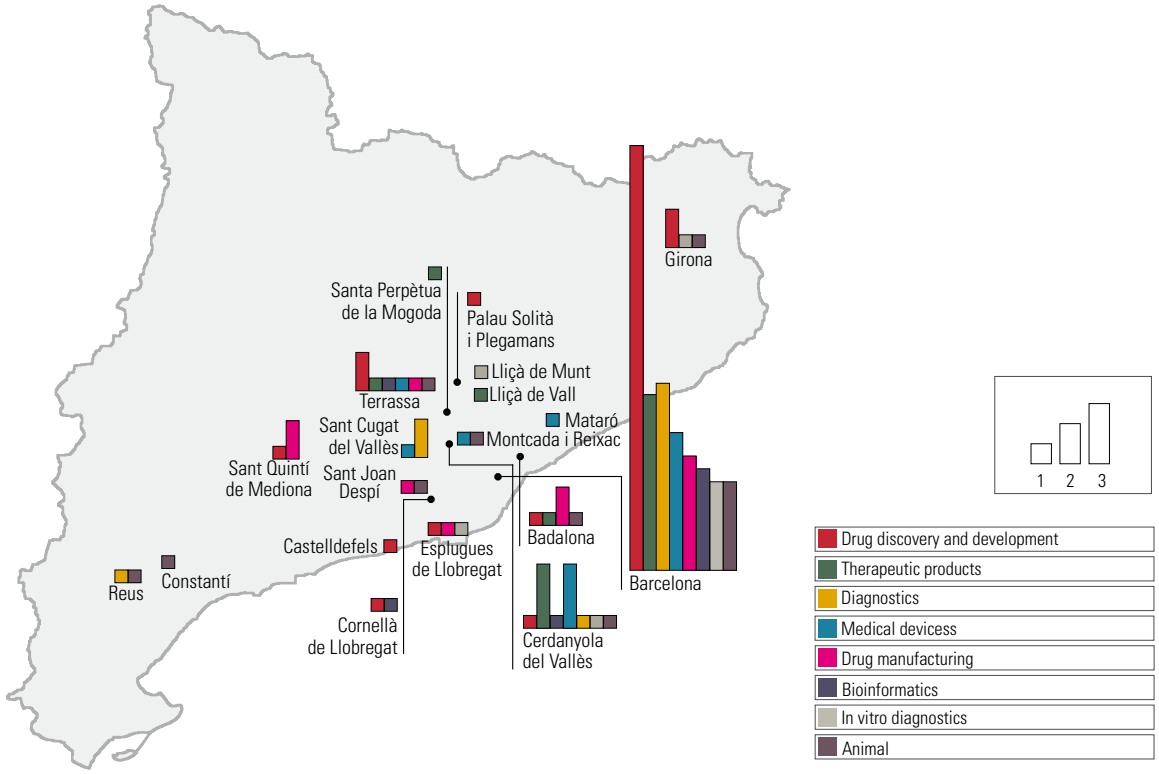
Fine chemicals is a key industry in Catalonia but only represents 7% of the BioRegion when we look at API (Active Pharmaceutical Ingredient) manufacturing in companies surveyed. However, we believe that this area in underrepresented because many companies filled out the survey about their pharmaceutical activities and did not include information about API production. In total, the fine chemicals sector in Catalonia is made up of 27 companies, representing 80% of the total Spanish sector. This includes trade organizations like Afaquim, Fedequim and Feique. Proof of this sector's importance is the bi-yearly Expoquimia fair. Many of these companies belong to pharmaceutical groups and are located in the areas surrounding the city of Barcelona, except for one notable exception (Medichem, in Girona). This group of companies has a yearly turnover of approximately 900 million euros, 75% from exports despite the fact that over the past years export turnover has decreased an estimated 6% due to competition from countries with lower production costs (*The Catalan Chemical Health Cluster*, Catalonia International 44, 2007).

Figure 15. **Main activities of companies in the BioRegion**



a. Drug discovery and development
b. Therapeutic products
c. Diagnostics
d. Drug manufacturing
e. Animal health
f. Agrifood
g. Agroindustry
h. Environment
i. Aquiculture
j. Bioprocesses
k. Fine chemicals
l. Biomaterials
m. Biofuel
n. Bioremediation
o. Medical devices
p. In vitro diagnostics
q. Image diagnostics
r. Electromedicine
s. Bioinformatics
t. Other

Figure 16. **Geographic distribution of companies by main activity**



Finally, in green biotech, the main activity in Catalonia is agrifood production (9%), not for general consumption but for research and therapeutic applications (functional food, nutraceuticals), with a strong concentration in Tarragona.

In Girona there is a moderate presence of companies focusing on drug discovery and development, as well as in vitro diagnostics and animal health.

It is important to note the low representation of companies in the Lleida area, which is mainly due to the youth of their facilities, like PCiTAL and IRB-Lleida, which carry out high-level research in oncology and systems biology. There is also an IRTA center with internationally renowned experts in agribiology and a degree in biomedicine offered at the University of Lleida.

Value chain for main activity

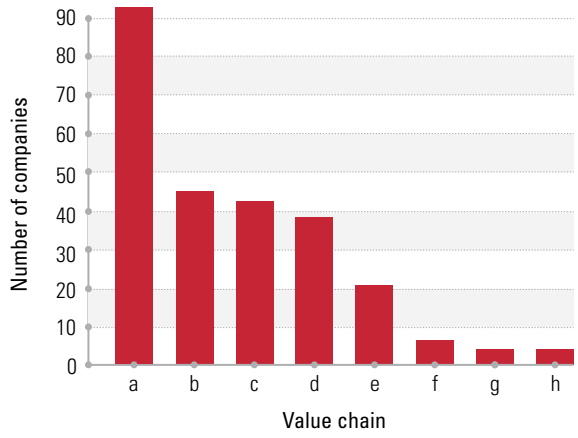
Among companies in the BioRegion we find all stages of the value chain, from idea to market. Moreover, many of the companies work in different areas of the chain, which again led to multiple responses on the survey.

Data collected shows (figure 17) that R&D and commercialization are the two stages of the value chain most companies in the sector focus on, with 81% (R&D) and 42% (commercialization) of the companies surveyed. Only 7% of companies work in distribution. In this small group there are two types of companies: a few that serve the whole value chain and small distributors that focus on a specific type of product.

Analysis of successive activities in the value chain (figure 18) shows the following results:

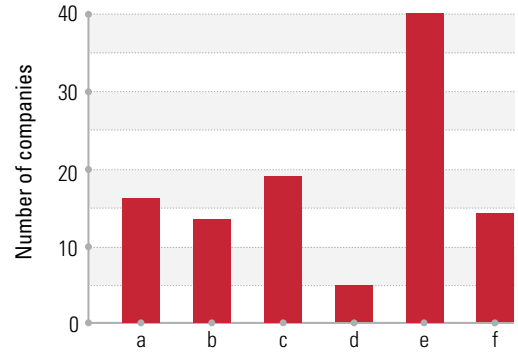
- 15% of companies surveyed work exclusively in R&D.
- 37% of companies combine R&D tasks with technical or consulting services (shown as 'other' in the graph), a mixed business model that we will discuss more in-depth later in this section.
- Only 12% of companies combine R&D with production.
- 18% of companies work on R&D, production and commercialization of products.
- Only 5% of companies cover the whole value chain.

Figure 17. **Value chain for companies' main activity**



a. R&D **b.** Commercialization	**c.** Production **d.** Service	**e.** Consulting **f.** Distribution	**g.** Training **h.** Other

Figure 18. **Combinations of value chain activities in companies**



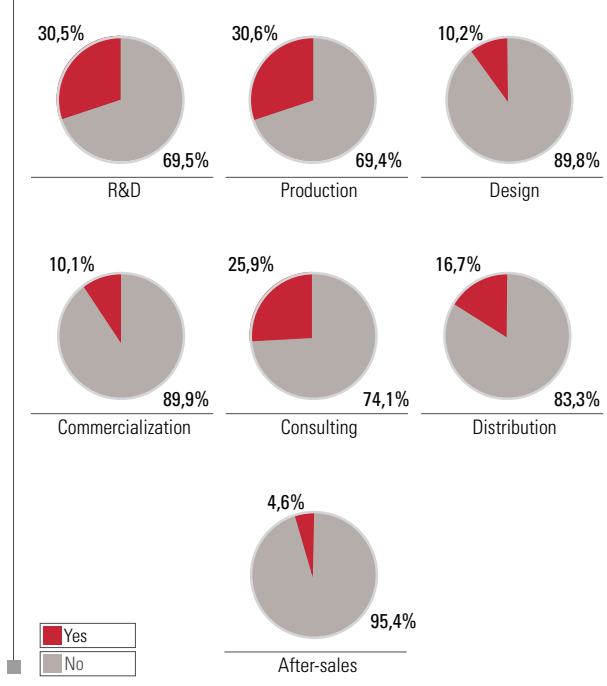
a. R&D **b.** R&D + Production **c.** R&D + Prod + Commercial **d.** R&D + Prod + Commercial + Distribution	**e.** R&D + Other **f.** No R&D

Companies that don't carry out R&D fall into many heterogeneous categories: medical technology companies, some diagnostics companies and a few multinational companies that only commercialize products in Catalonia and don't do research here.

The 5% of companies that do cover the whole value chain are found in the areas of drug discovery and development, diagnostics and in vitro diagnostics, medical devices, therapeutic products and animal health. In general they are pharmaceutical/veterinary companies —the so-called FIPCOs (Fully Integrated Pharmaceutical Companies)— and more consolidated medical technology companies. There are not yet any VIPCOs (Virtually Integrated Pharma Company), despite global trends discussed in Chapter 1.

If we focus our analysis on the areas of the value chain that are subcontracted to third parties (figure 19), we can see that non-critical R&D or routine trials, production and strategic consulting are the services most often outsourced (31%, 31% and 26% respectively). According to the survey carried out by the BEST Project (Farmaindustria, June 2009), of the 1,001 million euros the pharmaceutical sector invested in R&D in 2008, 39.2% went to externalized activities, subcontracted to hospitals, universities and public research centers.

Figure 19. **Activities subcontracted by companies in the BioRegion**



Demand for external consulting explains the high number of support companies that provide this service (section 7.1), as well as the growing number of CRO/CMOs working in the BioRegion. We must also add an important number of companies that provide some technical consulting services, although it is not their main activity. These companies are found mostly in bioinformatics and image diagnostics.

In the specific case of medical device manufacturing, according to Biocat studies on contract manufacturing in this sector, the subcontracting trend is focused mainly in specific steps of the value chain. Externalization is found in the phases from prototype production to storage. However, businesses keep R&D and design work inside the company, at most collaborating with other R&D centers, unlike biotech or pharma companies, which do subcontract research. Medical device companies also manage distribution of small batches or niche products internally. They also choose not to subcontract communication.

42% of companies that stated they commercialized products do so through different channels. 51% have their own distributor, though it is not always exclusive. This high percentage is due to the weight of large pharmaceutical companies and medical technology companies, which as we mentioned before do not normally externalize this activity. 44% of the companies surveyed have commercial agreements and 17% subcontract distribution. The few biotechnology companies that distribute are found in these last two groups.

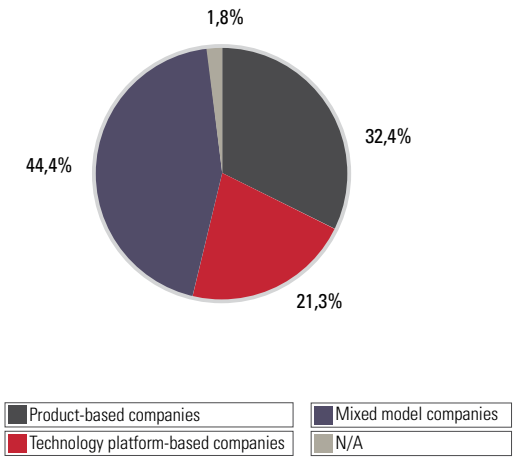
Internationalization

Additionally, companies stated that they mainly work in the Catalan (44%), Spanish (51%) and European (43%) markets, and less frequently in the South-American market (19%). However, very few are present in the North-American market (11%), despite this being the largest

biomedical market in the world. The North-American pharmaceutical market is estimated to move 300,000 million dollars per year, with growth of 1.4% (*IMS Market Prognosis International 2009-2013*, IMS Health, 2009), while the biological market moved some 60,000 million dollars in 2008, with inter-annual growth calculated at 20% (*Biogenerics*, Generic Pharmaceutical Association, 2009) and medical technology moved 98,000 million euros versus the 73,000 million euros moved by this subsector in Europe (*An Introduction to Medical Technology Industry*, Eucomed, 2009). The United States is also the preferred market for biotech investment, with nearly 1,400 million dollars, and medical technology investment, which neared 900 million dollars per year according to data from 2008, in a global market of 7,000 million dollars (PriceWaterhouse Coopers, Money Tree Report, 2008).

Asia (11%) and Africa (3%) are also minority markets for Catalan companies. Mainly multinational pharmaceutical or highly consolidated companies work in these markets and the number of SMEs is merely anecdotic. Only 20% of all companies report a global presence.

Figure 20. **Business model employed by companies in the BioRegion**



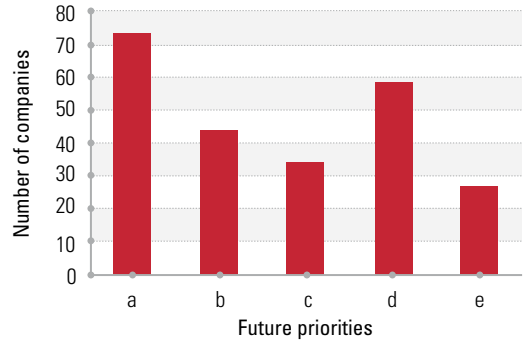
Companies in the BioRegion work mainly in the Catalan and Spanish markets (44% and 51% respectively), as well as the European market (43%) and to a much lesser extent in the United States (11%)

Business model

Regarding the business model companies employ (figure 20), the study shows that nearly half of the companies (44%) use a mixed model that combines product development (pharmaceutical or medical technology) with third-party services based on their own highly specialized science or technology platforms.

This preference for the mixed model gives companies a steady stream of income, thanks to their technology sales

Figure 21. **Future priorities for companies in the BioRegion**



or service fees, which covers part of the cost of developing new products. However, this model can decrease the amount of specialized venture capital investment they attract, as assets needed for the technology area of the company lead to an overestimation of the company's value. As mentioned in Chapter 1, this mixed model is often found in areas where the sector is still immature.

Previsions and priorities

We also asked companies about their priorities for the future (figure 21). The answers are in line with what we have seen regarding their current key activities. The majority of the companies surveyed (68%) prioritize R&D, while a significant number (55%) say that commercialization is one of the main activities they want to grow.

34% of companies want to increase their international presence. The most commonly considered option is that of establishing alliances (25% of companies surveyed consider this a priority). These are, in most cases, small companies that have been created recently. On the other hand, most large companies have already established many strategic alliances, as we will see in the next section.

Priorities for companies in the BioRegion include driving R&D (68%), commercialization (55%) and to a lesser extent, internationalization (34%)

In short

The vast majority of Catalan companies in the sector work in drug discovery and development and commercialization activities. Only a small group of companies cover the whole value chain, from initial research through commercializing a final product. Parts of the value chain are subcontracted to external providers, normally non-critical research. Companies mostly use a mixed business model, which is less frequent in more consolidated bioclusters. Market penetration focuses on Spain and Europe, with little presence in the United States, which is the most important market in this sector. Driving R&D and product and service commercialization are current priorities for most companies. However, internationalization is growing in importance, with one third of the companies surveyed listing this as a future priority.

7.3 Research activities

This section of the report focuses on biomedical companies, those that are devoted to human health: pharmaceutical, biotechnology and, to a lesser extent, medical technology companies, which have little representation in the sample for reasons discussed earlier. Specifically, this section looks at which therapeutic areas are the focus of product research, development and commercialization. Likewise, it shows which phases of the R&D&i process companies focus on, and their results, measured in number of patent applications. Finally, we evaluate the innovative technology they employ and to what degree they collaborate with other companies or public R&D entities to carry out their project.

Therapeutic areas

Catalan companies focus mainly on oncology, the nervous system, dermatology, metabolism and cardiology, as shown in the graph below (figure 22). Given that this classification does not take into account whether the products are in development or on the market, we crossed information from both sections to create the following graph (figure 23), showing which therapeutic areas have products in R&D stages or on the market.
Analyzing information from the five main areas, we can see that the whole value chain is represented in oncology, the nervous system, cardiology and metabolism, with special emphasis on first-stage research.

Dermatology, which was selected by 31% of companies surveyed, shows an important mix of first-stage research and market stages. It is well known that in Catalonia there are many pharmaceutical companies (Ferrer Group, ISDIN, Almirall) and some biotechnology companies (Advancell, Palau Pharma) that have research programs —mainly still in the preclinical discovery and development phases— in dermatitis, psoriasis and other dermatological pathologies. Moreover, in the commercial area, many pharmaceutical companies have agreements to license these products or OTC (over-the-counter) product lines, which explains this dichotomy. Among the Asebio member companies (*Asebio Report* 2008), dermatology represents nearly 5% of preclinical and clinical development, partly due to the fact that some pharmaceutical companies that do research in this area are not represented in this report.

Figure 22. **Therapeutic areas in companies**

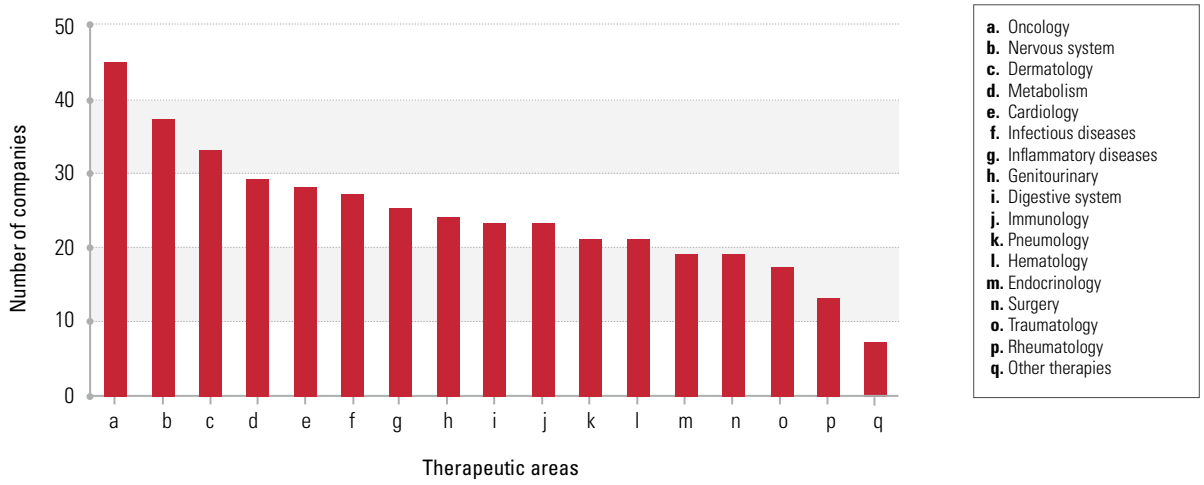
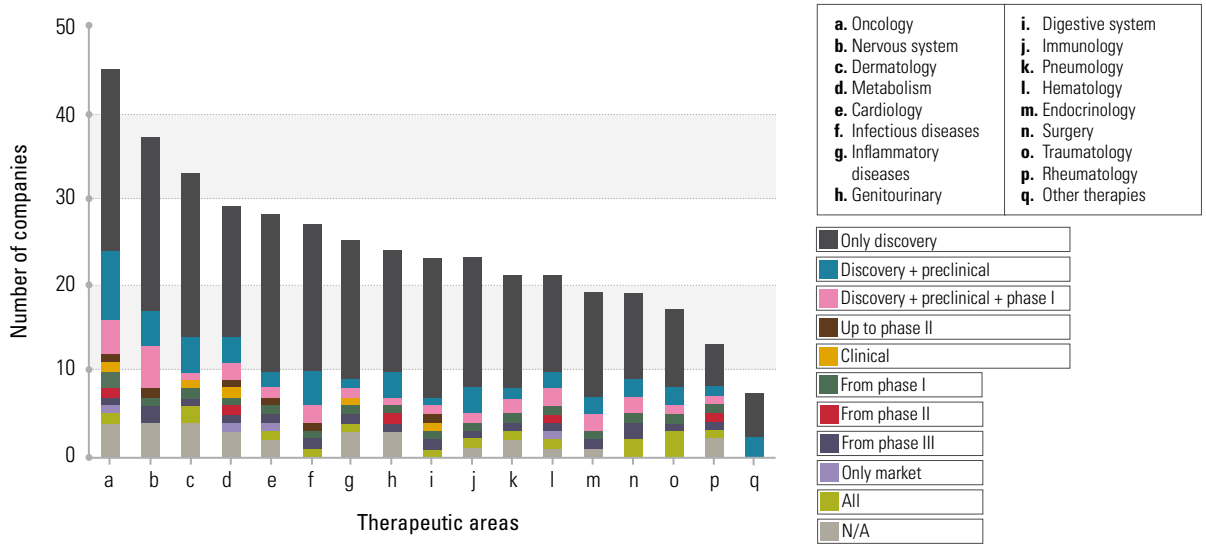


Figure 23. **Therapeutic areas in companies by R&D phase**



Dermatology is a growing market in industrialized nations. For example, psoriasis is considered the most common dermatological immune disease in adults (*Pathogenesis and therapy of psoriasis*, Nature 2007), leading to direct annual expenditure of 1,800 million de dollars, while atopic dermatitis leads to expenditure over 1,000 million dollars per year, plus the important economic losses experienced due to reduced productivity as a result of these pathologies, according to a number of reports from the American Academy of Dermatology.

Regarding the medical technology companies surveyed, which focus their activities on in vitro diagnostics and medical devices, the top therapeutic areas are: oncology, nervous system, dermatology and infectious diseases (figure 24).

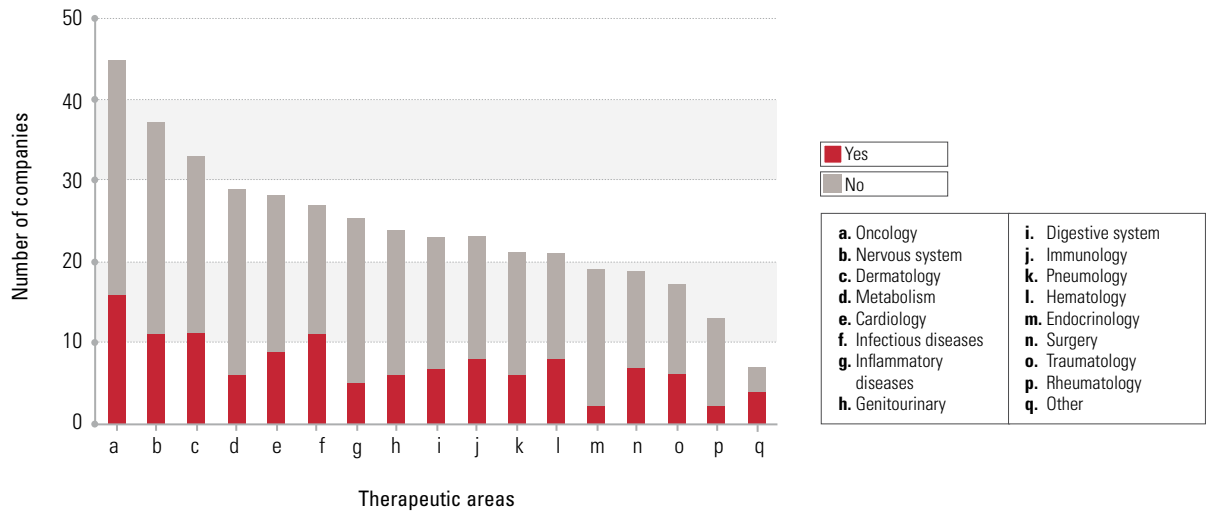
Catalonia invests more in pharmaceutical R&D than any other region in Spain: 381 million euros in 2008

The fact that oncology and the nervous system are priorities is in line with trends in the sector (the World Health Organization shows that cancer will become the number one cause of death in the coming years) and with the pharmaceutical industry's largest markets. For example, the *Beyond Borders* report (Ernst & Young, 2009) lists oncology (21%), the nervous system (15%), metabolism (11%), inflammatory diseases (11%), infectious diseases (9%), dermatology (7%) and the cardiovascular system (6%) as the areas with the highest concentration of phase III studies in Europe.

If we compare this with the therapeutic areas where research is carried out in Catalonia (*BEST Project*, Farmaindustria 2009), we see that the areas with the most activity are ranked as follows: oncology (25%), cardiovascular system (20%), infectious diseases (10%), nervous system (8%) and respiratory system (4%). However, metabolism and dermatology only make up 2.3% and 0.7% of research respectively.

For comparison, we can look at the priorities of the pharmaceutical and biotechnology industry in California (Silicon Valley and the Bay Area), which also focus on oncology and the nervous system (with 282 and 131 products in the development phase, respectively), followed by infectious diseases (115), inflammatory and immune diseases (92) and the cardiovascular system and hematology (88) (*California Biomedical Industry 2009 Report*, California Healthcare Institute and PricewaterhouseCoopers, 2009).

Figure 24. **Therapeutic areas of medical technology companies in the BioRegion**



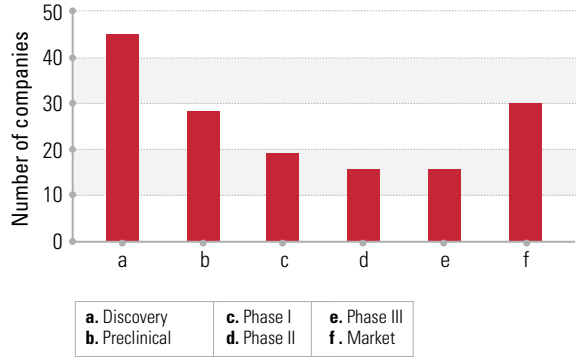
R&D phases

The Spanish pharmaceutical industry invested some 1,000 million euros in R&D in 2008, the majority of which went to clinical trials, 111 million to finished-product research, 87 to preclinical research and 162 million euros to basic research. Internal R&D expenditure was 614 million euros and subcontracted expenditure, 396 million euros. Catalonia has the highest percentage in Spain, with 47.6% of the internal expenditure and 22.5% of subcontracted research expenditure (*R&D in the Pharmaceutical Industry 2008*, Farmaindustria, 2009).

Only 56% of the Catalan companies surveyed work on drug discovery and development, which can be broken down as shown in the following graph (figure 25). However, among the companies that marked the option 'other', there are 10 companies that use a mixed business model and didn't mark any of the R&D phases. This suggests that they are very new companies, just starting up their platform and will develop products in the future.

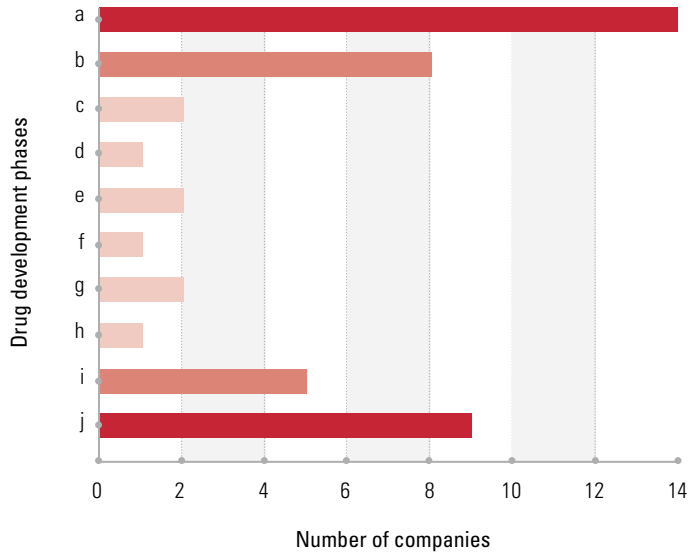
As mentioned in Chapter 1, only the pharmaceutical companies and some of the largest biotechnology companies can be considered FIPCO and cover all phases of research. Therefore, it is important to analyze the number of companies working in each of the phases of R&D (figure 26).

Figura 25. **Companies that develope drugs in each of the R&D phases**



We can see that the number of companies decreases as we move up the value chain from discovery to phase II (figure 26). In the Catalan industry, many companies only carry out discovery-level research. Very few companies do preclinical studies and even less have reached the clinical research phase: AB-Biotics, Advancell and Archivel farma in phase I, and Palau Pharma in phase II.

Figure 26. **Companies that carry out successive phases of drug development**



a. Only discovery
b. Discovery and preclinical
c. Discovery, preclinical and Phase I
d. Discovery through Phase II
e. Clinical*
f. From Phase I on
g. From Phase II on
h. From Phase III on
i. Only market
j. All

* Some of the phases (Phase I and/or Phase II and/or Phase III).

On the other hand, Catalan pharmaceutical companies cover the whole value chain, although they rarely do it with the same product but combine in- and out-licensing to nurture the chain, which they often develop through different therapeutic areas.

Finally, there is a group of companies that only work in specific phases. These are clinical CROs or large multinational pharmaceutical companies, which do most of their research in their country of origin and only carry out commercial and clinical activity in Catalonia.

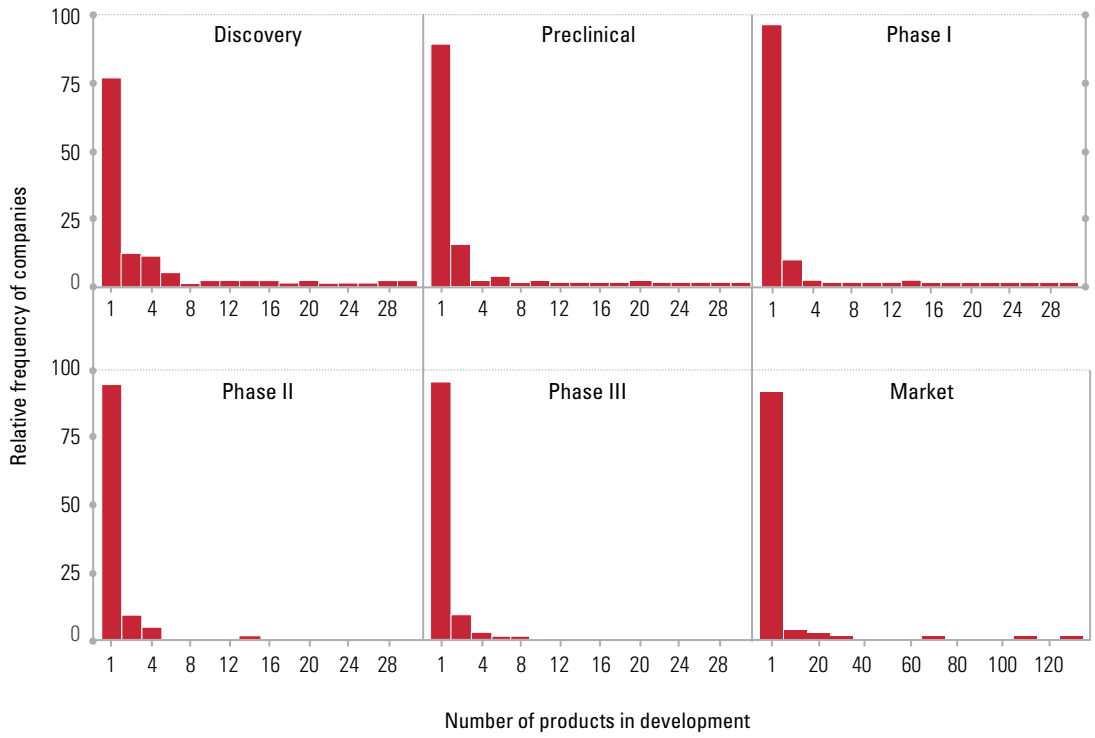
Number of products in development in each phase

This first *Biocat Report* doesn't give detailed information by company on the number of products in each phase of R&D, but treats this information globally. In the next table (figure 27) we can clearly see that most companies have a limited pipeline or portfolio of products: half only have 1 product, 25% have between 1 and 6, and the other 25% have between 6 and 30. This separation reflects the different stages of maturity we see in biomedical companies and emphasizes the sector's immaturity —which has already been shown in analysis of the R&D phases and business models—, as half of all companies have only one product or don't yet have any. Only pharmaceutical and in vitro diagnostics companies have more than 6 products in the development stage.

Technology or technology platforms used

The companies surveyed use a number of pioneering technologies, which are, in order of frequency, bioprocesses (15%), genomics (14%), nanotechnology and in silico technology (9%), biological sample analysis

Figure 27. **Products per company in each phase of drug development**



techniques and processes or PBS (6%) and, finally, crystallography (4%).

However, use of these techniques varies widely from one subsector to another, as we can see in figure 28.

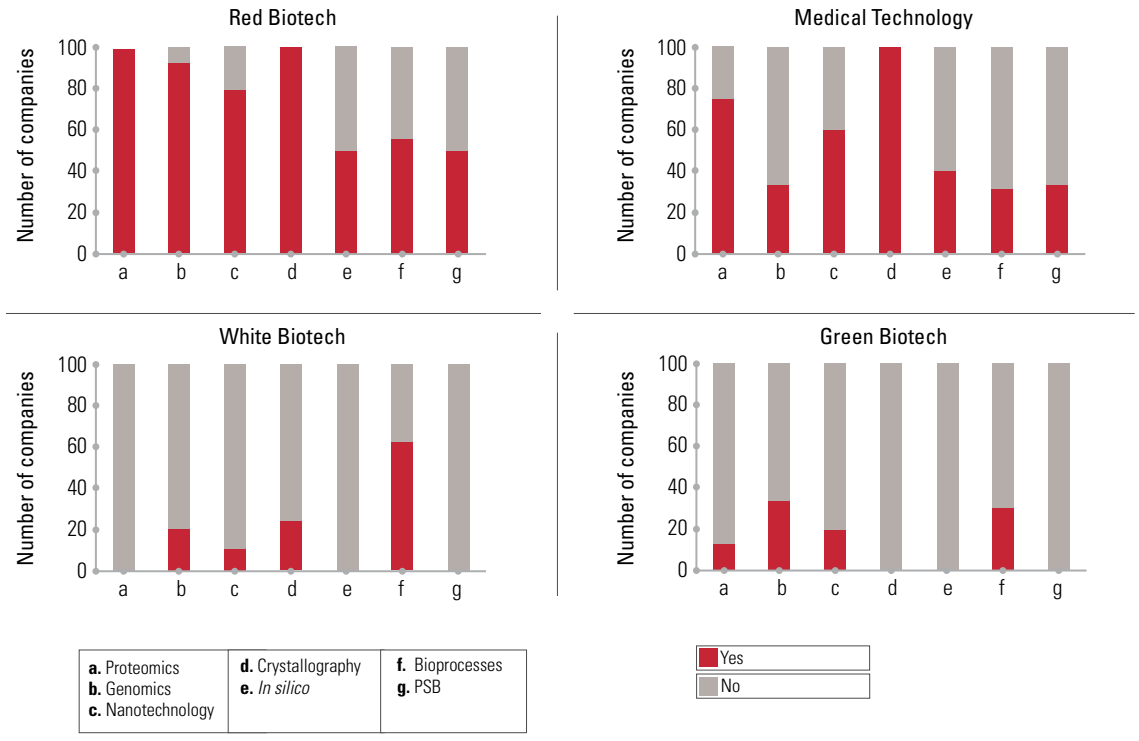
Some are specific to biomedicine (red biotech and medical technology), like proteomics, genomics and biological service platforms. Crystallography is used only in red biotech, as it is still almost exclusively used to analyze new chemical entities (NCEs). The other technology analyzed is more transversal: bioprocesses, originally from industrial biotech, can be used in all sectors, as can in silico technology and nanotechnology.

Patents and protection models

Regarding intellectual property protection, many of the companies surveyed were reticent to provide information (46% left this section blank). Those that did answer the questions in this section provided answers that varied widely, making the analysis presented in this section essentially qualitative.

Of the 54% of companies that answered (figure 29), 41% claim to use models other than patents to protect their intellectual property, like trademark registration, industrial secret or deposit before notary. Of the companies surveyed, 20% said they used patents. The average number

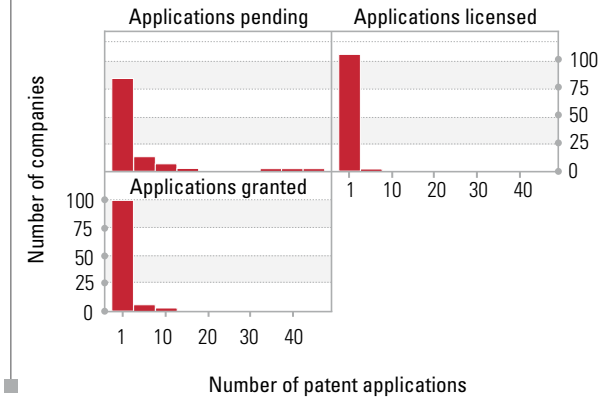
Figure 28. **Type of technology / technology platform used by companies in each subsector**



of patent applications per company is 5, but the large majority of companies that use patents to protect their intellectual property only have one or two, while a handful of companies —the oldest biotech companies and the pharmaceutical companies— have more than 10.

According to the *Asebio Report* 2008, 33 of the member biotech companies generated 117 biotech inventions, mainly in the human healthcare field. Of these inventions, 79% have applied for patents, up 40% from 2007. Of the Catalan companies included in the report, Grífols has the highest number of Spanish patent applications (11) and Palau Pharma has the most European patent applications (7). In the United States, Biokit (6), Palau Pharma (4), Grífols (3) and Oryzon Genomics (2) have applied for patents. 11% of companies surveyed say they license patents and 22% have acquired exploitation rights.

Figure 29. **Type and number of patents per company in the BioRegion**



In general, there is a trend towards subcontracting intellectual property protection to an external consultancy firm (56%), or university or hospital (6%), while only 38% of companies have a specific department devoted to intellectual property management. These, again, are mainly pharmaceutical companies and large medical technology companies.

Collaborations and consortia

In this point we will analyze two types of collaborations between companies, as well as participation in public/private consortia with universities, technology centers or research institutes. However, as seen in section 7.2, only 25% of companies state that this is one of their priorities for the future.

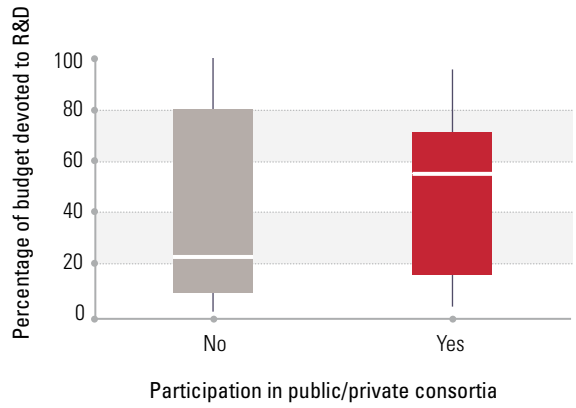
Regarding collaborations with other companies, 58% of companies surveyed say that they have at least one joint business project. On the other hand, 36% participate in public/private consortia with research centers or hospitals (27%), universities (27%), technology centers (19%) or other entities (5%).

Companies that participate in consortia devote 60% of their budget to R&D, compared to 20% in companies that don't participate

We can see a clear connection between R&D budget and participation in public/private consortia. The following graph (figure 30) clearly shows that the average percentage of the budget devoted to R&D for companies that participate in this type of consortia is nearly 60%, compared to 22% in companies that do not participate in any consortia. Furthermore, hardly any companies that participate in consortia devote less than 20% of their budget to R&D, as shown in the lower limit in this graph.

One of the driving forces behind consortia creation is the public administration's subsidy policies, including the Innovation Hub program (ACC1Ó), which 12% of companies surveyed have participated in; the CDTI (Ministry of Science and Innovation, MICINN) Cenit program (17%); and, on an international level, the successive framework programs (15% of Catalan companies participate in the 7th Framework Program).

Figure 30. **Relationship between R&D budget and participation in public/private consortia**



When we look at the type of partners in collaborations and consortia, nearly half of the companies analyzed (49%) work with Catalan partners; 25% with Spanish partners; and 19% with European partners. 6% collaborate with partners outside Europe, and the United States, despite its importance in research and market, is still one of the last countries that Catalan companies partner with, expect in isolated cases of pharmaceutical and diagnostics companies.

In short

Catalan companies in our sample focus mainly on oncology, the nervous system, dermatology, metabolism and cardiology. In these therapeutic areas, most of the companies work principally in the initial discovery phases. Few companies carry out clinical research, normally only those that carry out research in all phases, and this research focuses on oncology, the cardiovascular system, infectious diseases and the nervous system.

The pipeline generally has one or two the development phase and the number of companies with more than five is very low. Part of this research is carried out in collaboration with other companies and in public/private consortia, from which companies receive funding that has a positive impact on their research budget. Partners chosen for these collaborations are generally from neighboring areas (Catalonia, Spain, Europe), with very few partners from the United States.

7.4 Legal structure and capital

In this section we will analyze the structure of companies in the BioRegion. We aim to provide an overview of the different legal structures, sources of funding, turnover and profit margins, as well as information on the percentage of the companies' budget that is devoted to research. With the data collected we will try to estimate previsions for the sector's growth.

Legal structure

The majority of companies (59%) are private limited companies, while 36% are public limited companies, and 5% list other legal structures.

Most companies have a board of directors (76%), and half (51%) have a board of advisors.

Capital structure

Among companies analyzed, 85% have their own capital, meaning funds contributed by the founders or shareholders. Of these, 23% have no other type of capital. This happens mainly in two types of company: those that have been created very recently, which still only have the founders' capital, and some bioinformatics companies, which require less initial investment and, as a result, can maintain full legal and financial control.

External capital invested in this sector comes from both public and private funds; only 7% of companies surveyed have university shareholders.

According to the *RedOtri Report 2008* (RedOTRI Universidades, 2008), there are only isolated cases of university shareholders in companies in Spain, making up less than 0.09% of the network's funding. The same report highlights the fact that there is still much work to be done in technology transfer in order to foster the creation of and university participation in spin-offs. University/company collaboration, despite all the efforts and initiatives over the past years, is still far from what we see in large international universities. Harvard is a well-known example, with 32 start-ups created from technology developed at the university since 2006. The University of Cambridge is another example, participating in 68 companies and having received 1.7 million pounds sterling in return on their investments in five of these companies (*Cambridge Enterprise Annual Review, 1st August 2007 - 31st July 2008*, University of Cambridge, 2009).

In the chapter on private investment, the study looks at four basic types of funds: direct investment from other companies, that from private investors like business angels, venture capital and the stock market.

By percentage, the most important is direct investment from other companies (14%), which is in line with the large number of collaborations established between companies as analyzed in the previous chapter. This type of funding, which is known as corporate venture capital, allows for symbiotic strategies between consolidated companies and new biotech firms. These strategies often seek technical and not financial results, which is part of the biotech-pharma convergence mentioned in Chapter 1.

Internationally, we find some examples of this type of agreement, although they are based on slightly different models. Examples include GSK and Astra-Zeneca, which have alliances with different biotech firms that work on initial discovery phases (Cellzome and Biocompatibles, respectively). On the other hand, Englight Biosciences has signed so-called pre-competitive agreements (agreements to collaborate in the first stages of technology or platform creation) with Lilly, J&J, Merck&Co and Pfizer. Amgen holds options in different companies (Cytokinetics and Cephalon), which they allow to operate indepen-

dently, and Pfizer negotiates on early-stage intellectual property (*Beyond Borders*, Ernst & Young, 2009).

In Catalonia, some examples of pharmaceutical companies' growing interest in biotechnology include the Ferrer Group's participation in Oryzon Genomics and Gendiag; and the 8% share of the Swiss company Lonza owned by the Gallardo (owners of Almirall) family's holding company Plafin. Grífols has also joined this trend and currently holds a 1.5% stake in Belgian biotech company Cardio 3 Biosciences, which specializes in developing treatments for cardiovascular diseases and is also owned in part by the Mayo Clinic of Rochester (USA).

Regarding venture capital, 10% of companies said they have received first-round venture capital (between 1.5 and 4 million euros), while 5% declare second-round financing (4 to 10 million euros in round 2A). The fact that only 15% of companies in the sample have received venture capital shows the limited presence of professional capital from outside the company in this sector. This lack of venture capital investment is both the cause and result of the low number of venture capital funds working in Catalonia —which we have previously identified as one of the sector's greatest weaknesses and a clear indication of its immaturity. The causes behind this lack of venture capital invested in Catalan biotechnology companies are many and this report does not aim to give an exhaustive analysis of this topic. However, we must point out that biotechnology represents only 12% of venture capital investment in Spain (webcapitalriesgo, November 2009) and that the global recession has created an unfavorable environment, with a 20% decrease in venture capital investment in Europe in 2008 (*Beyond Borders*, Ernst & Young, 2009).

Despite the aforementioned limitations, some Catalan companies did receive financing from different venture capital funds and other private funds in 2008. According to the *Asebio Report 2008*, these companies include:

- **Oryzon Genomics.** Investors: Corsabe/Laboratorios Ordesa (9 million euros)
- **Era Biotech.** Investors: Highgrowth, BCN empren, Uninvest and private investors (4.60 million euros)
- **Archivel Farma.** Investors: Fonsinnocat and Archivel Technologies (1.7 million euros)
- **Palau Pharma.** Investors: Najeti Capital (1.7 million euros)
- **Neurotec Pharma.** Investors: private and administrative funds (CDTI and ACC1Ó) (1.1 million euros)
- **Aleria Biodevices.** Investors: Caixa Seed Capital and administrations (1 million euros)
- **AB-Biotics**. Investors: business angels (1 million euros)
- **Activery.** Investors: Sodena (0.75 million euros)
- Agrasys. Investors: Uninvest (0.36 million euros)
- **Neurosciences Technologies.** Investors: partners (0.13 million euros)
- **Advancell.** Investors: Talde (amount not available)

Other Catalan companies stated that they have received funds, mainly from the CDTI, but did not include the amount.

Only 9% of companies stated that they received private funding from business angels and 5% indicated that they received investment from other private funds. Recently, the Government of Catalonia has announced that it will stimulate private investment in new, entrepreneuring companies, including a number of incentives in the form of a new act regarding tax measures that will be included in the next budget. This way, up to 20% of this type investment made in 2010 will be able to be deducted from regional income taxes. Deductible investments can be made by buying shares of innovative companies that are traded on the alternative stock market (MAB), with a maximum of 10,000 euros. The other option is direct investment in new companies, defined as those founded no more than three years ago.

Only 6% of companies in our sample are traded on the stock market, which is mostly due to multinational pharmaceutical companies since Almirall and Group Grífols are the only publicly traded Catalan companies.

Because of their small size, most biotech companies find it difficult to generate funding through public trading of stock. The MAB, created specifically to give market access to companies with limited capital (designated type A meaning that they have between 9 and 50 employees and turnover of more than 10 million euros) has been a driving agent in other areas (AIM in Londres; Alternext in Paris). However, the study published by CataloniaBio in 2007 and co-funded by Biocat and the Department of Economy and Finance, *The Stock Market and its alternative markets as dynamizing agents for the biotechnology sector*, indicates a number of limitations on companies using the MAB as

a source of funding. This report also proposes measures to overcome these difficulties, including fiscal deductions on MAB investments.

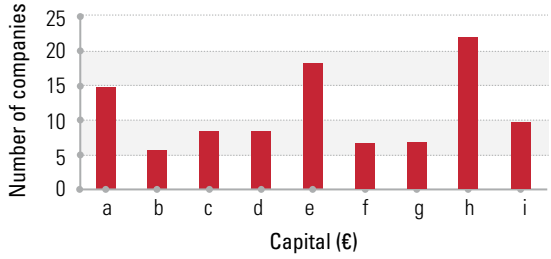
Regardless of the origin of the companies' capital, we see that most of them fit into three groups (figure 31).

- Less than 10,000 euros (15%), we can imagine that this group is made up of the youngest companies with founder capital.
- From 200,000 to 500,000 euros, including companies that have received seed capital.
- More than 2 million euros, which are the large, consolidated companies in the BioRegion or the few that have received venture capital.

By not creating divisions above 2 million euros in the survey, and given that 5% of companies stated that they have received second round venture capital, nearly all the companies that declared their budget was above this amount are large businesses.

If we look at the structure of business capital by year of foundation, we find that between 40% (2000) and 50% (2001) of companies created before 2002 have more than two million euros, although there are also some companies in this category that were created in 2006 (25%) and 2007 (10%).

Figure 31. **Capital of companies in the BioRegion**



a. < 10.000	**f.** 500.000-1.000.000
b. 10.000-50.000	**g.** 1.000.000-2.000.000
c. 50.000-100.000	**h.** > 2.000.000
d. 100.000-200.000	**i.** N/A
e. 200.000-500.000	

One of the facts that most stands out in the analysis of capital by year of foundation is that 30% of the youngest companies, founded in 2007 or 2008, have less than 10,000 euros in capital, from which we can deduce that either they were just created or, despite having been created two years ago, are not really active yet. Another 25% of these young companies have between 200,000 and 500,000 euros in capital, which is mainly from seed capital. If we compare this to more mature European markets or, especially, to the North-American market, we see that the capitalization cycle of our companies is very slow. In two years international companies normally have much more developed financing schemes and funds.

Related to this, 17% of companies said they have received seed capital, 18% received capital investment from the Catalan government, and 22% from grants like the Center for the Development of Industrial Technology's Neotec program (CDTI, MICINN).

Turnover

When analyzing this variable, we see that the largest group of companies (25%) has a yearly turnover of less than 200,000 euros (figure 32). Companies in this group are those that have been created recently, regardless of their business model, and companies with a product-based business model.

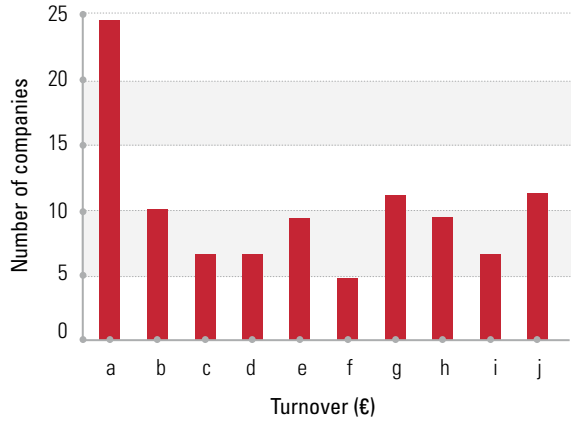
In the group with between 200,000 and 500,000 euros in turnover, we find 10% of all companies surveyed, with a high concentration of companies created after 2000, which mainly used a mixed business model. Another 10% of companies have more than 10 million euros in turnover, most of which were created in the 1980s or before. We must mention here that 11% of the companies that completed the survey did not include any information about their turnover.

35% of companies in the BioRegion have an annual turnover of less than 500,000€ and 30% see no profit

Profit

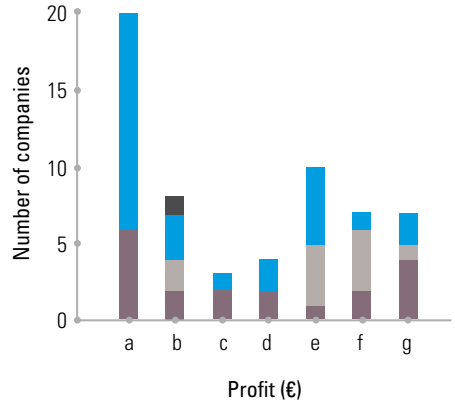
30% of companies in the sector, the majority of them in the red biotech subsector, see no profit and were created

Figure 32. **Turnover of companies in the BioRegion**



a. 0-200.000 **b.** 200.000-500.000 **c.** 500.000-1.000.000 **d.** 1.000.000-2.000.000	**e.** 2.000.000-5.000.000 **f.** 5.000.000-10.000.000 **g.** > 10.000.000	**h.** > 50.000.000 **i.** > 100.000.000 **j.** N/A

Figure 33. **Business models and profit of red biotech companies in the BioRegion**



a. <0 **b.** <25.000 **c.** 25.000-100.000	**d.** 100.000-1.000.000 **e.** 1.000.000-3.000.000 **f.** 3.000.000-10.000.000	**g.** >10.000.000

Product-based companies
Technology-based companies
Mixed model companies
N/A

in the past 10 years, which is in line with the most common business model in the sector.

When we look at data on red biotech companies' profit alongside information on their business model (figure 33), we see that a large percentage of companies that use a mixed business model, those that have platforms to sell services, see no profit, which indicates that most companies in the sample are very young and, although active, they are not yet making money.

35% of companies in the BioRegion have an annual turnover of less than 500,000€ and 30% see no profit

In the categories that go from 25,000 to one million euros we find mostly technology-based companies —which have a shorter time-to-market than product-based companies— and an important number of companies with a mixed model. Product-based companies (mainly pharmaceutical and some in vitro diagnostics companies) make up an important part of the categories from 3 million euros up, despite being few in number.

R&D Budget

84% of companies surveyed say that they earmark part of their budget for research and development, which is in line with the needs of a sector that is based on the results of research carried out. This variable is always discussed as the percentage of the company's total budget that is devoted to R&D.

Figure 34. **Percentage of companies' total budget devoted to R&D**

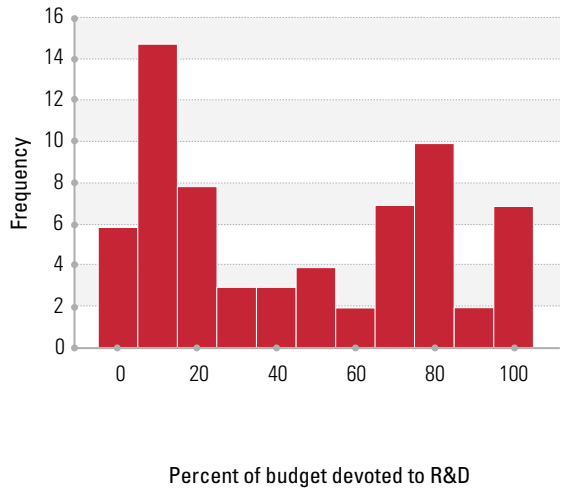
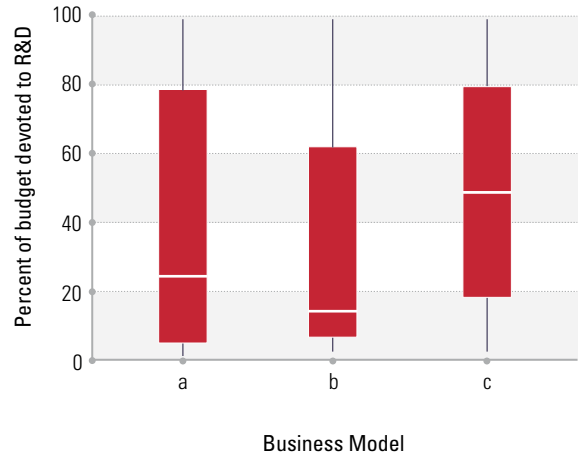


Figure 35. **Business model and percent of budget devoted to R&D**



a. Product-based companies
b. Technology-based companies
c. Mixed model companies
d. N/A

The analysis shows a model with peaks at both extremes (figure 34). On one hand, there are companies that devote up to 80-100% of their total budget to R&D, which is very common in small companies that are just beginning their project, have little structure and hardly any non-research related expenses. At the other end, there are companies that invest around 10% of their total budget in R&D, a scheme that is used mostly by large companies that focus on commercialization and have marketing departments, sales networks and business development areas that receive significant amounts of the budget. In this context, the impact of the R&D budget is diluted, even though the investment in absolute figures is larger. We see that, according to data from their respective web pages and the media, Almirall invests 15.4% of their turnover in R&D, while Esteve invests between 10% and 12% of their turnover in drug research and Ferrer Group invested 14% of their turnover in R&D in 2008.

In section 8.7 we will look more closely at R&D budgets in conjunction with factors like the type of organization and when it was founded.

The study of R&D investment in this chapter finishes with a look at its relationship to the companies' business model. The following graph (figure 35) shows that companies with a mixed model can devote most of their budget to R&D (on average 50% of their budget), which goes to developing the technology platform as well as future products, depending on the company's level of maturity. At the other end, technology-based companies invest less in R&D (15% average). Finally, product-based companies invest an average of 25% of their budget in R&D, though this group showed the widest range of data, from 10% to 80%, depending on the company's maturity. This data is in line with the requirements of each business model, which have very different times-to-market, R&D investment needs and economic returns.

Previsions for growth

We asked companies to estimate the growth in their turnover and whether they foresee an increase in capital or plan to put into action new growth strategies.

Most companies (70%) hope to increase turnover, while 20% do not foresee any growth in turnover and 10% did not feel comfortable making any type of prediction. Once again, it is surprising to see that expectations for increase in turnover do not vary much between the different business models, although we would expect young companies using a mixed business model to have more positive previsions than companies with other business models.

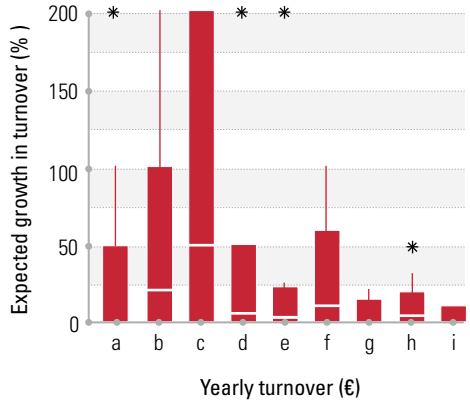
When we look at turnover in conjunction with expectations for growth (figure 36), we see that 100% of companies with between 5 and 10 million euros in turnover expect to increase this turnover (by an average of 10%, although some companies expect their turnover to increase by up to 58%). In contrast, only 60% of companies with two million euros in turnover and 50% of companies that have more than 10 million euros in turnover expect theiincome to increase. The latter only expect turnover to increase by 6% on average. Given that in absolute numbers the sample of companies is quite small, the results must be taken with caution.

Most companies, however, are found in the lowest categories (below 200,000 euros), where 70% of companies expect to increase turnover, but with a very wide range of expectations as to the level of increase. The most positive outlooks are found in the category with turnover of 500,000–1,000,000 euros, where some companies expect growth of up to 150%.

Regarding capital growth expectations, 62% of companies surveyed do not expect any increase and 9% provided no information. 28% of companies do expect an increase in capital, divided equally between venture capital, public investment, private investment and additional investment from current shareholders. None of the companies surveyed mentioned the possibility of trading shares on the stock market.

Finally, 26% of companies opt for other growth strategies, like mergers with other companies (7%), acquisition (11%) and even creating a new company (10%), which is an option considered most by the older companies that were created before 2000.

Figure 36. **Expected growth in turnover**



a. 0 - 200.000	**f.** 5.000.000 - 10.000.000
b. 200.000 - 500.000	**g.** > 10.000.000
c. 500.000 - 1.000.000	**h.** > 50.000.000
d. 1.000.000 - 2.000.000	**i.** > 100.000.000
e. 2.000.000 - 5.000.000	

In short

Companies in the BioRegion that participated in the survey are mainly public limited companies with external capital that mainly comes from other companies and very little venture capital investment. In any case, more than half say they do not foresee any increase in capital next year, none plan to publicly trade stock and few foresee mergers or acquisitions in the future. One fourth of all companies —mainly those that develop products— have an annual turnover of less than 200,000 euros, and nearly one third —almost entirely from the red biotech subsector— do not see any profit. Regarding previsions for the future, the majority of companies expect to increase turnover but only one fourth will opt for other growth strategies.

7.5 Human capital

This section will evaluate the number of workers and their qualifications in connection with R&D activity, as well as the companies' executive structure and the evolution of the founder inside the company's structure. We will also analyze whether the companies have internal training plans or career plans for their team.

Number of employees

The number of employees was not stated in absolute numbers, but in categories, which conditions the different comparative calculations, which in some graphs is expressed in ratios instead of percentage. Nearly 100% of companies answered this part of the survey.

Small companies, with less than 50 employees, represent more than 70% of the sample (figure 37). There were only 6 medium-sized companies, with 50 to 100 employees, in the total. There is a spike of 26 companies with more than 100 employees, 75% of which were created at least 30 years ago. 60% can be classified as micro-companies, with less than 10 workers. Half of the companies in this group have five people on salary and were mostly founded after 2000, which shows again the sector's youth and immaturity.

In order to evaluate the number of R&D workers as a percentage of the total, we established a base 1 ratio that allows us to establish weight of this type of employee in each category (figure 38).

This shows that companies with less than 5 employees have a ratio of 0.95 to 1 in research-dedicated personnel. This indicates that nearly all their employees carry out R&D tasks. At the other extreme, most companies with more than 100 employees have a 0.5 to 1 ratio of R&D workers. The widest variation is found in companies with 20 to 100 employees, which have ratios of between 0.5 and 0.95.

Education

As is to be expected, these companies, which are knowledge-based, employ a high percentage of university graduates (88%), and MAs, MSs and MBAs (55%) (figure 39). The number of PhDs is also noteworthy (83%), which is

Figure 37. **Number of employees per company**

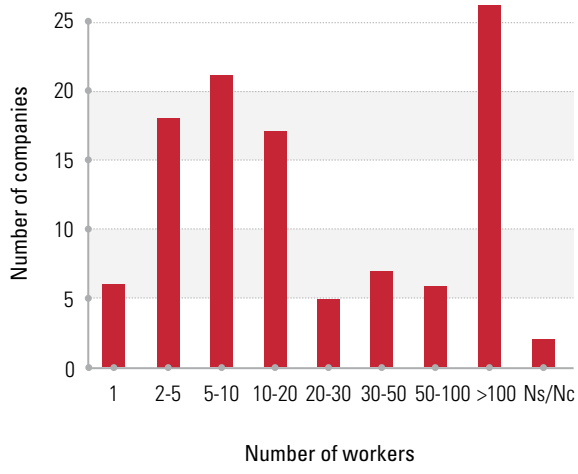


Figure 38. **Proportion of R&D workers to total number of employees**

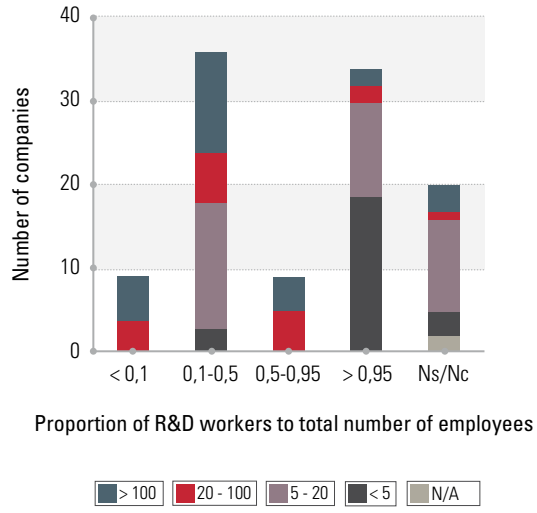
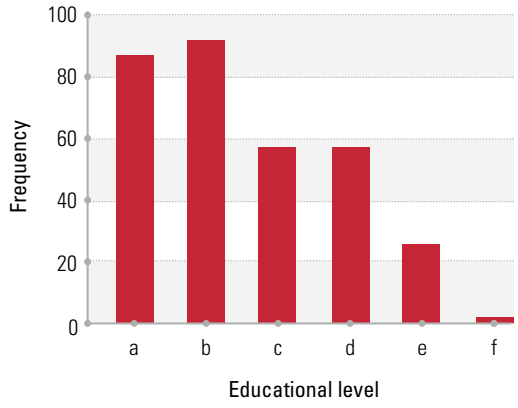


Figure 39. **Educational level of employees**



a. PhDs **b.** BA or BS **c.** MA, MS or MBA	**d.** Diploma/Advanced vocational training **e.** Interns **f.** Secondary school

difficult to find in companies that are not intensely devoted to research.

Of all the companies that carry out R&D activities, 48% have requested subsidies from the Torres Quevedo Program (MICINN) to hire PhDs and technologists, 16% have applied for Beatriu de Pinós grants (AGAUR) and only 0.01% of the companies have students from the Marie Curie grant program (EU), probably due to the fact that the Catalan business sector is relatively unknown to European students.

Regarding internal training programs, approximately half of all companies (50%) say that they have a plan, mainly focusing on red biotech topics, while 20% have no plan and 30% gave no information.

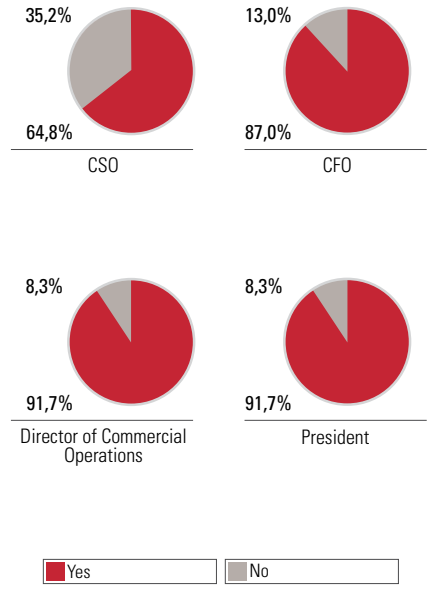
44% of companies have career plans, generally multinational companies and some small companies, while 23% have no plan and 33% didn't respond.

Company management

87% of companies surveyed have a CEO, 38% of which come from the life science sector and 38% are specialized in business management and administration. 30% of these executives have multiple degrees, 26% in engineering or chemistry and the rest from other degrees.

85% of companies surveyed have a CSO (Chief Science Officer) and 54% have a president, which in some cases is also the CEO. 65% of companies have a CFO (Chief Financial Officer), and those that don't were created after 1998 and generally have less than 20 employees. Only 56% have a Director Commercial Operations, despite the fact that commercialization is the second most common activity of companies; in companies created after 2000, only 40% have a Director Commercial Operations, depending on the level of business development, as in large companies these functions are normally carried out by different people.

Figure 40. **Position occupied by the company founder**



And the founder?

The founder of the company normally plays an important role in management. In 62% of the companies the founder is the CEO. This was the case in 46 of the companies in the sample, all founded after 2000, and in 7 companies founded more than 30 years ago. Only in a small number of cases has the founder left management to occupy another position, generally scientific or technical management (35%), as shown in the following graph (figure 40). 6.5% stay on as a member of the board of directors.

In short

Companies in the BioRegion are mainly micro-companies and small companies, with all or nearly all their employees carrying out R&D activity. This concentration of personnel in R&D is inversely proportional to the age of the company. As companies in this sector are knowledge-intensive, their personnel are highly qualified, with a high percentage holding PhDs or university degrees. Company founders mainly occupy the position of CEO and in few cases hold other positions, normally in scientific or technical management.

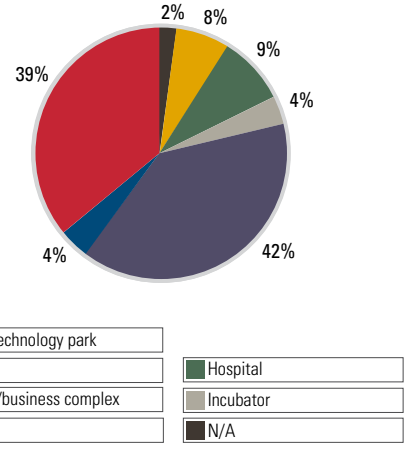
7.6 Development area

Of the companies surveyed, 42% carry out their activity in a science/technology park and 39% are located in an industrial complex (figure 41). There is a connection between the environment where the company was created and that in which they develop their activity: 59% of companies of industrial origin stay in an industrial complex, while 90% of companies that came out of research environments stay in a science/technology park or an incubator, which can be explained by the difference in culture and mentality of the personnel, on one hand, and the need for research-intensive services on the other.

Most companies (59%) rent their premises, while 37% own their laboratories or production plants. The majority of companies that own their premises are large companies, 59% have more than 100 employees and 41% come from a pharmaceutical company. However, 71% also use external facilities, of which 52% are science and technology services and 17%, large infrastructures.
Regarding space, 31% of companies have less than 100 m^2, mainly in bioincubators (17 companies with less than 5 employees and 5 with less than 20, all founded in the past decade). Another 31%, made up of different types of companies, generally with 20 but some with 100 employees and mostly created in the past decade, have up to 500 m^2. Companies in the third group (31%) have more than 1,000 m^2 (companies with 20 to 100 employees) and a small group of companies with more than 100 employees have more than 10,000 m^2 and were created in the 1980s or earlier.

36% of companies could not estimate their space needs in the next two years, 16% expect to need 200 m^2 and another 16% predict that they will need between 1,000 and 5,000 m^2.

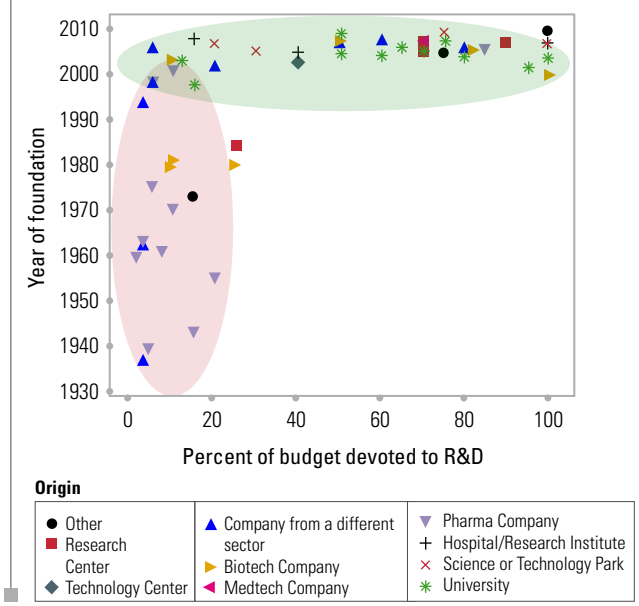
Figure 41. **Environment where companies carry out their activity**



In short

There is a clear trend among companies to stay in an environment related to their origins: an industrial complex if they were created out of another company, and a science/technology park or incubator if they are from the academic sector The space occupied by the majority of newly formed companies is rented, and there are three large groups of companies when we look at the amount of space they occupy (less than 100 m^2; up to 1,000 m^2 and more than 1,000 m^2), which depends on the number of workers. Most companies also use external science or technology facilities.

Figure 42. **Relationship between year of foundation, origin and R&D budget**



7.7 Trends observed

In the last section analyzing companies in the BioRegion we aim to show how different variables we have looked at previously on an individual basis relate to each other in order to provide an overview of companies in the biotechnology, biomedicine and medical technology sector. This type of analysis or sector map will be extended in future editions of the Biocat Report. The aim is to generate indicators that allow us to differentiate the types of company that make up the BioRegion and the characteristics of each one.

In the first graph, we relate year of foundation with origin (where they company came from) and the R&D budget (figure 42). This graph shows that through the end of the 1980s, the sector was made up almost exclusively of pharmaceutical companies, and that most companies in this sector were created after 2000. The graph also shows that, as we have mentioned previously, pharmaceutical companies (mainly concentrated in the red oval) devote less than 20% of their budget to R&D. This percentage is substantially lower (although often in absolute numbers) than what companies that came out of science parks and universities devote to R&D, mainly biotechnology or medical technology companies (mainly concentrated in the green oval), which are younger and more research-intensive.

We have also established the relationship between the year of foundation and the phases of R&D carried out in the company (figure 43). In this graph we can see that companies that only carry out discovery activities or discovery and preclinical research are concentrated at the top of the graph: they are young companies with more than 60% of their budget devoted to R&D, which clearly corresponds with the definition of biotechnology companies suggested by Bioworld International and discussed in Chapter 1 (small, dynamic and research-intensive companies). Once again the FIPCO are the oldest companies and those that proportionally –but not in absolute numbers–, invest less in research.

Finally, if we look at the relationship between the percentage of the total budget devoted to R&D, the proportion of PhDs in the company and their turnover (figure 44), we see a group of companies with large turnover (more than 10 million euros and, in some cases more than 100 million)

that correspond with low percentages of total budget invested in research and a lower proportion of PhDs. On the other hand, we can see a group of companies with low turnover (from 0 to 200,000 euros) that have a wide range of percentages of budget devoted to research (generally more than 50% of the total budget) and a high number of PhDs on staff. Once again, the differences between biotechnology companies and pharmaceutical companies in scientific strategy and culture can be clearly seen in the industrial sector in the BioRegion of Catalonia.

Figure 43. **Relationship between year of foundation, budget and phases of R&D in drug development companies**

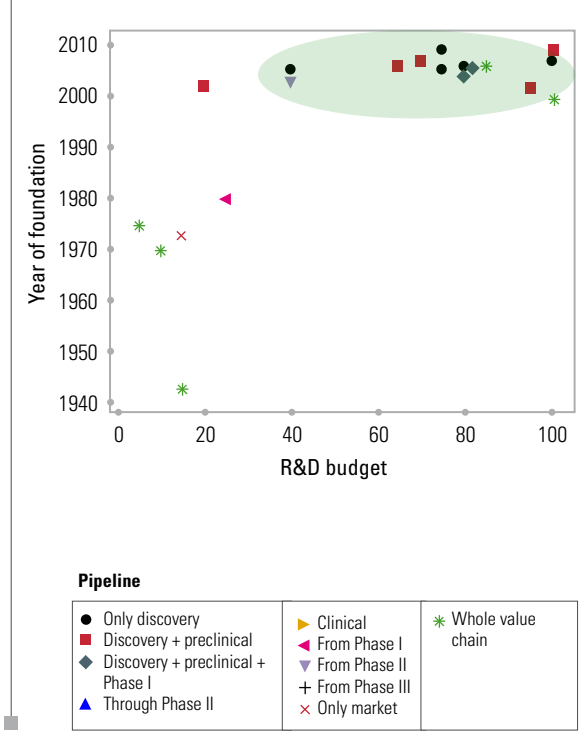
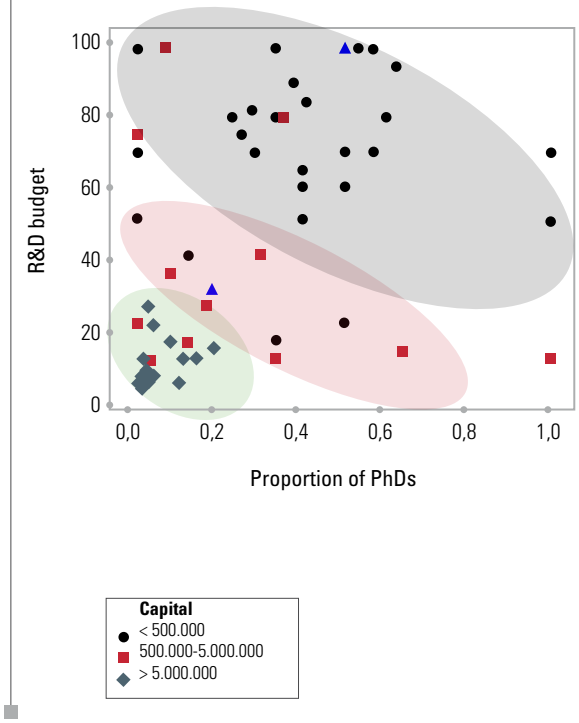


Figure 44. **Relationship between PhDs, R&D budget and capital**



In short

This analysis of companies provides a snapshot of the biotechnology sector in Catalonia: a group of young, research-intensive companies with little capital and provisions for growth, that contrasts with more consolidated pharmaceutical companies both scientifically and culturally. Most companies come from a business or academic environment, though some come from hospitals, and stay in the same environment in which they were created. Furthermore, these still immature companies normally have the founder in the position of CEO, receive public start-up capital or subsidies but little venture capital, and use a mixed business model, combining product with technology platform. A large proportion of companies focus on biomedicine, and a lower proportion on industrial biotech (white) or green biotech. In biomedicine, the main therapeutic areas are oncology, the nervous system, dermatology, metabolic diseases and the cardiovascular system. This varies a little depending on the phase of R&D or the market analyzed, but is in line with international priorities overall.

8. Analysis of research centers

The public research system in the fields of biotechnology, biomedicine and medical technology in Catalonia is complex and wide reaching. It is made up of an important number of centers, hospitals, universities and research groups that are often interrelated. A global analysis of this system requires exhaustive and rigorous study. In this first report, as we mentioned in chapter 5, Biocat has evaluated the research centers and some data on research groups. Therefore, when looking at the conclusions reached in this chapter on the areas of research and sectors of activity, we must keep in mind that research centers are only one part of the public research system in Catalonia.

The data used to carry out the analysis presented in this chapter comes from different sources. Firstly, the information received through surveys sent to the heads of the group of centers in the BioRegion. And, secondly, information from the *Biocat Directory* and data provided by the Catalan Administration. The origin of all data provided is noted.

Under the heading of research centers, we have grouped mainly public bodies that are part of the Catalan System of Science and Technology: CERCA research centers, CSIC research centers and hospital research institutes, which according to data from the Commission for Universities and Research (February 2009) includes:

- 38 research centers from the CERCA program, with the Catalan Government as a stakeholder, 20 of which carry out their activities in the fields addressed in the *Biocat Report*. Of these, 19 filled out the survey.
- 11 hospital research institutes (HRI) with the Catalan Government as a stakeholder, 6 of which filled out the survey.
- 24 CSIC research centers, 11 of which carry out activities in the fields discussed. Of these, 9 filled out the survey.

As a complement to this information, we have also included data from the Technology Centers that participate in the ACC1Ó's newly created TECNIO network. These centers, created out of business demand to provide technological support and facilitate technology transfer from universities to business, play an important role in the system as innovation agents by developing research projects. Again, we invited those that carry out activities in the fields discussed in this report to participate. Specifically, 6 technology centers chose to participate, 4 of which are considered advanced technology centers.

We have included the first aggregate data on research groups provided by the Agency for Management of University and Research Grants (AGAUR) as well as data on the academic population from the Commission for Universities and Research, in order to give an overall view of the research being carried out in the fields of biotechnology, biomedicine and medical technology. This first report doesn't include centers that are run by bodies other than those mentioned previously, like those run by various universities. Likewise, universities and hospitals are not included in the sample surveyed, except for the aforementioned HRI.

In order to compare the data on research centers with that on companies in the previous chapter, we have again divided them into subsectors using the colors of biotech —red, green and white biotech, and medical technology— (see table 5), taking into account the area of knowledge and research developed. This standardization will allow us to do a stronger comparative analysis of the most common research areas in future editions of the *Biocat Report*.

Participation in the survey was 83%; 40 of the 48 centers invited to participate filled out the survey (see list of participating centers in the section with the bibliography and tables).

8.1. Overview

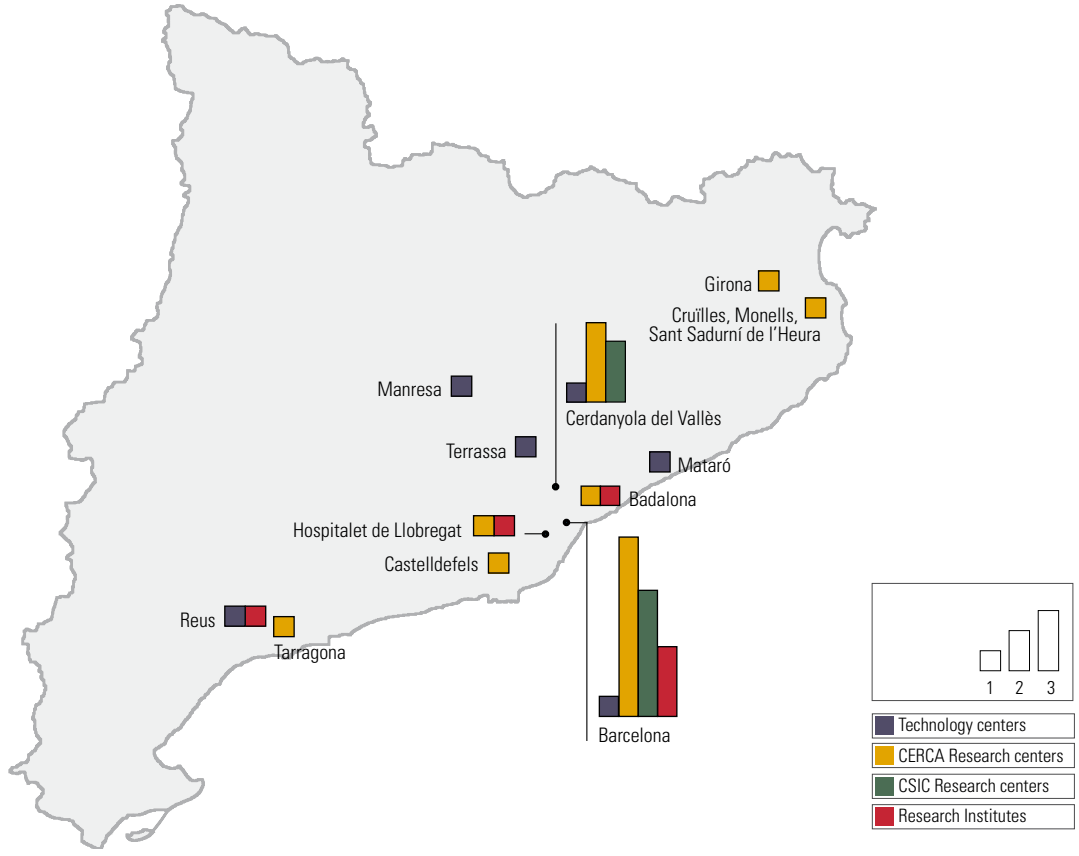
In this section we will analyze the specific importance of each type of research center included in the study, the subsectors in which they carry out their activities, their geographic distribution and age.

Once again, we must take into account than many centers carry out activities in more than one sector, which led to multiple answers in many of the variables analyzed.

By analyzing the specific importance of the research centers included in this report, we see that 47.5% are CERCA centers, 22.5% are CSIC research centers, 15% are HRI, and the other 15% are technology centers (figure 45)

The relevance of these research centers as key members of international biomedical clusters is clear. Therefore, keeping in mind issues discussed in chapter 3, in Cambridge (United Kingdom) there are 30 research centers; in Germany, there are 20 in Berlin's BioTOP and in the Munich Biotech Region there are three Max Planck institutes and one research center dedicated to the environment and healthcare; in France there are 20 research centers at the GIP Genopole.

Figure 45: **Geographic distribution by type of center**



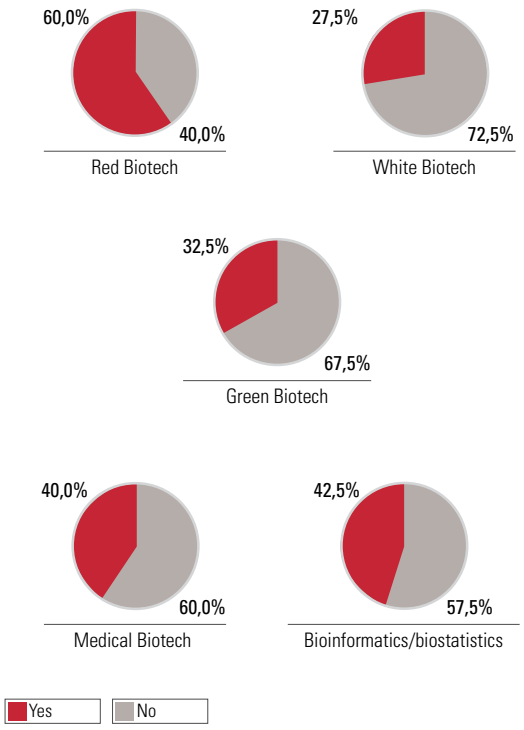
Subsectors of activity

Research centers in the sample analyzed mainly carry out biomedical research —which will later be applied mainly to red biotech (60%) and medical technology (40%)—, although an important part of the research can be applied to white biotech and one third of the centers carry out research that can be associated with green biotech (figure 46).

83% of the technology centers and an important part of the research centers carry out research that can be applied to white biotech, with important activity in the fields of nanotechnology, new materials and the chemical sector. Regarding green biotech, apart from the group of research centers that work in the agrifood and environmental fields, an additional 66% of technology centers carry out research in this area, including two HRI that work in the environmental field and participate in studies on occupational epidemiology, environmental health, respiratory health, contamination and environmental toxicology, among others.

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

Figure 46. **Subsectors of activity in research centers**



Regarding geographic distribution (figure 47, on the next page), we find representatives from all the subsectors in the Barcelona metropolitan area, as we do in the Vallès Occidental. In the Maresme area we find biomedicine and activities linked to industrial biotechnology, and in Manresa (Bages) we find medical technology and industrial biotechnology. In the Tarragona area there is a strong presence of green and industrial biotech, with research applicable to red biotech located in Reus, while the centers in Girona tend to focus on medical technology, according to the sample we analyzed.

Year research centers were created

Research centers in Catalonia were created in two different periods. The oldest centers, from the mid-1980s and 1990s, are mainly CSIC centers, with a few CERCA and most of the HRIs (figure 48). The second group, with one

Figure 48. **Year of establishment for research centers**

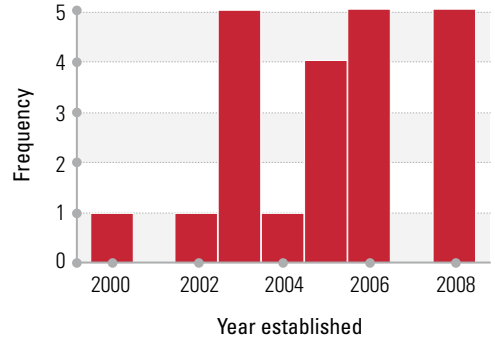
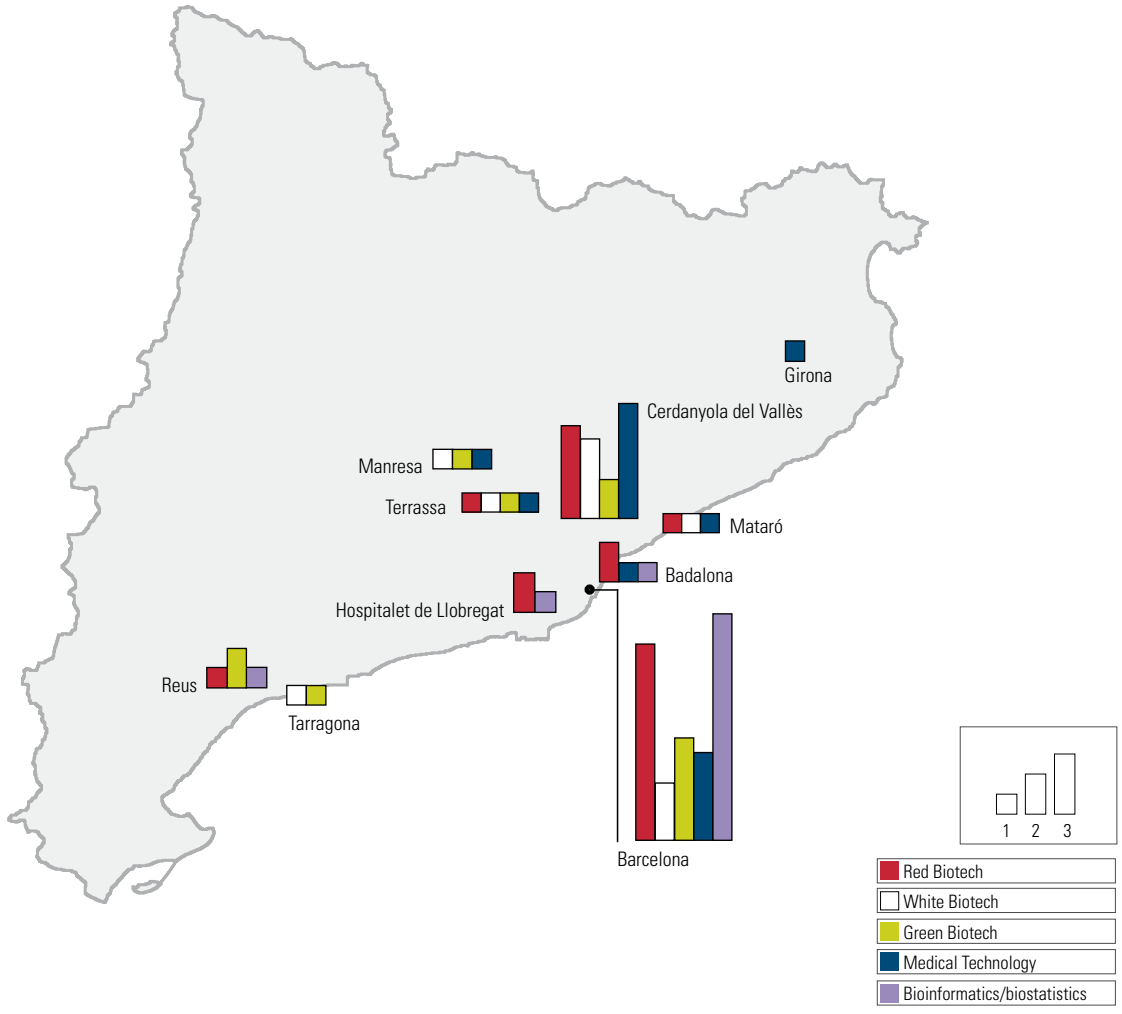


Figure 47. **Geographic distribution of centers in the BioRegion by subsector**



spike in 2003 and another in 2005, includes the technology centers and CERCA centers, respectively. The rest of the HRIs also belong to this second group, created thanks to the research policies driven by the Catalan Administration as part of the third Catalonia Research Plan (2001-2004), which aimed to consolidate the research system, focusing on driving centers and large-scale facilities, as well as supporting large research projects.

In short

This first report has evaluated CSIC and CERCA centers as well as HRIs and technology centers that carry out research in the BioRegion of Catalonia. The CSIC centers were established in the 1980s while

the rest of the research centers are from the decade starting in 2000 and are mainly located in the Barcelona metropolitan area. Regarding the subsector of activity, most centers carry out biomedical research, although a significant percentage of research can be associated with applications in white and green biotech and nearly half the centers surveyed see bioinformatics and/or biostatistics as a transversal tool and research subject.

8.2. Areas of activity

This section will describe the type of activity or sector of knowledge the research centers participate in. Given that, in addition to research, the centers carry out other activities related to the technical knowledge they develop, we will also evaluate the other functions they perform.

Main activities

Taking into account that research is the main activity of these centers, we have analyzed the main areas this research can be applied to (figure 49). Research that can be applied to red biotech and medical technology makes up the majority of that carried out and focuses on product discovery, diagnostics (in vitro, image) and medical devices, which corresponds to the results of our analysis of companies (section 7.2). However, the logical difference with respect to companies is that a lower percentage of centers are devoted to drug manufacturing (3% centers vs. 15% companies), as in centers this activity is normally related to developing new processes and analytical technology and not manufacturing active ingredients.

Bioinformatics is also an area with higher representation among companies than centers (33% vs. 13% respectively) and biostatistics, which was just a small minority in companies and therefore not discussed, has more importance among centers (23%), associated with new data-mining technology and in silico predictions linked to the omic sciences.

With regard to research associated with white biotech, the percentages for bioprocesses and fine chemicals are around 6%-8%, equivalent to what we saw in companies. However, there are many more centers working on biomaterials (20% centers vs. 4% companies). Bioremediation (8% centers vs. 3% companies) is another emerging area, as indicated in the article by Dr. Castells in Chapter 3 of this report.

Figure 49. **Areas of application for centers' research**

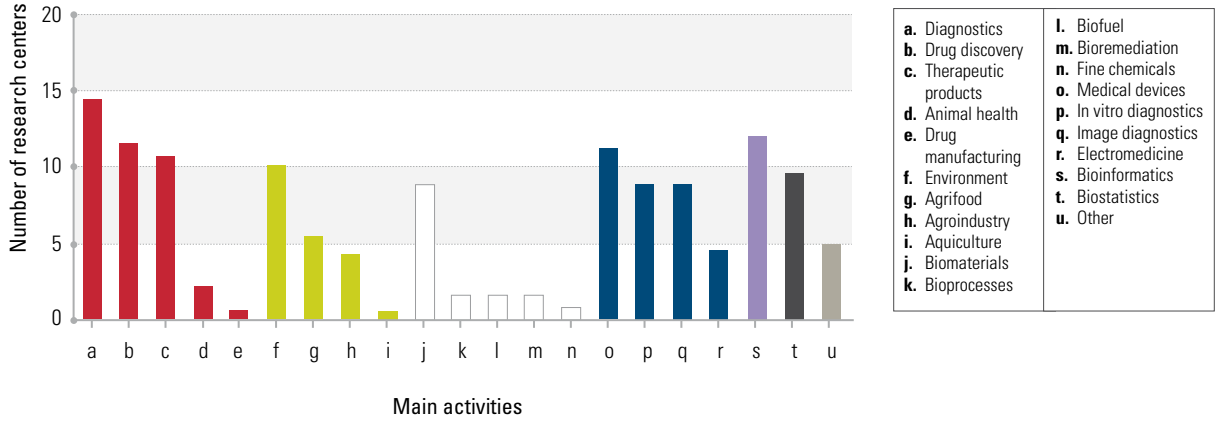
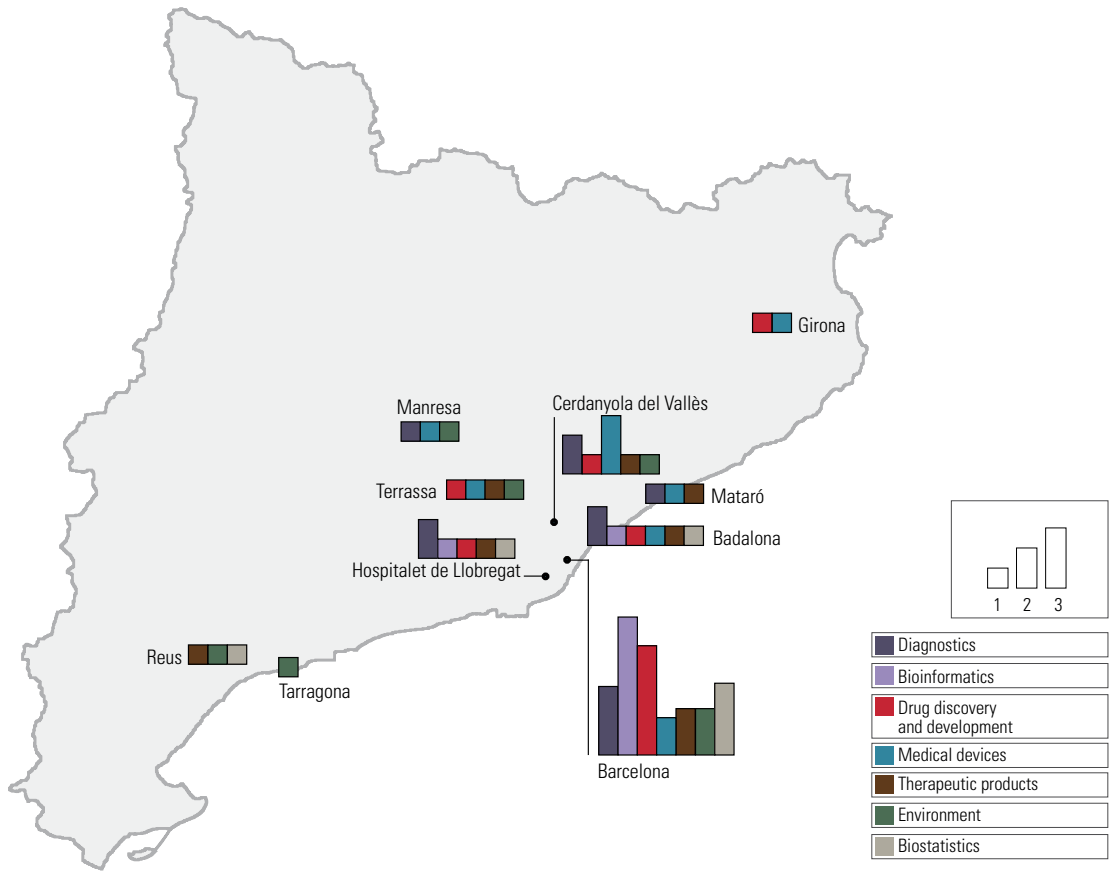


Figure 50. **Geographic distribution of centers by main activity**



In research linked to green biotech there are marked differences between centers and companies regarding the activities related to the environment (25% vs. 4%, respectively), while the importance of agrobiology and agrifood research is similar in both types of organization.

By geographic distribution (figure 50), we can see that Girona, where we have identified the presence of the medical technology subsector, focuses on activities related to medical devices, although they also carry out activities related to red biotech, like drug discovery. In the Tarragona area we find a predominance of activities related to the environment, biostatistics and therapeutic products.

Other activities

The research centers develop a variable number of activities and functions, in addition to research itself (figure 51). Thus, half of the centers surveyed said they carry out technology and knowledge transfer activities, to which we have devoted a chapter of this report (section 8.6), including indicators related to collaborations and the number of spin-offs created, while section 8.3 covers indicators related to patent licenses.

Noteworthy among the other functions preformed in these research centers are training, carried out in 52% of those

Figure 51. **Other activities of research centers**

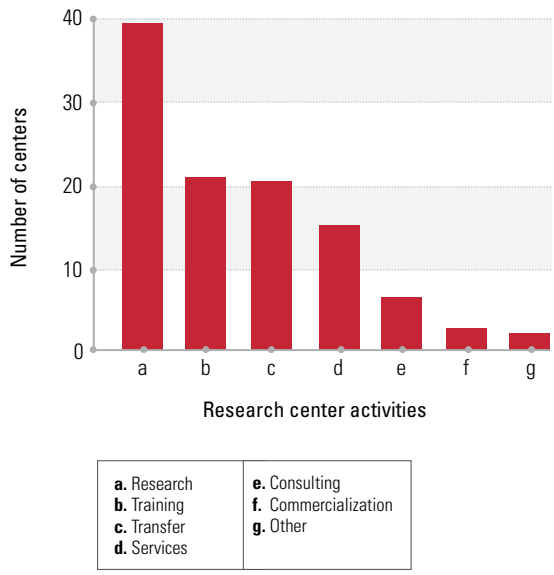
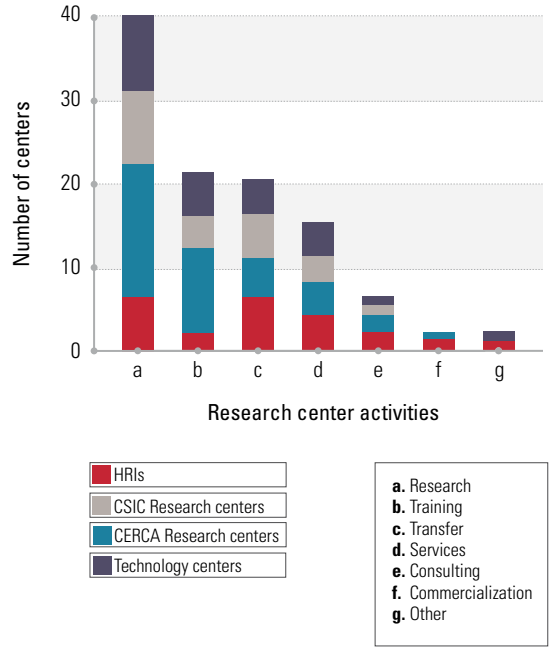


Figure 52. **Activities by type of center**



surveyed, and service provision (50%). Logically, these activities are much less important than more business-related ones, like consultancy and commercialization.

When we analyze the distribution of these activities by type of center (figure 52), and exclude research, which is a priority for all of them, we can see small variations in the priorities established among the other activities. Technology transfer, despite being important to all according to their responses, carries more weight in technology centers, which is inherent in their model. The main differences can be observed in training —which 42% of the CERCA centers studied said they carried out and a lower percentage of the other types of centers— and commercial activity, a small minority found mainly among technology centers.

In short

Research centers in our sample focus mainly on biomedicine and, to a lesser degree, on biomaterials and the environment, areas that can be related to white and green biotech, respectively. Apart from research, their main activity, they also carry out technology transfer and training tasks (which has an important weight in CERCA centers), and to a lesser degree, service provision.

8.3. Research activities

Research is a very broad concept and can have many different aims and focuses. Thus, 77% of the centers surveyed said they carry out basic research, an activity the technology centers did not include in their responses. Additionally, nearly 90% of the centers said they also do applied research, meaning that focused on obtaining new products, services and processes. However, due to the way the survey was designed we can't evaluate the specific weight given to each type of research, an indicator that will be included in subsequent editions of the *Biocat Report*.

On the other hand, this section basically focuses on biomedical research —given that this area has enough data to analyze—, and only makes occasional reference to research related to industrial or green biotech applications.

Thus, we will discuss the therapeutic areas in which research is carried out in the centers analyzed as well as the development processes they take part in. In those centers that participate in development projects, we aim to identify which stages of the research process they take part in. We will also evaluate the results of their research, which we understand to be shown through scientific production and patent applications. We will also evaluate the main innovative technologies employed.

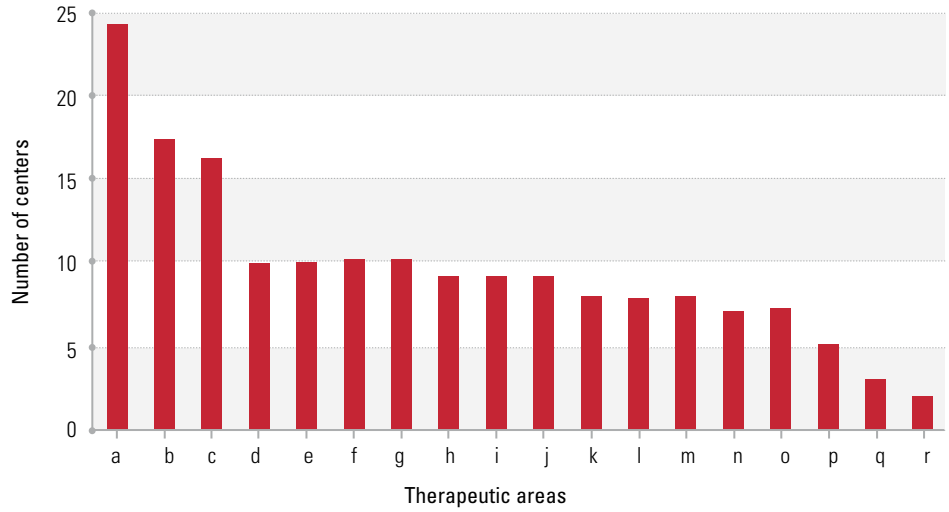
Therapeutic areas

As we have mentioned in previous sections, almost all the research centers develop activities related to human healthcare (60% red biotech and 40% medical technology). We therefore focus our analysis on the therapeutic areas they research.

Public biomedical research in Catalonia is strong in oncology, the nervous system and cardiology

We should point out the predominance of oncology (60%), the central nervous system (42%) and cardiology (40%). Infectious diseases, metabolism, hematology and pneumology are all studied by the same percentage of centers (25% per area). In the case of infectious diseases, there is

Figure 53. **Therapeutic areas in research centers**



an important effort dedicated to tuberculosis and malaria research. Dermatology also carries considerable weight among the areas studied in research centers (22.5%).

Comparing the data from the centers surveyed to data available on clinical research in Catalonia (*BEST Project*, Farmaindustria, 2009), we can confirm the importance of oncology and cardiology. On the other hand, research on the central nervous system, a priority for both centers and companies, carries less weight in the clinical data, from which we can deduce that the centers surveyed carry out mainly non-clinical research (basic research and drug discovery).

If we compare the results with data on international centers, the priorities are fairly similar. As an example on a European level we can take the Inserm (Institute National de la Santé et de la Recherche Médicale), in France, which focuses on neuroscience, cancer, infectious diseases, the circulatory system, metabolism and nutrition; the Edinburgh BioQuarter (which includes the University of Edinburgh's College of Medicine and the Queen's Medical Research Institute) identifies neurosciences, oncology, cardiovascular, infectious diseases and inflammation as their main priorities, with important efforts in translational medicine according to information published on the Scottish Enterprise website. Finally, in the United States, the National Institute of Health (NIH), made up of 27 research centers, has three centers devoted to different areas of cancer research and two devoted to mental health; in cardiovascular research they carry out 10,011 clinical trials; in the field of infectious diseases their priorities include vaccines against tuberculosis, malaria and AIDS; autoimmune diseases and applied research on non-invasive and imaging techniques, for which they have a bioengineering center, are also priorities for this North-American research body.

When we analyze the main therapeutic areas of centers that carry out medical technology research, we find that 89% of the centers work on traumatology, 80% on rheumatology and 63% on cardiology and surgery. These results are in line with the importance of prosthesis, implant, stent and valve development, and with the efforts made in Catalonia regarding new biomaterials and bioengineering.

Regarding geographic distribution, Terrassa and Manresa show some activity in oncology and cardiovascular research, respectively, due to the presence of technology centers established in traditional industrial areas that carry out part of this research in laboratories located in other research-intensive structures. In Girona, Hospital Dr. Josep Trueta focuses on all four of the top therapeutic areas and has become an international benchmark in cardiology for research sudden cardiac death.

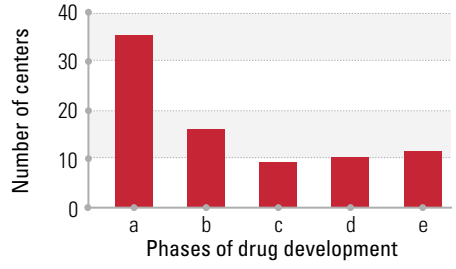
Finally, of those centers that carry out applied research and participate in drug development processes, we analyzed which phases of the process the participate in.

Catalonia carries out more clinical trials (52.4%) than any other region in Spain

Thus, as shown in figure 54, there is a lot of activity in discovery and preclinical research at the CERCA and CSIC centers. However, this activity is also carried out at some HRIs, both internally and in collaboration with other centers, as part of their efforts to increase translational research that links clinical data from patients with the discovery of pathological mechanisms of diseases or with new mechanisms of drug action.

Applied clinical research is carried out in all phases of regulatory clinical trials, mainly in HRIs. As we mentioned in Chapter 6, Catalonia carries out more clinical trials than any other community in Spain, more than half of the total (52.4%), with 2,309 trials approved in 2007 (*Annual Report*

Figure 54. **Types of research in centers**



on the National Health System 2007-Catalonia, Ministry of Health and Social Policy– Government of Catalonia, 2008).

When we analyze the phases of clinical trials carried out in HRIs according to the results of the survey, we see a certain predominance of phase III and phase II trails, and to a lesser extent phase I. This data is in line with that provided by the *BEST Project* (Farmaindustria, 2009), according to which phase III studies make up 58% of all industry-funded trials. However, there is some discrepancy as to phase I studies, which according to the same study make up 4% of the pharmaceutical industry, while the data from the centers surveyed shows that 23% of the trials done in these centers are phase I. This difference is probably due to the fact that studies that are not funded by the pharmaceutical industry —in Catalonia, 203 independent clinical trials were applied for and 71 approved in 2007 and a small part of the first studies carried out by biotechnology companies that aren't counted in the Farmaindustria study.

Technology and technology platforms

Following the same structure as Chapter 7, we also analyzed the use of a wide range of innovative technologies in the research centers. Overall, use of these technologies is much higher in research centers than in companies, none of which used more than 15% of the technology evaluated (see section 7.3).

The predominance of genomics and proteomics is noteworthy, employed by 53% and 43% of the centers respectively, which in some cases isn't used as a tool, but is the main focus of their research. In silico technology is also important (25%), which is mainly associated with fields that lead to applications related to red biotech and green biotech, like the improvement of seeds and varieties, for example (figure 55).

Nanotechnology, which is a transversal tool, is applied in 30% of the centers and, as mentioned in Chapter 1, is one of the five technologies of the future. 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 (*Nanotechnology: what is it and how does it affect us?* Catalan Foundation for Research and Innovation, 2009). Furthermore, according to the National Medical Library in the United States, which belongs to the NIH, Barcelona has the second highest number of scientific publications on nanomedicine in the world, after Boston and ahead of London, Los Angeles and Houston. This fact was included in the Catalonia Research and Innovation Plan 2005-2008, which identifies nanotechnology as one of the seven strategic sectors.

Barcelona has the second highest number of scientific publications on nanotechnology in the world

Bioprocesses (10%) are employed mainly in the white and green biotech subsectors, with some applications in red biotech. As indicated in the article by Dr. Castells in Chapter 3 of this report, bioprocesses use living materials (biological agents, enzymes, microorganisms, etc.) to substitute processes that were previously carried out chemically or to create new processes that are more efficient and sustainable, both economically and environmentally.

We have already mentioned the growing impact of bioinformatics and biostatistics (20%), which, like the omic sciences, are both a service and a main area of research in some centers. Crystallography (15%) and PSB (biological service platforms, with 10%) are also frequently employed.

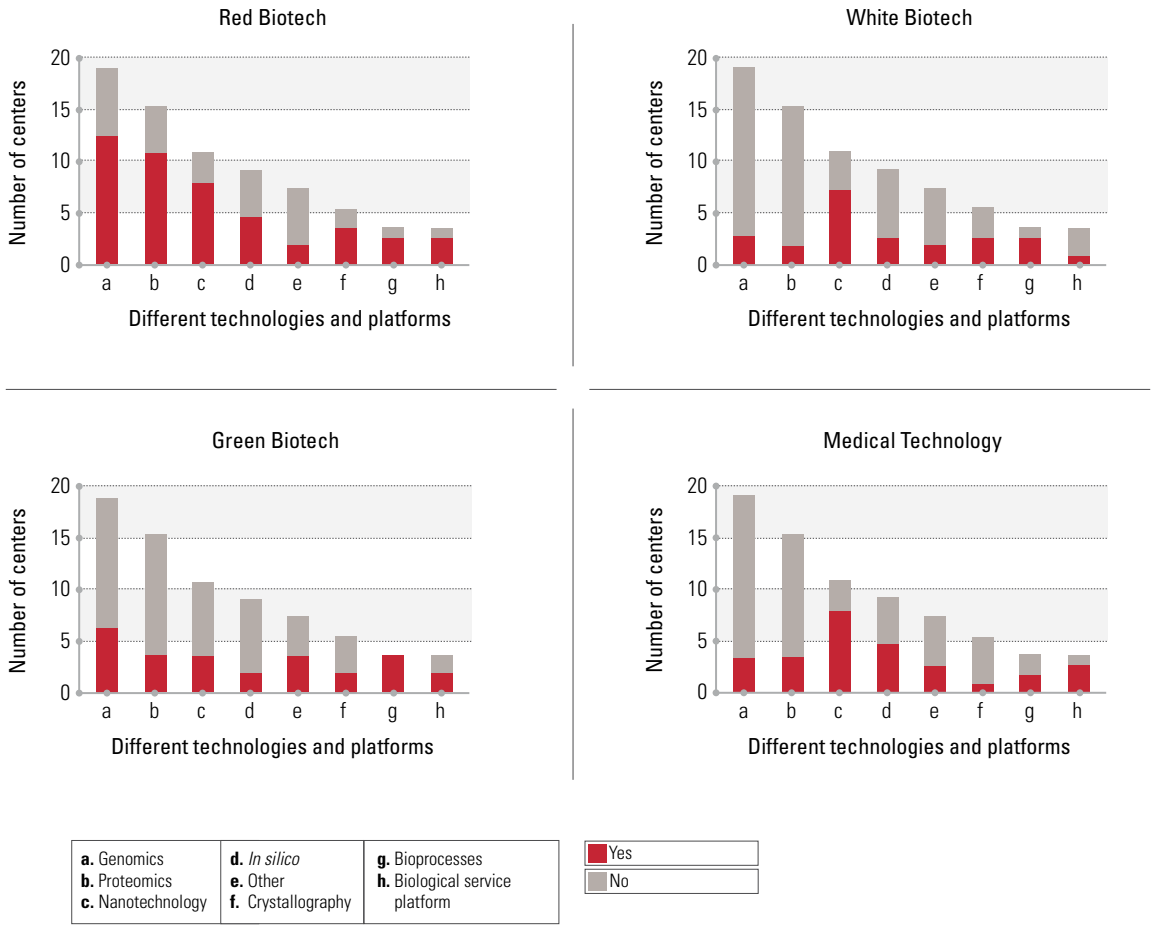
Patents and other protection models

Regarding the protection of knowledge generated by the centers, we have obtained data on the instruments they employ and the support structures they use to manage it.

Regarding protection models, 75% of the centers surveyed said they use patents and 27.5% said they use other protection models. Only 5% of the centers surveyed did not answer this question.

If we look at patents, we can see that the average number of patent applications is 7 per center. However, there are

Figure 55. **Technology and technology platforms in centers by subsector of activity**

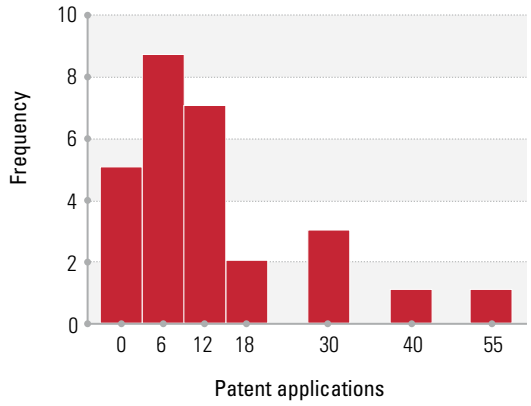


some centers that apply for up to 35 or 40 patents (figure 56), which are the large, consolidated institutions with many foreign researchers. Although the question was included in the survey, we can't give specific information regarding the number of applications made in Spain and Europe, because the dispersion of the data makes this analysis unadvisable.

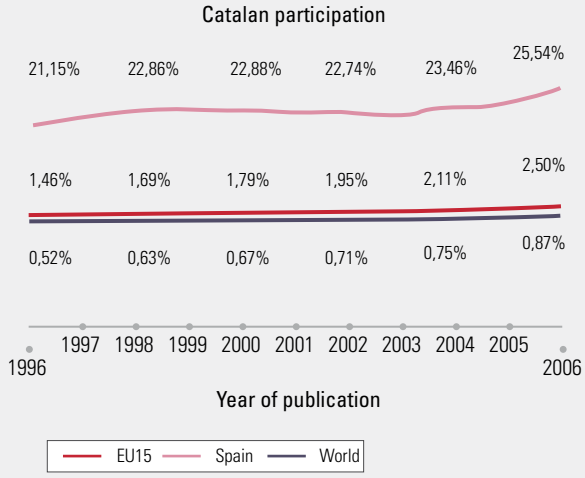
When we analyze the number of patent applications by type of research linked to different subsectors, we can see that the most active centers are those that carry out research that can be applied in white and green biotech, with an average of 9 applications per center, similar to the number of patents in bioinformatics. The centers with the least number of patents are those that do research in medical technology, with an average of just 5 applications per center, mainly because this type of technology commonly uses other protection models.

Centers also license patents, with an average of 1.5 licenses per center, and very few acquire patents (an average of 0.4 patents per center).

Figure 56 . **Number of patent applications per center**



Square 10. **Scientific production in Catalonia compared to Spain, Europe and the world**



Source: *Bibliometric characterization of scientific production in Catalonia 1996-2006,* CIRIT, 2008

Other knowledge-protection models, which are employed in one fourth of the centers (27.5%), include copyrights, utility models, brands, variety registers, intellectual property registers and industrial secret.

Finally, we evaluated which type of services the centers surveyed employ to protect their knowledge. We found that 58% of the centers have an internal department to carry out these functions, although 43% of the centers use services provided by other public bodies (universities or hospitals) they are associated with, and 60% of the centers contract private external services.

Scientific production

In absolute terms, scientific production in Catalonia has grown significantly over the past decade, reaching 25.54% of the total production in Spain (square 10). This scientific production comes mainly from the university sector (64.2%), followed by the healthcare sector, which accounts for one third of all publications (28.0%). Public research centers sign 14.4% of all scientific productions and, at a much lower level, companies and other stakeholders (*Bibliometric characterization of scientific produc-*

Square 11. **Catalan un iversities' biomedical production**

In this sector, by production volume (number of documents), the most active disciplines are:
- Biochemistry and molecular biology (2,363)
- Neurosciences (1,311)
- Pharmacology (1,095)
- Microbiology (1,057)

According to the average number of times a document is quoted, the most visible disciplines are:
- Gastroenterology and hepatology (18.93)
- Peripheral vascular disease (17.76)
- Hematology (17.54)
- Genetics (17.07)
- Oncology (15.99)
- Forensic medicine (17.43)
- Biochemistry and molecular biology (15.40)

Source: *Bibliometric characterization of scientific production in Catalonia 1996-2006,* CIRIT, 2008

Figure 57. **Scientific production by type of center**

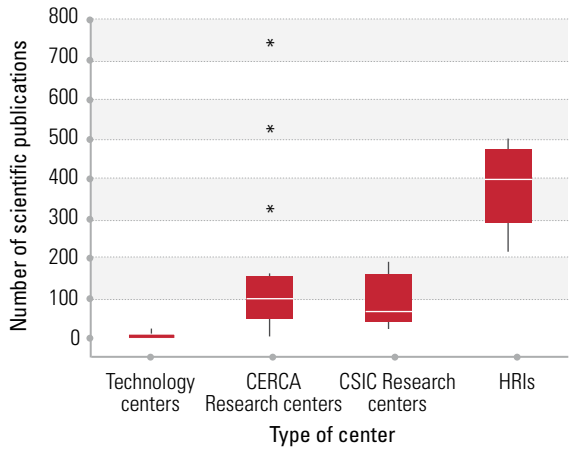
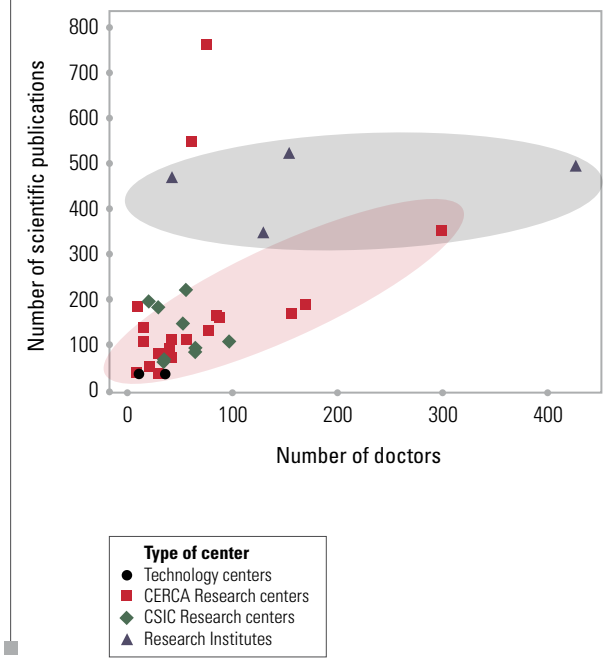


Figure 58. **Scientific production by number of doctors and type of center**



tion in Catalonia 1996-2006, CIRIT, 2008). Squares 10 and 11 give complementary information about scientific production in Catalonia.

If we analyze the scientific production in research centers surveyed, it becomes clear that this indicator varies widely depending on the type of center, which has led us to evaluate them separately (figure 57). CERCA and CSIC centers produce an average of 99 and 72 indexed publications respectively, while HRIs produce an average of 398 publications per center.

Thus, the research activity of the HRIs in 2007 resulted in 1,793 publications, with a global impact factor of 6.189 and an average impact factor of 3.45 (*Bibliometric characterization of scientific production in Catalonia 1996-2006*, CIRIT, 2008).

When we analyze the relationship between the difference in number of publications and the structure of the center, number of researchers, it becomes clear that the HRIs and CSIC centers maintain a stable number of publications regardless of the number of doctors in each center, although this is not the case for CERCA centers (figure 58). In the latter we detected a proportional growth factor linking the number of publications and the number of doctors each center has: the more doctors, the more publications. This proportionality has two exceptions, which are the CERCA centers that are linked to hospitals —which although they belong to the CERCA program on an administrative level, behave as HRIs and, therefore, have a very high percentage of publications. The reason for this difference in number of publications can be found in the type of data they collect: HRIs and CERCA centers liked to hospitals publish medical research results, which a large majority of the CERCA and CSIC center can't do.

This data is in line with that established by the study *Evolution of scientific production on biomedicine in Spain 1981-2006* (REDES, 2008), according to which 56.9% of all publications in Catalonia come from the biomedical field, with activity in the healthcare sector (hospitals) that is often equal to or above this. The healthcare sector

also shows an increase in visibility (proportion of quotes per document) and a progressive internationalization of its publications: thus, 10.9% of all documents are signed by researchers from, on average, 5-6 entities from different countries.

Finally, the technology centers generate very few publications. This is an inherent part of their structure and financing system, which is partially private, making this indicator of number and impact of publications non-critical. Their research is mainly applied and close to the market, therefore in this regard they act more like an industry than a public center.

Research groups

Given that this first *Biocat Report* did not directly survey research groups, which are a key part of the public research arena, we have collaborated with the Agency for Management of University and Research Grants (AGAUR). This entity provided aggregate data for the disciplines previously selected by Biocat, which correspond to the sector this report focuses on (biotechnology, biomedicine and medical technology) for the Catalan research and innovation system.

AGAUR manages the main line of grants funded by the Government of Catalonia to support research groups, which is the SGR. This call for proposals, in addition to providing basic funding for the most highly evaluated groups, also establishes a map of research groups in Catalonia in all areas of research.

The last SGR call for proposals 2009-2013 received proposals from 1,518 research groups, made up of 22,120 researchers, which is a significant number if we consider that Catalonia has an estimated total of 25,000. In this call for proposals, nearly 36 million euros were granted (*Statistics on 2009 SGR resolution*, AGAUR, 2009).

The typology of these groups and their specific weight, according to the classification used in the 2009-2013 call for proposals is:

- GREs (emergent research groups) make up 24% of the total. These are groups with a limited joint history (from 2005 or later to the date of the proposal) that aim to consolidate the group under the framework of this call for proposals. They must be made up of at least three members (two doctors) and a maximum of ten.
- GRCs (consolidated research groups) represent 71% of the total. These are groups in which most members have a shared work history over the past four years, with the resulting cohesion and convergence of their respective lines of research, joint scientific publications, common projects, technology transfer activities and awareness raising activities. They must be made up of at least five members (three doctors).
- GRSs (singular research groups) account for 5% of the total. This type doesn't meet the criteria to be considered a consolidated research group but does have a cohesive and distinguished shared work history, developed over the past years.

42% of the SGR call for proposals for 2009-2013 (AGAUR) is devoted to research groups related to biomedicine and biotechnology

The growth in the call for proposals 2009-2013 with regard to 2005-2009 is significant, both because of the total grant money awarded (with an increase of more than 50%) and the number of applications received (nearly 40% more). The area that experienced the highest growth in applications was medical science and healthcare, which received 68% more applications than in previous years, although science continues to be the dominant subject in total number of applications.

84% of the total 1,518 applications to the 2009 call for proposals, were evaluated favorably: 33% of the teams received official recognition as a Government of Catalonia Research Group and 51% were awarded grant money.

By discipline, science was most successful in the 2009-2013 call for proposals, with more than 59% of applications awarded grants, while in other subjects only around 50% of applications received funding (figure 59).

However, given that the 1,518 applications come from five subjects, two of which are clearly outside the focus of this

Figure 59. **Evolution of research group grant applications to call for proposals by subject area**

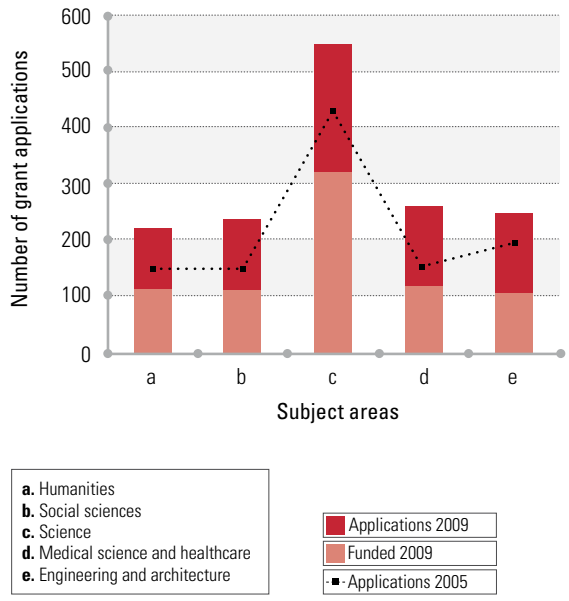
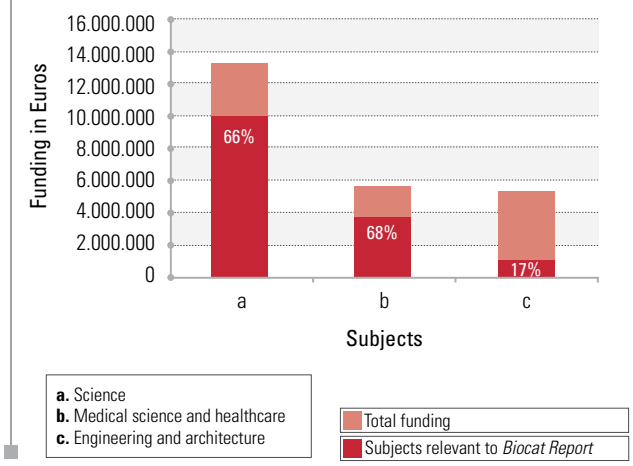


Figure 60. **Research group funding in subjects relevant to *Biocat Report***



study (humanities and social sciences) and in the other three (science, medical science and healthcare, engineering) not all disciplines would be included in the Biocat Report, only 38% of the applications would be included in our evaluation, the percentage that received funding can be seen in figure 60 and would represent a total of 15 million of the 36 million euros granted.

By type of group, this 38% of applications is distributed as follows: 40% to Consolidated Groups (of the total of 71% classified as such), 34% to Emerging Groups (versus 24% of the total) and 34% to Singular Groups (of the 5% of the total). If we look at the emerging and singular groups, we see that they are gaining importance in the areas this report studies.

The number of research groups that participate in the different nation-wide network programs, like CIBER (Network of Biomedical Research Centers) and RETICS (Cooperative Healthcare Network Research Centers), is also noteworthy.

The CIBER program brings together research groups that belong to different public or private bodies and have lines of research or objectives related to the same area of public health. The CIBER program aims to carry out top-level research, integrating all the knowledge in the country and driving technology transfer.

Catalonia, with 33.85%, has more groups that participate in this program than any other region in Spain (figure 61), a total of 87 with at least one in each of the nine existing CIBER groups (Annual Report on the National Healthcare System 2007, Ministry of Health and Consumer Affairs).

The RETICS are organizational structures made up of biomedical research centers or groups from at least four different Spanish regions, associated with the Carlos III Healthcare Institute. Their main objective is technology transfer and they are funded through an agreement with the Ministry of Health and Consumer Affairs and Farmaindustria (Order SCO/709/2002, of 22 March, Official State Gazette, 2002). For the 2007 call for proposals, for projects to last four years, the budget earmarked for RETICS was 8 million euros (Ingenio 2010). Catalonia has a total of 63 networks with an investment of nearly 19 million euros.

Figure 61. **Catalonia's participation in Ciber research groups**

Ciber research groups in 2007

	Ciber 01	Ciber 02	Ciber 03	Ciber 04	Ciber 05	Ciber 06	Ciber 07	Ciber 08	Ciber 09	**Total**
Catalonia	12	18	8	7	8	8	11	9	6	**87**
CIBER Total	35	41	23	31	34	22	36	17	18	**257**

Ciber 01: bioengineering, biomaterials and nanomedicine
Ciber 02: epidemiology and public health
Ciber 03: physiopathology of obesity and nutrition
Ciber 04: hepatic and digestive diseases
Ciber 05: neurodegenerative diseases
Ciber 06: respiratory diseases
Ciber 07: rare diseases
Ciber 08: diabetes and metabolic diseases
Ciber 09: mental health

*CIBER: Network of Biomedical Research Centers
Source: *Annual Report on the National Healthcare System 2007* – Ministry of Health and Consumer Affairs, 2008.

In short

The five therapeutic areas where research centers focus their efforts are, from most to least, oncology, the nervous system, the cardiovascular system, infectious diseases and metabolism. All centers carry out basic research and 90% stated that they carry out applied research. Of this applied research, evaluated by their drug development activities, the CSIC and CERCA centers focus their research on discovery and preclinical research. The HRIs focus less on these phases and more on applied clinical research, with a growing effort going to translational research.

The knowledge generated through this research is protected mainly using patents, however, these still generate relatively few licenses. On the other hand, there is an important volume of scientific production, with a high impact factor at CERCA and CSIC centers and, above all, at the HRIs.

The most commonly used cutting-edge technologies are the omic sciences, for research related to red and green biotech, and nanotechnology, a transversal tool for all the subsectors, which has international benchmark centers where the main part of research is carried out.

Finally, the areas of biotechnology, biomedicine and medical technology represent more than one third of the research currently being carried out in research groups recognized by the Government of Catalonia.

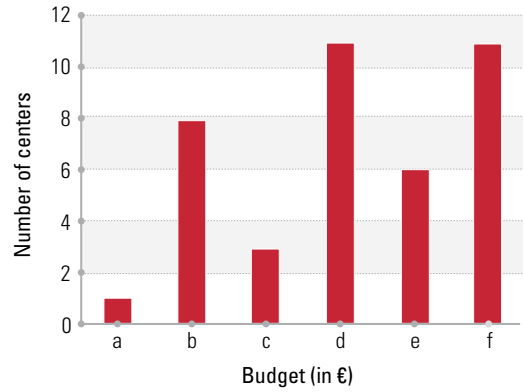
8.4. Resources

In this section we will look at the resources used in the research centers to carry out their activities. We have evaluated financial (budget) and structural (space) resources, as well as the legal structure that supports them. We haven't included human capital because we believe it deserves a chapter of its own.

Legal structure

Regarding the legal structure of these research centers, most are set up as a private foundation (78% of CERCA centers; 83% of HRIs and 100% of the technology centers). Occasionally we see centers that are established as a consortium, made up of universities, hospitals and public or private entities, or those that are public companies. This is slightly different in the CSIC centers: one third are consortia and the other 66% depend directly on the CSIC, meaning they are public research organisms (OPI).

Figure 62. **Budget of research centers**



a. 100.000€ - 200.000€	**d.** 2.000.000€ - 5.000.000€
b. 500.000€ - 1.000.000€	**e.** 5.000.000€ - 10.000.000€
c. 1.000.000€ - 2.000.000€	**f.** > 10.000.000€

Research budget

The funding structure in the research centers is complex, because their funds often come from different bodies. These are mainly public bodies, like local or regional administrations, ministries of the national government and various European bodies. There are also funds that come from private charities (Vall d'Hebron Oncologic Research Foundation, Esther Koplowitz Biomedical Research Center, etc.), from donations (funds collected and managed by the TV3 Marató Foundation, for example) and sponsors (financial institutions like Banc Santander, or the social areas of different savings banks that have grant or subsidy programs for research projects, like the IRSI-Caixa, etc.).

It is important to clarify in this section that the total budget is considered research budget. Therefore, unlike the section on companies, we have not compared the percentage of the budget devoted to research to the total budget. Thus, according to the results of the survey, the centers can be divided into three groups according to their budget (figure 62).

20% of all centers surveyed have a budget of between 500,000 and 1,000,000 euros, which is made up mostly of the technology centers. 28% of the sample has a budget of between 2 and 5 million euros, corresponding to a large part of the CERCA centers (nearly 65%) and the CSIC research centers. Another 28% of the centers, mainly HRIs and the remaining CERCA centers, fall into the category of more than 10 million euros.

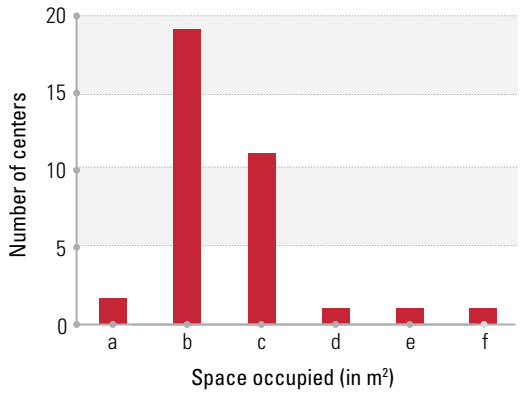
According to data provided by the Commission for Universities and Research (DIUE) for 2009, the 2008 working budget for CERCA centers in the areas of relevance to the Biocat Report was slightly more than 221 million euros. This budget is divided into competitive funds (33.5% public and 5.3% private) and non-competitive funds (51.1% public and 10.1% private).

In 2008, the Department of Health earmarked approximately 16.2 million euros in direct expenditure for research support programs and research centers and facilities and 132 million euros in indirect expenditure. In 2009, they invested nearly 209 million euros (24.6 million in research support and facilities and 184 million in indirect expenditure), which is a 28% increase in the budget set aside for research.

Space occupied

Regarding space, nearly half of the centers (48%) have between 1,000 and 5,000 m2 and 28% of the centers have between 5,000 and 10,000 m2 (figure 63). 18% of the centers have less than 1,000 m2. By type of center, nearly two thirds of the technology centers have less than 1,000 m2, however the distribution is highly random among the other types of centers.

Figure 63. **Space occupied by research centers**



a. 500 - 1.000	**d.** > 10.000
b. 1.000 - 5.000	**e.** > 20.000
c. > 5.000	**g.** > 50.000

In short

The centers in our sample are mainly private foundations that are funded through public funds and, to a lesser extent, private funds. Their research budget varies quite a bit, the lowest being the technology centers, around 1 million euros per year. Nearly one third of the sample, however, has around 1 million euros per year per center—mainly HRIs. The average space occupied by each center is between 1,000 and 5,000 m2.

8.5. Human capital

This section will look at the number of employees and their qualifications related to the research activities carried out. As with the budget, in research centers we considered all employees to be research employees, unlike in the companies, especially those that are more consolidated and have an important part of their team working on production and commercialization tasks.

This section will also look at the future of the sector: students currently studying degrees in these disciplines and the new degrees that will help them join the labor market. The information given here regarding the Catalan academic arena is based on data provided by the Commission for Universities and Research (DIUE).

Number of employees

Distribution of number of employees is fairly heterogeneous, with highly variably groups. We could not establish any relationship between number of workers and the year the center was established, but there is some correlation between the type of center and number of employees (figure 64).

Thus, in general, the centers with the most employees are the HRIs, which also have the largest budget. These institutes employ an average of 496 people, but have more than 650 in some cases and rarely have less than 230 employees, as shown in the lower limit of the box-plot below.

There are considerably fewer employees at the CERCA and CSIC research centers than at the institutes; the average is 101 and 138, respectively, with some exceptions.

The majority of the technology centers have an average of 25 employees. The total number of workers at these technology centers is often very large but for the *Biocat Report 2009* we asked them to include data only on those that carry out research in biotechnology, biomedicine or medical technology.

Education

Due to the inherent characteristics of the research centers, most of their employees hold advanced degrees

Figure 64. **Number of employees by type of center**

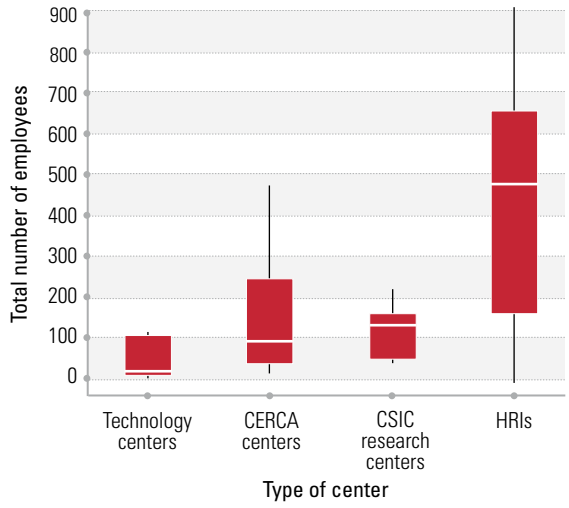
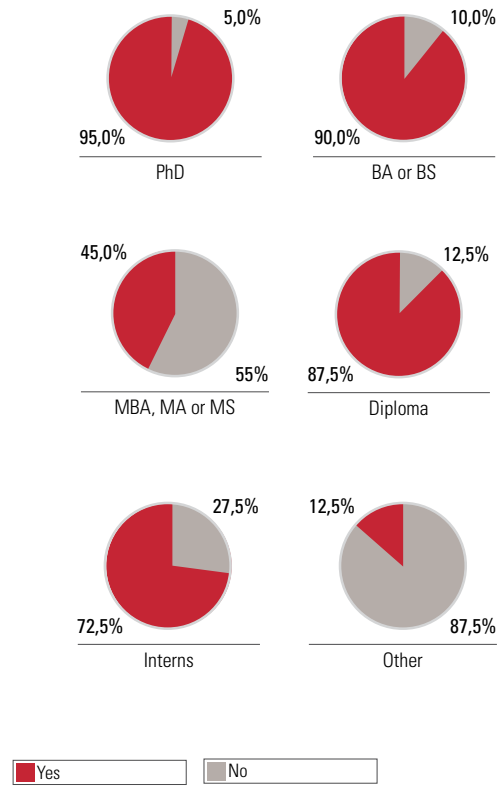


Figure 65. **Education of professionals at research centers**



(95% PhDs) and bachelors degrees (90%) (figure 65). Unlike what we saw regarding the companies in the sector, there is an important presence of employees with diplomas in the research centers (88%). Furthermore, 45% of these professionals have studied masters or MBAs.

We included interns in this section (73%), although this designation is more about professional status than an academic degree, because they are normally pre- and post-doctoral students that don't have a full-time position at the center.

When we looked at the relative proportion of these degrees at each center, we saw that normally more than one third of the staff hold PhD, BA or BS degrees and approximately 10% of the total hold diplomas or work as interns.

However, we can observe differences by type of center and educational level. The technology centers have a lower proportion of PhDs, but there is no difference between the other types of centers in this regard. The HRIs, on the other hand, have the highest number of employees with bachelor's degrees, diplomas and interns, which is related to the fact that they have a higher number of employees overall.

Students from the sector at Catalan universities

In this section we will discuss the current academic panorama in Catalonia, based on data provided and published by the Commission for Universities and Research (DIUE). First of all, we will evaluate the degrees that fit this sector and after we will look at the number of students, graduates and professors in each degree.

The Catalan university system is currently made up of 12 universities (7 public and 5 private). By number of students, the private universities make up 10% of the total; distance learning, 19%; and the majority of students go

to public universities, with 71% of the total. These universities have more than 17,000 professors, nearly 220,000 students and offer 881 degrees, 88% of which have been designed in accordance with the criteria laid out by the European Higher Education Area (EHEA).

Approximately 18% of these degrees, or 155 EHEA degrees, are related to the subjects of this report (biotechnology, biomedicine and medical technology). These degrees are offered in 10 universities, but the University of Barcelona, the Autonomous University of Barcelona and the Polytechnic University of Catalonia offer nearly 60% of the total (figure 66).

Of the 18% that apply to our area of interest, 48% are in science, 28% in health sciences, 21% in engineering and architecture and 3% in social and legal sciences. We've included this last area due to the growing number of degrees offered in technological innovation management, including a degree focusing on the creation of innovative companies (Master in Creation and Management of New Technology-Based Firms at the UB). Biotechnology is taught at 6 of the 10 universities.

Furthermore, of this 18% of degrees related to the sector, 26 completely new degrees were inaugurated this year. Of these, the ones with the most applications were: the UPC's degree in biomedical engineering, the UB's degrees in biomedical science and biotechnology, the UAB's degrees in environmental biology, biomedical science and genetics (*Beginning of the 2009-2010 School Year*, Press Release from the Department of Innovation, Universities and Enterprise, 2009).

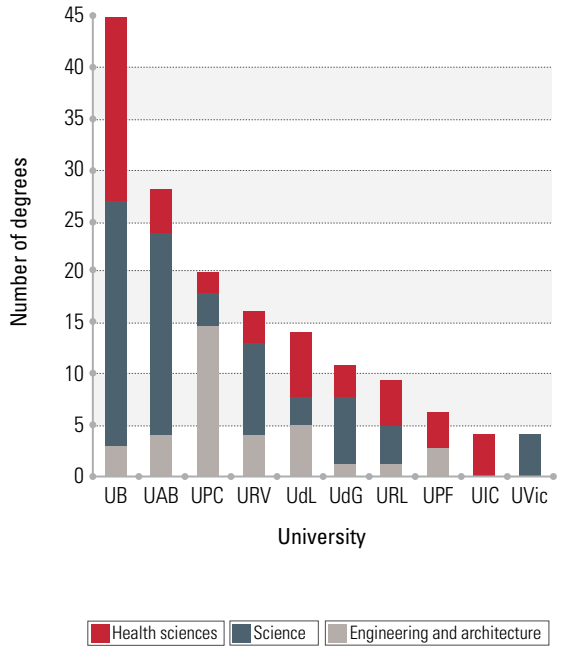
Biomedical engineering and biomedical sciences are the most popular new degrees

Regarding the number of students and the PDI (research/teaching professors) that hold a PhD, the data used is from the 2007-2008 school year. Due to the changes in the educational system in this period of time, there may be a certain bias in the results obtained compared to current data.

Square 12: **European Higher Education Area (EHEA)**

The European Higher Education Area (EHEA) fosters quality and international competitiveness among international higher education centers in Europe, allowing European university graduates to enjoy increased mobility and occupation. This system is based on a comparable structure of degrees and in the long run will allow Europe to foster its own economic and social growth. The Bologna Declaration of 1999 is the initial reference point for this process. Degrees that existed before the European Higher Education Area were divided into cycles (1st cycle, 1st and 2nd cycle, 2nd cycle and 3rd cycle) and were based on lecture credits. The new system establishes three types of degrees: bachelors, masters and PhDs.

Figure 66. **University degrees offered in Catalonia in biotechnology, biomedicine and medical technology**



When evaluating the number of students, we took into account new students, continuing students and new graduates:

- New students (4,800 students in the areas related to the report): 54% in science, 31% in health sciences and 15% in engineering and architecture.
- Continuing students (226,000 total students, 11% of which correspond to the areas related to the report): health science (40%) is the most popular, followed by science (38%) and then engineering and architecture (22%).
- New graduates (4,600 graduates in the areas related to the report): 40% in science, 42% in health sciences and 18% in engineering and architecture.

The number of PDI that hold a PhD and teach subjects related to the focus of this report represents one third of the total (29%). The universities have made an important effort to reduce the number of students per professor in all areas of study, not just those related to this report. Thus, the number of research and teaching personnel has grown by 2.8% annually, decreasing the number of students per professor from 15 to 11, which brings us closer to Harvard (9.5) and better than Cambridge (15.5) and the Sorbonne (17.9) (according to data from 2007-2008 found on their respective web pages).

In short

The number of employees varies quite a bit between the different types of centers in our sample. The HRIs have the highest number of workers: nearly three times more per center than the rest of the centers analyzed. These workers mainly hold PhDs and bachelors degrees, but there is a noteworthy percentage with diplomas or working as interns.

Regarding students, an important percentage of all students study degrees in disciplines related to science, health sciences and engineering.

8.6. Technology transfer

In this analysis of research centers in Catalonia, we have begun to collect indicators of how research results are transferred to areas where they make an impact on the general public's quality of life. In this first report we have evaluated patent generation and the corresponding licenses (see section 7.3), joint projects with companies, and the creation of new companies.

Catalonia has the best return on the 7th Framework Program in the State (40%)
Two thirds of Spanish hospitals funded are in Catalonia

Creation of public/private consortia

Of the sample of research centers surveyed, 78% stated that they participate in public/private consortia and 18% said they didn't participate in any type of consortia.

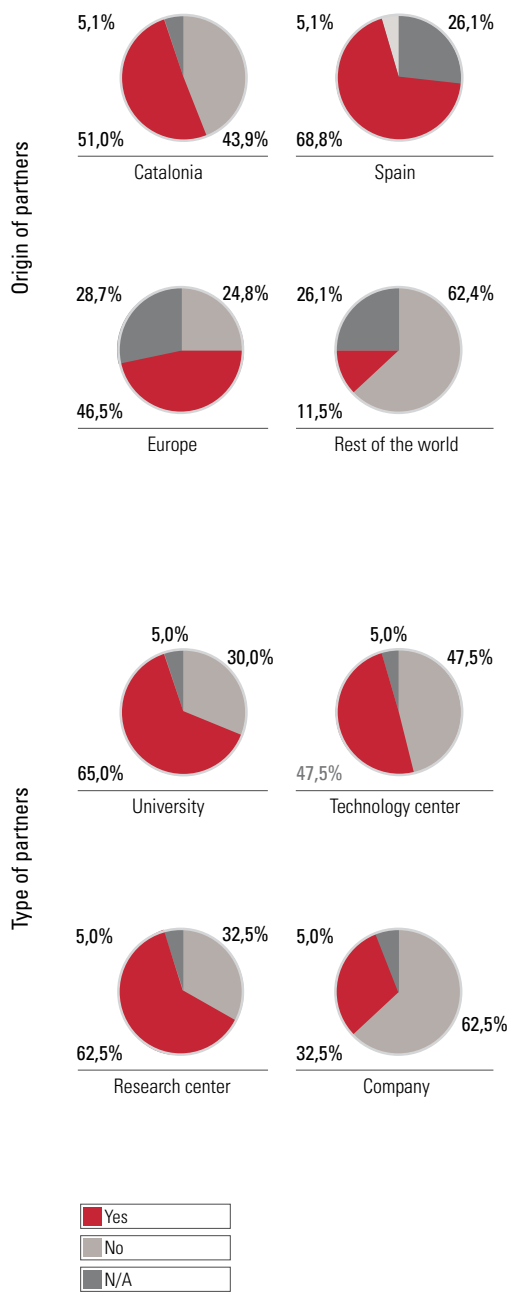
These consortia are mainly made up of Spanish partners and, in second place, Catalan partners. Less than half of the consortia have European partners and very few have partners from the rest of the world (figure 67). Regarding the type of partners that make up the consortia, the proportion of public research entities is clearly higher than that of companies, which only represents one third of all partners.

In the report *VII Programa Resultados Provisionales de la segunda convocatoria del tema "Salud,"* (Center for the Development of Industrial Technology, 2008), which analyzes the results of the 7fP-2007-HEALTH-B call for proposals, Catalonia is the second ranking Spanish region by level of return, with 37% of the 32.3 million euros obtained in Spain.

The report drafted by the CDTI points out the results obtained by public research centers, which make up 29.7% of the return on the national total.

Hospitals make up 19% of the entities that received funding and, when we analyze the list, we can observe that 9 of the 14 hospitals that received funding are from Catalonia.

Figure 67. **Participation of research centers in consortia**



Apart from the hospitals/HRIs, the CSIC research centers have the most projects approved (9) in Spain.

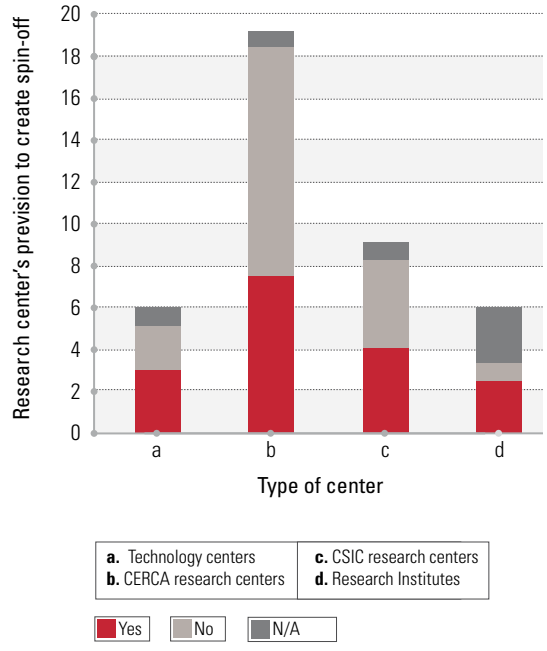
By area, 8.3% of all projects funded are from biotechnology and 76.7% are in translational research, which is in line with the data obtained from the research centers regarding their research priorities.

Spin-offs

Nearly half (45%) of the 40 centers that answered the survey claim to have created at least one spin-off. By type of center, the number that has created spin-offs is: 8 of the 19 CERCA centers, 2 of the 6 HRIs, 3 of the 5 technology centers, and 4 of the 9 CSIC centers. There is no correlation between the age of the center and the number of spin-offs created.

Regarding previsions for the future (figure 68), 50% of the technology centers expect to create new companies,

Figure 68. **Prevision of spin-offs by type of center**



which is in line with their focus on research– and 44% of the CSIC centers also declare this intention. On the other hand, only 33% of the HRIs expect to create new companies, which is in line with the data showing a low number of companies that originated in the hospital environment. 42% of the CERCA centers expect to create a new company, although if we take into account that nearly all of these centers were founded in 2005 it is logical that they are just starting to have results that can be applied to create a spin-off.

There is a positive relationship between centers that have created new companies and those that expect to do so in the near future: 61% of those that have already created a company aim to repeat the process, however 65% of the centers that haven't created any spin-offs don't expect to do so.

In short

Regarding technology transfer, using the number of patents licensed, public/private consortia participated in and spin-offs created as indicators, we must point out that the centers surveyed still generate few licenses, although two thirds of them do participate in consortia. These consortia have partners that are mainly from Spain or Catalonia and are mainly from the public sector, with only one third from the business sector. Regarding spin-offs, nearly half of all centers state that they have created a new company and an important number, above all technology centers, expect to create more in the future.

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9. Conclusions

This report has aimed to be a first analysis of the components of the BioRegion of Catalonia as a whole and, for the first time, to look at the activities of companies and research bodies in the public sector.

In order to provide this global vision we have carried out a strictly descriptive analysis based on data collected from a sample of 108 companies and 40 research centers —of a total 368 bodies invited to participate— and information collected in the Biocat Directory —which contained 874 listings at the time of evaluation. The scope of the study is therefore limited, as we had to work with a sample that represents only some of the entities that make up the sector and stresses the need to encourage participation in the next editions of this report in order to guarantee that we have reliable indicators to design future policies and strategies. Another limitation we have faced in drafting this report was the lack of specific public references for the biotechnology sector regarding economic parameters, the impact of R&D&i measures, and personnel. We often had to extrapolate sectorial data from more general studies. In any case, these facts have been included in the text whenever possible in order to provide context and to contrast with the data collected.

In spite of these difficulties, this first analysis of the sector has brought to light some interesting considerations about the state of biotechnology, biomedicine and medical technology in Catalonia.

Biotechnology has the potential to become a strategic sector for our regional economy. With a growing number of applications, new job opportunities for qualified professionals and the driving nature of quality basic research, the Catalan biotechnology sector brings together all the necessary elements of a solid model for economic growth. In order to take advantage of this potential, a biotech cluster must include hospitals, universities, research centers and companies, but also quality infrastructures, technology platforms and, most importantly, access to specialized capital that understands the long development cycles that characterize the sector, and experienced professionals to lead the process. Many of these elements are already present in the BioRegion of Catalonia, to some degree. Regarding facilities, Catalonia is on par with other consolidated European bioclusters, like the aforementioned ones in Cambridge (United Kingdom) and Berlin (Germany). However, in addition to these strengths, we have also detected many elements of the sector that are not yet mature, which will be discussed next, and must be addressed in the next few years.

Catalonia has made a strong commitment to public research by creating a significant number of research centers in the past decade, and this community is pioneering as to the model followed by foundations and research institutes linked to hospitals. In line with this commitment, in 2008 160 million euros were earmarked for biotechnology research (more than 220 million for CERCA centers according to data from the Commission for Universities and Research, and 148 million euros invested by the Department of Health in research support programs and infrastructures [see section 8.4]). The result of this continued support has been a group of HRIs with highly qualified research personnel that are very competitive on an international level, both in number and quality of publications. However, they still need to improve in technology transfer, measured in number of patents (average 7 per center) and number of licenses (average 1.5 per center per year).

These centers —often linked to science parks— have also become hubs around which young companies con-

centrate, as proximity to basic and applied research, as well as top-notch scientific and technological services, is key to research-based business models that use innovative technology that, as we saw in the section analyzing centers, is available in the BioRegion.

The rate at which new biotech companies are created in Catalonia —25% in 2008, and 27% in 2007, according to Asebio reports— is above the average of many European bioregions and that of the Spain as a whole (21.8% for 2006-2007 and 24.5% for 2005-2006, according to the aforementioned reports). In any case, entrepreneurial drive is still insufficient for a country with the eighth largest economy in the world. According to the Global Entrepreneurship Monitor (GEM) for 2008, Spain has a HAE rate (Highgrowth Expectation Entrepreneurial Activity) below 0.5%, ranked with France, Belgium, Finland, Greece and Japan, clearly lower than innovation-based economies like the USA, Canada, Island or New Zealand, whose HAE rates are up to 15 times higher.

As this study shows, approximately 50% of new companies originate in the business sector and the other half in public research centers. However, there is still little spin-off from the public sector, which is one of the indicators used to evaluate the level of technology transfer in this report. This lack of transfer is not in line with the Catalan and Spanish administrations' investment in research, nor with the high level of research carried out by centers, as manifested in the number of publications generated and their impact. The low number of spin-offs is especially noteworthy in the case of HRIs, which account for only 5% of all new biotech companies, although the data collected shows that they have the highest number of researchers, largest budgets and generate the most publications. In this regard, Catalan HRIs are far from international benchmarks like the Hadassah University Hospital in Israel, which manages over 250 patents through their technology transfer company, Hadasit, which is traded on the Tel Aviv stock market. Fortunately, this situation is beginning to change and nearly half the centers surveyed said they expect to create new spin-offs in the future.

Companies created recently in the BioRegion are mainly microcompanies, with highly qualified personnel (83% have PhDs), that devote around 80% of their budget to R&D. In general, they opt for a mixed business model (44%) that combines product research with the creation of innovative technology platforms to serve third parties. In the majority of these companies the founder holds an executive position and there are few qualified business management and development experts, all of which are characteristics of an immature sector. With regard to their capital, there is a clear predominance of public venture capital investment and a lack of specialized venture capital, which still focuses on seed money and first-round funding (scarcely 5% of companies reach second round funding). As we have mentioned, this creates a catch 22: the companies are immature and therefore cannot access specialized venture capital, however they cannot mature because they don't have access to this funding. Therefore, measures must be taken to improve business strategy and access to funding in order to break this cycle.

Fortunately, over the past years, in line with the worldwide convergence of biotech and pharma, there has started to be more contact between small biotech companies and more mature local businesses. This was recently demonstrated in the collaboration between the Ferrer Group and Oryzon Genomics, as well as other family-owned pharma companies with international biotech businesses. These initiatives must be extended, since Catalonia has the highest level of internal (47.6%) and external (22.5%) R&D investment in Spain (Farmaindustria, 2009), in addition to being the main fine chemical producer in the country (80%). We should also mention the first merger between Oryzon Genomics and Crystax, carried out in the first months of 2009, as a strategy to increase critical mass and gain in complementarity, indicators that the sector is maturing.

Both companies and research centers participate in consortia, a policy strongly encouraged by the public administration over the past years (Nuclis d'Innovació, CENITS, 7th Framework Program) to foster consolidation of the sector through larger-scale projects. However, these consortia are established with mainly local partners and lack internationalization strategies: few activities in this area are developed with European partners (19% of companies and 25% of centers) and there is still little contact with the United States (less than 6% of companies and less than 11% of centers), which is the international benchmark in many research areas and in the biotechnology market.

What is clear in this first report is that, in the biomedicine field, Catalonia's strengths lie in the oncology and the nervous system, both therapeutic areas in which we find all the elements of the value chain from basic research that generates ideas and publications in the most prestigious journals through hospitals with translational research and companies developing products —although the pipeline is not yet particularly deep given the youth of these companies. We must also highlight the potential we have seen in cardiovascular research (mainly in centers) and dermatology (in companies), as well as infectious diseases, a niche market that is often overlooked by large multinational companies, allowing small companies and centers to work collaboratively. All of these knowledge areas are in line with large-scale global trends, where Catalonia can compete on an international level, given the quality of our research, and attract qualified professionals, European program funds and venture capital for companies. These are areas in which we can encourage the creation of specialized networks to generate new synergies and boost potential.

In line with the trends mentioned in the first chapter regarding tools of the future, Catalonia excels in nanotechnology research and has shown strong growth in the bioinformatics field. Section 8 showed the importance of Catalan nanotechnology research, with internationally renowned centers and a pioneering position as to scientific publication in this discipline. Regarding bioinformatics, Catalonia has top-notch researchers and large-scale facilities (like the MareNostrum supercomputer), which drive wide-scope life sciences research projects, leading to growing number of spin-offs in this field.

Despite Catalonia's preeminent position in the fields of red biotechnology and biomedicine (64% of companies focus on this activity and 60% of centers), green biotech is noteworthy for its potential. Only 17% of the companies surveyed work in this field, but research being carried out in 32.5% of the centers analyzed could be applied in this subsector. Activity in this area focuses on improving plant genetics, achieving better volume and resistance in production, biocontrol and animal production. The importance of environmental research stands out, as well as its lack of representation in business activities, leading us to believe that this could be a field for future growth.

Industrial biotechnology, with the improvements it contributes to industrial bioprocesses on one hand, and the generation of innovative biomaterials on the other, represents an opportunity for Catalonia in the future if we are able to incorporate this technology into the traditional industrial fabric to optimize efficiency and costs, as well as opening new markets. The worldwide economic impact of producing chemical compounds derived from biotechnology (10% of total production) will be an estimated 80,000 million euros in 2010 and Europe leads global enzyme production with 80% of total production. Catalonia has a growing industry in both areas.

In short, the Catalan biotechnology, biomedicine and medical technology sector has important strengths and a growing business fabric that has the potential to become a driving force for the country's economy and strategy if long-term political measures are established to favor consolidation of a knowledge-based economy in Catalonia.

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Glossary

Applied research	Research that uses scientific knowledge to develop new products and technology or services to benefit society.
Basic research	Also known as fundamental or pure research, it is carried out with the aim of advancing scientific knowledge of basic principles, leading to the creation of new theories or the modification of existing ones.
Biodrug or biological drug	Pharmaceutical product made from biological materials (microorganisms, plant or animal substrate, cell fragments, animal or human fluids), as opposed to "traditional" drugs that are obtained chemically.
Bioengineering	Series of engineering techniques applied to the field of biomedicine to develop healthcare products or technology (medical devices or diagnostic or therapeutic tools)
Biofuel	Fuel made from raw materials that are biological, renewable, mainly from plants, or biodegradable.
Bioinformatics	Application of computational technology to manage, analyze, simulate or predict data that is biological in origin.
Biomarker	Substance measured for indicators of a disease or alterations in the body.
Bioremediation	Decontamination techniques that use natural processes to eliminate harmful chemicals from the environment.
Biosimilar	Copy of a biotech drug that works in the same way and treats the same disease but is not identical to the original drug because it is created from a new cell line using production processes that are not identical to those used to create the original biotech drug.
Business angel	Individual that invests capital in a newly created company in exchange for stock.
CEO	Chief Executive Officer. In charge of managing and leading a company. In Catalonia this position is normally called general director.

Clinical research	Research to develop new drugs, which evaluates the safety and effectiveness of the drug in humans. Made up of a number of successive phases or stages (phase I, phase II, phase III and phase IV).
Clinical trial	Experimental study of a product, substance, medication, diagnostic or therapeutic technique to evaluate its effectiveness and safety for human consumption.
Cluster	Group of companies, research organizations or groups, and facilities with interconnected support systems that belong to a specific business sector and geographic area. The group shares a common strategy, innovating spirit and aim to increase the competitiveness of its participants.
CRO	Contract research organization Service company specialized in developing one or more areas or research, mainly clinical trials.
Generic	Type of drug with the same formula and chemical composition, both in quality and quantity of active ingredients.
Genomics	Techniques used to study how genome sequences work and evolve as well as their origin. It uses interdisciplinary knowledge from the fields of molecular biology and biochemistry, computer sciences and statistics, mathematics, physics and chemistry.
GMO	A genetically modified organism has undergone a gene transfer, through human intervention, using genetic engineering tools, giving it new properties.
ICT	Information and communication technology. Group of techniques and advanced tools that allow data to be stored, processed and transmitted.
Incubator	Space that aims to create and develop companies in their first stages, providing management support and access to scientific and technological infrastructure.
In vitro diagnostics	Techniques that use human or animal tissue and fluids to diagnose diseases or changes in the body.
Nanomedicine	Medical discipline based on the application of nanotechnology to science and medical procedures in order to cure diseases or repair damaged tissue such as bones, muscles and nerves.
Nanotechnology	Disciplines of applied sciences applied to the study and development of materials on a scale of less than 100nm (nanometers), on an atomic or molecular level.
Phase I	Clinical research phase in which the drug being studied is administered to healthy volunteers in order to judge its safety.

Phase III — Clinical research phase in which comparative clinical trials are carried out to demonstrate the effectiveness of the drug in a representative sample of patients. The results of this study allow the drug to be approved and put on the market.

Phase IV — Studies carried out once a drug is on the market in order to test new therapeutic applications, establish the safety of the drug in normal clinical conditions and in special samples.

Pipeline — In biotech and pharmaceutical companies, this term refers to the group of compounds (drugs) in the R&D stage.

Preclinical study — Experimental drug study that uses animals to test the effectiveness and safety of the drug.

Proteomics — Area that connects proteins with the genes that encode them, studies the group of proteins that can be obtained from a genome, and develops the necessary technology to analyze any cell protein.

Spin-off — Company created in the environment of a public research entity (university, research center or institute) through the entrepreneuring initiative of one or more participants (researchers, doctors).

Spin-out — Business initiative that originates as a division or subsidiary of an existing company and later becomes an independent company. Often the original company owns stock in the new company.

Start-up — Company that, in venture capital jargon, is in the initial stage, normally less than two years old.

Technological springboard — Support structures that drive technological improvement in Catalan universities by creating new technology-based companies or incorporating knowledge in existing companies through product and/or service innovation.

Technology transfer office — Exchange structure in charge of dynamizing and promoting relationships between the scientific and business arenas in order to benefit research capacity and results.

Venture capital — Financial activity that provides temporary capital for "high-risk" companies –those that have difficulty finding other sources of financing –in the mid and long term.

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Companies and centers that participated in the 2009 Biocat Report

Participating companies*

AB-Biotics
Advancell
Agrasys
Aleria Biodevices
Alma IT
Almirall
Althia
Amgen
AMPbiotech
Anapharm
Anaxomics
AntibodyBcn
Antonio Matachana
Archivel Farma
Aromics
Arquebio
Avinent
BCNPeptides
BCNInnova
Biocontrol Technologies
Bioglane
BioIngenium
Biokit
Bionanomics
Bionatur technologies
BioSystems
Biovet
Brudy Technology
Catfosc
Centre d'Imatge Molecular
Crystax
D'Enginy Biorem
Enantia
Endor Nanotechnologies
Esteve
Eyytoo Bioscience
Ferrer Incode
Flowlab
Fresenius Biotech
Gem-med
Gendiag
GP Pharm
Hartmann
Hartington Pharmaceutical
Hexascreen
IHT
Infinitec Activos
Infociencia
Intelligent Pharma
Isdin
Janus Developments
Kymos Pharma
La Morella Nuts
Laboratorios de análisis Dr. Echevarne
Laboratorios Gebro Pharma
Laboratorios Leti
Laboratorios Menarini
Laboratorios Reig Jofré
Lasem
Merck
Micologia Forestal Aplicada
Microart
Microbial
Nedken Solutions
Neos Surgery
Neuroscience Technologies
Neurotec pharma
Ninsar Agrosciences
Omnia Molecular
OrigoGen
Oryzon Genomics
Palau Pharma
Panrico
Pierre Fabre
Prous Institute for Biomedical Research
Q-Genomics
RAL
Recerca Clínica
Reprogenetics
Sabirmedical
Salupharma biosimilars
Salvat Biotech
Sanofi Aventis
Semillas Fitó
Sepmag Technologies
Sevibe Cells
Síbel
Starlab
SVS
Takeda Pharmaceutical
Telstar
Thrombotargets
Topping
Tpro
Transbiomed
Trial Form Support
Trifermed
Uquifa
Vecmedical
X-Ray Imatek
Zambon

*those that agreed to be listed in the report

Participating centers

ASCAMM Technology Centre
Barcelona Digital Technology Centre
Center of Regenerative Medicine in Barcelona (CMRB)
Center for New Agrifood Technology and Processes (CENTA)
Center for Research in Agrigenomics (CRAG)
Center for Research in Environmental Epidemiology (CREAL)
Barcelona Center for International Health Research (CRESIB)
Center for Animal Health Research (CRESA)
Center for Genomic Regulation (CRG)
Computer Vision Center (CVC)
Cardiovascular Research Center
Center for Nanoscience and Nanotechnology Research (CIN2)
Nutrition and Health Technology Center (CTNS)
Cetemmsa Technological Center
CTM Technology Centre
Catalan Institute of Nanotechnology (ICN)
Institute of Chemical Research of Catalonia (ICIQ)
Catalan Institute of Oncology (ICO)
Institute for Bioengineering of Catalonia (IBEC)
Institute of Evolutionary Biology (IBE)
Molecular Biology Institute of Barcelona (IMBM)
Institute of Materials Science of Barcelona (ICMAB)
Institute of Photonic Sciences (ICFO)
Institute of Environmental Assessment and Water Research (IDAEA)
Institute for High Energy Physics (IFAE)
Institute of Predictive and Personalized Medicine of Cancer (IMPPC)
Institute of Biomedical Research (IRB Barcelona)
Bellvitge Institute for Biomedical Research (IDIBELL)
Research Institute of Hospital de la Santa Creu i Sant Pau
Research Institute of Hospital Universitari Vall d'Hebron
Institute of Agro-Food Research and Technology (IRTA)
Girona Biomedical Research Institute (IdibGi)
Health Sciences Research Institute of the Germans Trias i Pujol
Pere Virgili Institute for Health Research (IISPV)
August Pi i Sunyer Biomedical Research Institute (IDIBAPS)
Institute of Biomedical Research of Barcelona (IIBB)
Municipal Institute for Medical Research (IMIM)
Barcelona Institute of Microelectronics (IMB-CNM)
Leitat Technological Center
Vall d'Hebron Institute of Oncology (VHIO)

Survey distributed to participating companies and centers

Company survey

1. Company activity

1.1 Which of the following are your company's **main areas of business?**

- ☐ Drug discovery/development
- ☐ Diagnostics
- ☐ Drug manufacturing
- ☐ Therapeutics
- ☐ Animal health
- ☐ Bioinformatics
- ☐ Biostatistics
- ☐ Biomaterials
- ☐ Bioprocesses (other industries)
- ☐ Fine chemicals (not drugs)
- ☐ Agroindustry
- ☐ Aquiculture
- ☐ Biofuel
- ☐ Agrifood industry
- ☐ Environment
- ☐ Bioremediation
- ☐ In vitro diagnostics
- ☐ Image diagnostics
- ☐ Medical devices
- ☐ Electromedicine

1.2.1 Which of the following are your company's **main activities?**

- ☐ R&D
- ☐ Production
- ☐ Service
- ☐ Commercialization
- ☐ Consulting
- ☐ Distribution
- ☐ Training
- ☐ Other (list)

1.2.2. Which activities do you subcontract (totally and/or partially)?

- ☐ R&D
- ☐ Production
- ☐ Design
- ☐ Commercialization
- ☐ Consulting
- ☐ Distribution
- ☐ After-sales
- ☐ Other (list):

1.3 Which of the following describes your business model?

- ☐ Product-based
- ☐ Technology-based (technology platform and/or service)
- ☐ Mixed model (product + technology platform)

1.3.1 If you are a product-based company or use a mixed model, how **many products do you have in the pipeline for each of the following phases?**

- ☐ Discovery
- ☐ Phase I
- ☐ Phase II
- ☐ Phase III
- ☐ Market
- ☐ Preclinical
- ☐ Other (list)

1.3.2 If you are a technology-based company or use a mixed model, which types of technology?

- ☐ Proteomics
- ☐ Genomics
- ☐ Nanotechnology
- ☐ Crystallography
- ☐ *In silico*
- ☐ Bioprocesses
- ☐ Other (list)

1.4 Which of the following describe the main therapeutic areas of your products and/or services?

- ☐ Oncology
- ☐ Dermatology
- ☐ Digestive system
- ☐ Metabolism
- ☐ Infectious diseases
- ☐ Cardiology
- ☐ Pneumology
- ☐ Rheumatology
- ☐ Inflammatory
- ☐ Hematology
- ☐ Endocrinology
- ☐ Traumatology
- ☐ Nervous system
- ☐ Immunology
- ☐ Genitourinary
- ☐ Surgical
- ☐ Other

2. General information

2.1 What is your company's legal structure?

☐ Joint-stock company (Inc.) ☐ Limited company (LLC) ☐ Other (list)

2.2 How many promoters/founders does the company have?

2.3 Does the company have a Board of Directors?

☐ Yes ☐ No

2.4 Does the company have a board of advisors (strategic)?

☐ Yes ☐ No

2.5 What is the company's origin?

☐ University ☐ Biotech company ☐ Research center ☐ Hospital/Research institute
☐ Science/technology park ☐ Pharma company ☐ Technology center ☐ Company from another sector

2.6 In which of the following areas does your company mainly operate?

☐ University ☐ Incubator ☐ Business/industrial area or complex
☐ Science/technology park ☐ Hospital ☐ Other (list)

2.7 Do you have your own laboratories and/or production plants?

☐ Mainly rental ☐ Mainly owned ☐ Other (list)

2.8 Does your company need to use external and/or complementary scientific/technological facilities or equipment?

☐ Yes ☐ Large-scale equipment ☐ CT Services ☐ Other: ☐ No

3. Human resources

3.1 How many employees does your company have, in total (2009)?

☐ 1 ☐ 5-10 ☐ 20-30 ☐ 50-100
☐ 2-5 ☐ 10-20 ☐ 30-50 ☐ >100

3.2 How many R&D employees?

☐ 1 ☐ 5-10 ☐ 20-30 ☐ 50-100
☐ 2-5 ☐ 10-20 ☐ 30-50 ☐ >100

3.3 Do you have a CEO ?

☐ Yes ☐ No

3.4 CEO's training:

☐ Life sciences/health ☐ Engineering ☐ Other (list)
☐ Business management ☐ Chemistry /environmental studies

3.5 Founder/s position in the company:

☐ CEO ☐ CFO ☐ Other (list)
☐ CSO ☐ Director Commercial Operations

3.6 Do you have a CSO (Chief Science Officer)?

☐ Yes ☐ No

3.7 Do you have a CFO (Chief Financial Officer)?

☐ Yes ☐ No

3.8 Do you have a Director of Commercial Operations?

☐ Yes ☐ No

3.9 Do you have a President?

☐ Yes ☐ No

3.10 Professional Training. How many employees hold each degree? (approximately)

☐ PhD ☐ MBA, MA or MS ☐ Interns
☐ BA or BS ☐ Diploma / Advanced vocational training ☐ Other (list)

3.11 Do you have an internal training plan?

☐ Yes ☐ No

3.12 Do you offer an internal career plan?

☐ Yes ☐ No

4. Economic/financial information

4.1 Capital

☐ <10.000€ ☐ 50.000€ - 100.000€ ☐ 200.000-500.000€ ☐ 1.000.000€-2.000.000€
☐ 10.000-50.000€ ☐ 100.000€ - 200.000€ ☐ 500.000€-1.000.000€ ☐ >2.000.000€

4.2 Yearly turnover (sales)

☐ 0€ - 200.000€ ☐ 1.000.000€ - 2.000.000€ ☐ 5.000.000€-10.000.000€ ☐ >50.000.000€
☐ 200.000€ - 500.000€ ☐ 2.000.000-5.000.000€ ☐ >10.000.000€ ☐ >100.000.000€
☐ 500.000€ - 1.000.000€

4.3 Profit

☐ <0€
☐ <25.000€
☐ 25.000€ - 100.000€
☐ 100.000€ - 1.000.000€
☐ 1.000.000€ - 3.000.000€
☐ 3.000.000€ - 10.000.000€
☐ >10.000.000€

4.4 Did the founder/s contribute to the company's capital?

☐ Yes
% (optional)?
☐ No

4.5 Have you received external capital investment?

☐ Venture capital (1st round)
☐ *Business Angels*
☐ Venture capital (2nd or successive rounds)
☐ Company/ business group
☐ University (other public funds)
☐ Other public funds (list)

4.6 Do you have R&D budget?

☐ Yes
Approximate percentage?
☐ No

4.7 Have you received subsidies or public grants?

Catalonia (regional government)
☐ Concepte
☐ Gènesi
☐ Innoempresa
☐ Internationalization (ACC1Ó)
☐ Núcleos de innovación
☐ Beatriu de Pinós
☐ Other (list)

Spain (national government)
☐ PROFIT
☐ Neotec
☐ Torres Quevedo
☐ CENIT
☐ Other (list)

Europe
☐ 7FP
☐ Marie Curie
☐ Other (list)

4.8 Is your company's stock traded publicly on the stock market?

☐ Yes
☐ No

5. Business development

5.1 How many of each type of patent do you hold?

☐ None
☐ National
☐ PCT
☐ Additional countries
☐ Other (list)

5.2 How many patents are you currently applying for?

5.3 How many patents do you license to third parties?

5.4 How many patents do you license from third parties?

5.5 Do you use other IP protection measures?

☐ Yes
Which (list)?

☐ No

5.6 What IP management resources do you have?

☐ Internal department

☐ Institutional services (University – Hospital)

☐ External agency (consultancy)

☐ Other (list)

5.7 Do you participate in any joint R&D projects with other companies?

☐ Yes
Which?

☐ No

5.8. Do you participate in any public/private R&D partnerships?

☐ Yes

☐ No

5.9. Where are your partners from, mainly?

☐ Catalonia

☐ Spain

☐ Europe

☐ Other (list)

5.10. What type of partners do you have?

☐ University

☐ Technology center

☐ Research Institute / Hospital

☐ Other (list)

6. Commercial development

6.1 What commercialization channels do you use?

☐ None
☐ National

☐ PCT
☐ Additional countries

☐ Other (list)

6.2 Market presence

☐ Catalonia
☐ Spain

☐ Europe
☐ North America

☐ South America
☐ Asia

☐ Worldwide
☐ Other (list)

6.3 Which international congresses, fairs and meetings do you participate in (those you consider most effective/ strategic)?

7. Future growth

7.1 Do you foresee an increase in turnover compared to 2008?

☐ Yes % increase ☐ No

7.2 Do you plan to increase capital?

☐ Yes
☐ No
☐ Yes, from public investors (universities, neotec..)
☐ Yes, with additional investment from current shareholders
☐ Yes, from additional investors (Not CR)
☐ Other (list)

7.3 Do you plan to merge with another company?

☐ Yes ☐ No

7.4 Do you plan to be taken over by another company?

☐ Yes ☐ No

7.5 Do you plan to create a new company (spin-out)?

☐ Yes ☐ No

7.6 What are your priorities for 2009?

☐ R&D
☐ Launching new product/s
☐ Internationalization
☐ Sales and marketing
☐ Alliances/Consortia
☐ Other (list)

7.7 What are your work space/land needs?

Space currently occupied (in m^2):
☐ <50 m^2
☐ 50-100 m^2
☐ 100-200 m^2
☐ 200-500 m^2
☐ 500-1000 m^2
☐ 1000-5000 m^2
☐ >5000 m^2
☐ >10.000 m^2

Space needed 2 years from now?
☐ 50-100 m^2
☐ 100-200 m^2
☐ 200-500 m^2
☐ 500-1000 m^2
☐ 1000-5000 m^2

Do you authorize Biocat to publish the name of your company in the list of participants in the study?

☐ Sí ☐ No

Center survey

1. Center activity

1.1 Which of the following are your center's main areas of activity?

- ☐ Basic research
- ☐ Drug discovery/development
- ☐ Diagnostics
- ☐ Drug manufacturing
- ☐ Therapeutics
- ☐ Animal health
- ☐ Other (list)
- ☐ Bioinformatics
- ☐ Biostatistics
- ☐ Biomaterials
- ☐ Bioprocesses (other industries)
- ☐ Fine chemistry (not drugs)
- ☐ Agroindustry
- ☐ Aquiculture
- ☐ Biofuel
- ☐ Agrifood industry
- ☐ Environment
- ☐ Bioremediation
- ☐ In vitro diagnostics
- ☐ Image diagnostics
- ☐ Medical devices
- ☐ Electromedicine
- ☐ Other (list)

1.2. Which of the following are your center's **main activities**?

- ☐ R&D
- ☐ Service
- ☐ Commercialization
- ☐ Transferencia tecnológica
- ☐ Training
- ☐ Consultancy
- ☐ Other (list)

1.3 What type of research do you do?

- ☐ Basic research
- ☐ Applied research
- ☐ Preclinical
- ☐ Phase I
- ☐ Phase II
- ☐ Phase III
- ☐ Market
- ☐ Other (list)

1.4 What type/s of **technology/services** do you provide?

- ☐ Proteomics
- ☐ Genomics
- ☐ Nanotechnology
- ☐ Crystallography
- ☐ *In silico*
- ☐ Bioprocesses
- ☐ Other (list)

1.6 Which of the following describe the main therapeutic areas of your **products and/or services**?

- ☐ Oncology
- ☐ Dermatology
- ☐ Digestive system
- ☐ Metabolism
- ☐ Infectious diseases
- ☐ Cardiology
- ☐ Pneumology
- ☐ Rheumatology
- ☐ Inflammatory
- ☐ Hematology
- ☐ Endocrinology
- ☐ Traumatology
- ☐ Nervous system
- ☐ Immunology
- ☐ Nefro-urinary
- ☐ Surgical
- ☐ Andro-gynecology
- ☐ Other (list)

2. General information

2.1. How many employees does your company have, in total (2009)?

- ☐ 10 -25
- ☐ 25 -50
- ☐ 50-100
- ☐ 100-200
- ☐ 200-300
- ☐ >300
- ☐ >500

2.2. How many R&D employees?

- ☐ 10 -25
- ☐ 25 -50
- ☐ 50-100
- ☐ 100-200
- ☐ 200-300
- ☐ >300
- ☐ >500

2.3. How many employees hold each degree? (approximately)

- ☐ PhD
- ☐ BA or BS
- ☐ MBA, MA or MS
- ☐ Diploma / Vocational training
- ☐ Interns
- ☐ Other (list)

2.4 Budget

☐ 500.000€ - 1.000.000€ ☐ 2.000.000€ - 5.000.000€ ☐ > 10.000.000€
☐ 1.000.000€-2.000.000€ ☐ 5.000.000€ - 10.000.000€

3. Scientific production and IP management

3.1 How many scientific publications did you generate last year (2008)?

3.2. How many patents of each type do you hold?

☐ None ☐ National ☐ PCT ☐ Additional countries

3.3. How many patents are you currently applying for?

3.4. How many patents do you license to third parties?

3.5. How many patents do you license from third parties?

3.6. Do you use other IP protection measures? Which (list)?

☐ Yes ☐ No

3.7. What IP management resources do you have?

☐ Internal department ☐ Institutional services ☐ External agency (consultancy) ☐ Other (list)

4. Joint R&D projects

4.1. ¿Participa en algún consorcio público-privado de I+D?

☐ Yes ☐ No ☐ Which?

4.2. Where are your partners from, mainly?

☐ Catalonia ☐ Spain ☐ Europe ☐ Other (list)

4.3. What type of partners do you have?

☐ University ☐ Technology center ☐ Research Institute / Hospital ☐ Other (list)

5. Future growth

5.1. Have any companies (spin-offs) been created from your center?

☐ Yes ☐ No ☐ Which?

5.2. Do you plan to create any companies (spin-offs)?

☐ Yes ☐ No

5.3 How much space do you currently occupy (m2)?

☐ 500-1000 m^2 ☐ >5000 m^2 ☐ >20.000 m^2
☐ 1000-5000 m^2 ☐ >10.000 m^2 ☐ >50.000 m^2

Do you authorize Biocat to publish the name of your center in the list of participants in the study?

☐ Yes ☐ No

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