REPORT
biocat

CATALAN LIFE SCIENCES - STATUS AND ANALYSIS

COMMITTED TO VALUE-DRIVEN GROWTH

2013

Biosciences
and innovation

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HEALTH, DRIVING FORCE FOR INNOVATION

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HEALTH, DRIVING FORCE FOR INNOVATION

HEALTH, DRIVING FORCE FOR INNOVATION

Honorable Mr. Boi Ruiz
Minister of Health for the Government of Catalonia

The *2013 Biocat Report* shows that Catalonia is a leader in research and innovation in Spain, which is particularly noteworthy in the biosciences. One of the things this report confirms is the important role public health systems are destined to play around the world, but especially in Europe, in driving innovation in the biomedical arena. Of the numerous organizations involved in this activity, many are research centers, hospitals or science parks, in which the public health system plays a very important role. Demographic and economic pressures facing these systems are making research and innovation not just the best option but an absolute necessity in order to accomplish our basic goals: offering the best possible healthcare while ensuring the sustainability of the system.

This report doesn't speak only of health, because biotechnology has many applications —in energy, agrifood and industry, for example— that can have a huge impact on economic development. Of these I would like to highlight its impact on food production and improvement processes, given the enormous implications these have on general health and wellbeing. However, the report does recognize, in its various chapters, the key role the different stakeholders in the healthcare system—especially the 17 university hospitals and various hospital research institutes associated with them— have had and will continue to have in the development of the biotechnology, biomedicine and medical technology sector in Catalonia. These entities, as a whole, employ more than 5,500 researchers and stand out not only for their quality care but also for their scientific production, which puts some of them at the top of national rankings and in noteworthy positions in Europe and the world.

The study highlights Catalonia's capacities in research into oncology and mental and degenerative diseases, but also that 33% of all research groups work in hospitals and hospital institutes with significant contributions in cardiovascular diseases, diabetes, HIV-AIDS, inflammatory diseases, surgery and rare diseases, among others.

The importance of research in the Catalan hospital arena has been recognized by Spain, with five of our institutes —IDIBAPS, IDIBELL, IGTP, VHIR and IBB-Sant

Pau— accredited by the Institute of Health Carlos III. This recognition validates the prestige of the whole system, which this report looks at in depth through a wide range of indicators, from number of clinical trials carried out —more than 1,500 each year— through the number of spin-offs from this arena —twelve between 2006 and 2012.

Despite these positive indicators, the percentage of the Catalan GDP devoted to R&D is still far from the average in the European Union. Here at the Department of Health we believe it is essential to continue driving research and innovation in our health system. We must support basic research in diseases with a high social impact —above all those for which no effective therapy is currently available— but we must also boost clinical research, seeking out effective knowledge transfer, bidirectional dialog and the effective involvement of the business sector in order to have treatments and products to improve patient wellbeing.

The *2013 Biocat Report* also poses important questions: How can we involve patients more in biomedical research decision-making and processes? How can we harness the needs and knowledge of healthcare professionals to boost innovation in processes and medical technology? How can we manage —and better take advantage of— the flood of data we get from monitoring patients using new information technology? How can we develop personalized medicine that will enable use to learn the genetic basis of diseases and each patient's genomic profile?

How we are able to address to these issues as a system and as a country will determine the development of the biomedicine and biotechnology sector in Catalonia, and its future economic and social transcendence. We have more than one hundred technology companies working to serve the health sector, with a significant contribution to Catalonia's GDP. This sector has great potential for growth, given the paradigm shift underway. The pharmaceutical sector and that of medical and information technology are both players and beneficiaries of the innovation dynamics in the health sector. The ongoing dialog between these companies and stakeholders in the healthcare system is key to bringing about innovations that are needed to better care for a growing, ageing population. Furthermore, the contribution of biotechnology companies —25% of which are devoted to research and production of new therapeutics and diagnostics in Catalonia— and research centers and universities is essential to finding solutions to the new challenges we are facing, from orphan drugs to gene therapies and telemedicine.

For all of this it is extremely important to have tools like this report that give us a global overview of the sector, and highlight the various stakeholders involved along with their strengths and weaknesses; that compare what is being done in Catalonia with the overarching global trends; that identify opportunities and pose challenges; that tell us, in short, the tools we have to build a future in which we can guarantee economic growth and improved wellbeing.

COMMITTED TO VALUE-DRIVEN GROWTH

Montserrat Vendrell
CEO of Biocat

You have before you the *2013 Biocat Report. Catalan life sciences - status and analysis. Committed to value-driven growth*. Compiling, analyzing and contextualizing the information in this new edition —the third— of our report hasn't been easy and has required significant effort and vision. Our aim has been, on one hand, to demonstrate the assets here in Catalonia in this key sector, from groups conducting research at universities and research centers through clinical researchers doing trials on new molecules in patients, as well as the numerous innovative companies. On the other hand, we've aimed to analyze the global trends that unavoidably affect the evolution of the biosciences sector —emerging markets, demographic pressures, the expiration of patents on a large number of drugs and the need to reinvent prevailing research and development models— and draw a portrait of their present and future impact on the evolution of the sector here at home.

This analysis shows a multidimensional panorama, with many positive assets but also hurdles and obstacles that we must be able to address at this moment of paradigm shift and strong international competition. The two key challenges identified through this analysis are, on one hand, growth —the need for the good projects we have here to take on the necessary size to allow them to develop their full potential— but also, and especially, boosting value, understood as the capacity to transform knowledge into innovations that reach the market and into effective improvements to quality of life.

The BioRegion of Catalonia

There are 512 companies working in the life sciences arena in Catalonia, with joint turnover of €11,527 million (2011), more than 33,000 employees and volume of business that contributes to 5.8% of the Catalan GDP. Of these, 194 are biotechnology companies, 40 are pharmaceutical corporations, 54 are medical technology firms, and the rest are investors, suppliers or service companies. The information discussed in chapter II of the report shows that, since 2000, the number of companies has practically doubled. More than 80% of these are SMEs and the majority of them are micro-companies. There was a turning point in this upward trend, however, in 2010, and in 2013 the number of companies that disappeared surpassed that of those created. The impact of the crisis can be seen in the fabric of small companies, still far from marketing products and highly dependent on public grants in these early stages, many of which have disappeared.

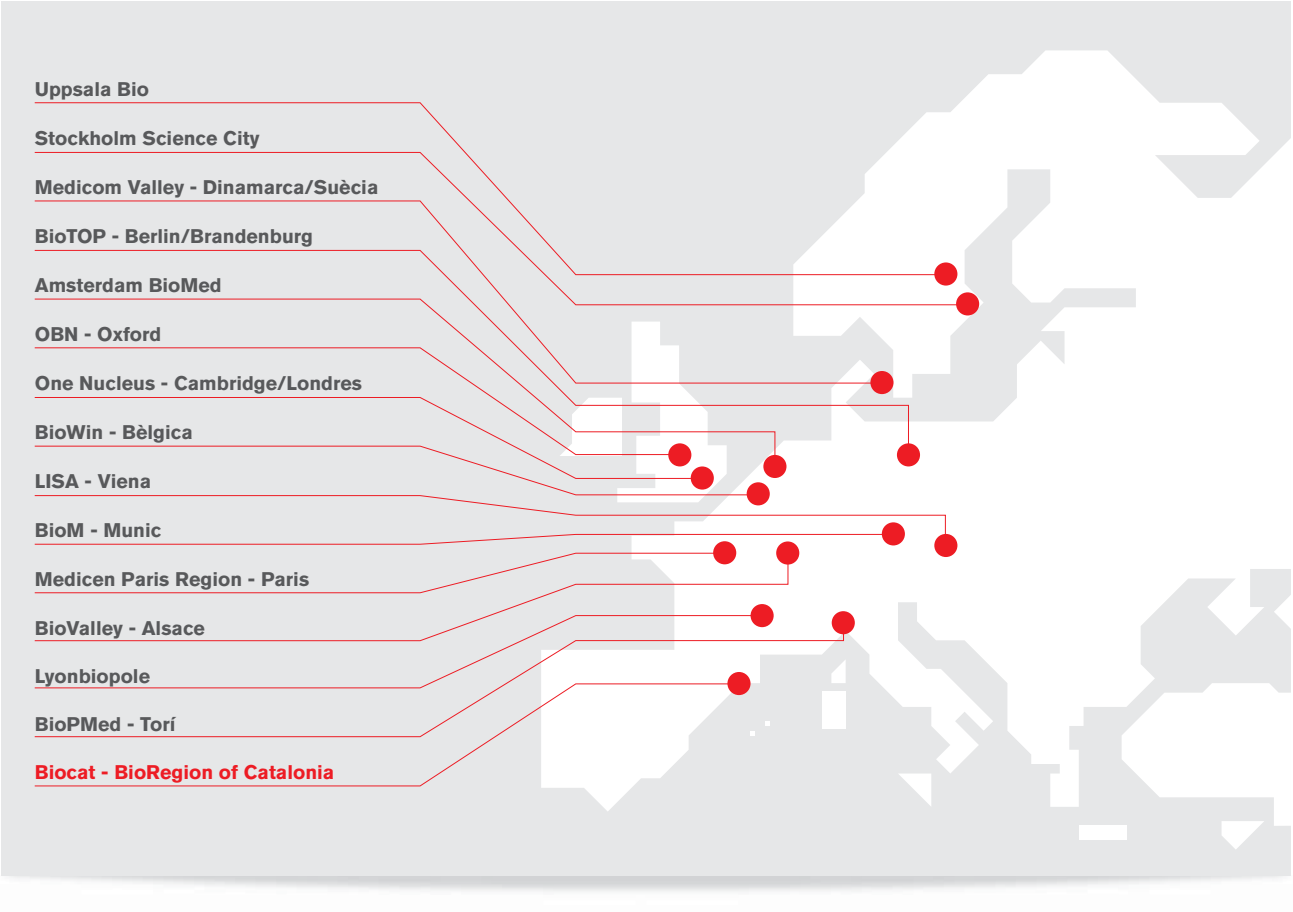
The commitment to creating local research centers governed by criteria of excellence, accountability and autonomous management has contributed to putting research in Catalonia among the leading regions in Europe. 56 centers associated with the life sciences employ 7,200 people, 4,500 of which are researchers. A good indicator of the quality of research conducted in Catalonia is the volume of international funds attracted. If we look at the number of grants from the European Research Council (Starting and Advanced), Catalonia has been awarded more than half of all those in Spain. Likewise, Catalan groups have received 28.7% of the funds granted in Spain under the 7th Framework Program. The research groups linked to the 17 university hospitals and 11 universities offering life sciences studies also contribute to these indicators.

A significant number of centers and companies in the sector are located in science and technology parks. There are more than twenty science and technology parks in Catalonia that have played a key role in the creation of a large number of companies in our sector, as well as in creating environments to facilitate interactions among new companies, large corporations and research centers. Built over the past two decades thanks to soft loans, many of them are now facing the need to pay off debt at a time when demand has stagnated. Making them sustainable in the middle and long term is a challenge we must tackle, revising their business models and the value proposition they offer.

Finally, the BioRegion boasts top-notch large-scale scientific facilities like the BSC (Barcelona Supercomputing Centre), ALBA synchrotron and CNAG (National Genome Analysis Center), which are key today for frontier research. Technology to analyze large quantities of data, resolve structures and carry out mass genome analyses will make the difference in the health systems of a not-so-distant future.

Catalonia's assets position the region among main European bioclusters with whom it maintains stable collaboration.

Main European bioclusters



Funding

Access to funding continues to be the main challenge to the sector's growth. Between January 2012 and September 2013, investment in companies in the life sciences sector in Catalonia (€43.68 million in venture capital) more than doubled that seen in 2010 and 2011 (€19.53 M). This is in addition to the €8.6 million obtained on the stock market through capital increases carried out by AB-Biotics and InKemia-IUCT Group, the two Catalan biotechnology companies traded on the Alternative Stock Market (MAB).

Despite the increase in private funding seen over the past two years, the current panorama is extremely difficult for small research-based companies, whose viability depends on access to public funding, as this funding has practically disappeared: CDTI resources for R&D projects in companies fell 50% in 2012 and that from ACC10 more than 70%. An aversion to risk taking, lack of knowledge regarding the sector, the absence of success stories and lack of appropriate incentives makes it difficult to mobilize private funding and compromises the viability of many companies in the BioRegion.

Global trends: generating value

The health sector is undergoing a profound transformation on many levels. Healthcare expenditure represents between 9% and 10% of the GDP in the most developed countries in the OECD (17% in the USA), and this percentage is growing faster than the GDP each year (3%). We're living longer and the progressive ageing of the population means that by 2050 the proportion of the population over 65 will double, making up 37% of the active population.

With nearly zero economic growth in most European countries, it is clear that it will be difficult to tackle this growing demand while maintaining the basic principles of accessibility, quality and equality if we don't bring about a paradigm shift: changes in how it is organized, measured and funded; changes in the role of doctors, patients, payers, regulators and suppliers. We must innovate in the way these stakeholders relate to each other, and each one must reconsider its function within a joint agenda. This is why now, more than ever, we need joint planning spaces that look beyond the short-term pressure we are all feeling.

This setting requires us all to be more efficient, and to rethink each link in the chain. And technology has a lot to do with this: biotechnology, molecular diagnostics, information technology, new medical devices. These allow us to personalize treatment (be more efficient), to choose the right treatment (be more effective) but also to rethink where and how therapies reach patients and, even, how patients are jointly responsible for treatment. The end goal: to contribute value —understood as the result achieved from each euro invested— to society.

As discussed in chapter III, the pressure to cut healthcare expenditure, alongside other external and internal challenges (drop in sales of more than €100,000 million due to loss of patent protection, increasing cost of research without resolving productivity), is leading the pharmaceutical industry around the world to rethink their business model. This restructuring mainly affects their R&D strategy. On a global level, Novartis, Merck, and Astra Zeneca, to name just a few, have closed whole research headquarters in order to make more efficient use of these human and financial resources.

In this case, we have also seen new collaboration methods among companies, investors, and clinical and academic institutions appear to accelerate innovation and increase the efficiency of a process that has hit its ceiling. One of them is the creation of open innovation and knowledge networks to address scientific challenges and promote participation of all stakeholders in the value chain. Agreements between pharmaceutical companies and hospitals, companies creating their own incubators, diagnostic, biotechnology and medical technology companies offering joint patient services, and patients' associations spearheading the development of specific molecules are just a few examples.

Here at home, we aren't strangers to this new panorama that has been dubbed "the new normal". Some intrinsic elements of our ecosystem make the effects of these trends even more significant.

First of all, we are **lacking local champions** to dynamize the ecosystem. Despite the presence of large national companies, like Grífols and Almirall, or multinational corporations like Amgen, the majority of our business fabric is made up of SMEs and less than 10% of companies post turnover of more than €100 million. To this we must add the difficulties in building **public-private projects**, due to either the lack of culture or the difficult situation. Let's take clinical research for example: Catalonia is a leader in clinical research in Spain, with 55,5% of all trials conducted. Catalan hospitals are capable of attracting a large number of trials individually, which are often the main source of revenue for these centers. However, other countries, with smaller hospitals, have been able to offer a highly competitive, integrated range of services, with coordinated processes and dialog. This can be seen in Scotland, which has implemented a strategy that has helped attract multinational pharmaceutical companies and large CRO to the area (Pfizer, Quintiles, etc.).

Our challenge now is to move from individual initiatives to a higher level in order to become more competitive. We can't allow ourselves to duplicate efforts, facilities and resources at this time of budget cuts, but, in particular, we must continue to build on what we have now if we don't want to be left behind.

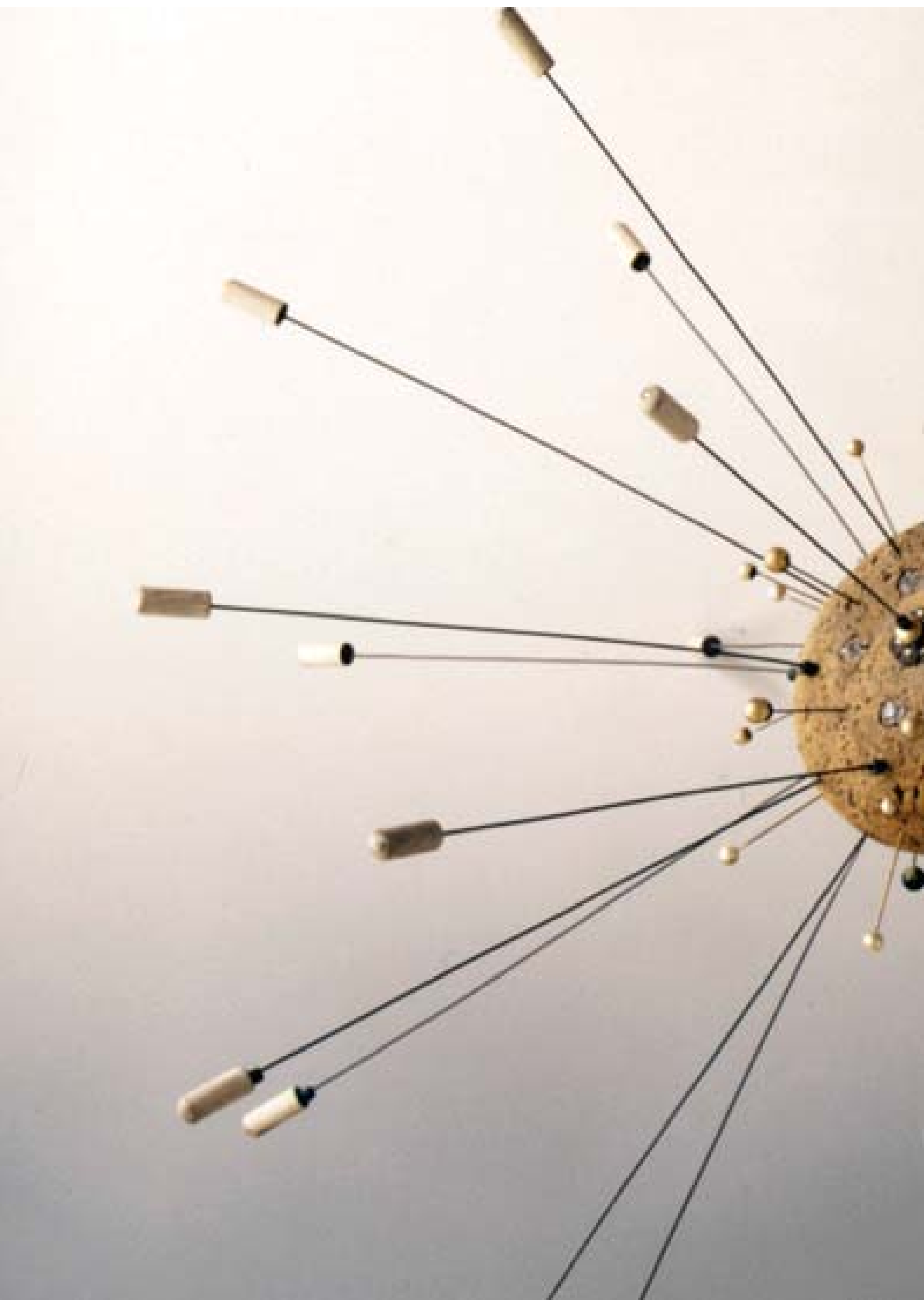
Our greatest pending task is still **transferring research**, and the capitalization of our source of innovation, which is the clinical arena. There continues to be a disconnect between business and research, and too large a gap between our indicators regarding scientific excellence and innovation. Israel, for example, which isn't much bigger than our country, generates 20 times more start-ups from research centers. The unemployment rate is 6.5%, compared to 22.8% here at home. Beyond the driving force of its defense industry, Israel has been able to develop a knowledge-transfer system with two key elements: a top-down vision, with ongoing commitment from the government in research and transfer; and the creation and endowment of public-private bodies around the centers that generate knowledge that are charged with transferring the results.

In Europe, under the framework of Horizon 2020 and the RIS3 strategy (Regional Innovation Smart Specialization Strategy), instruments are aligning in this direction. The European Union wants its research investment to have a greater impact on productive innovation, and a significant part of the €80,000 million that will go to the Horizon 2020 program between 2014 and 2020 will move in this direction, as will the more than €2,500 million that will go to the European Institute of Innovation and Technology. Accessing these funds will be key to growth in the coming years.

It is difficult, in a nation in crisis and an environment of risk, to attract private international capital. The role of local investors, spearheading new transactions, the vision of pharmaceutical companies, searching for innovative projects in their surroundings, and the growing interest in instruments like the MAB will play a key role in this process.

We've seen significant growth over the past 15 years, as shown in this report (see also previous reports from 2011 and 2009), as a result of good economic times and a combination of elements in the ecosystem. However we now need a true, ongoing commitment. In this time of international, financial and economic crisis (particularly in Spain), we need brave decisions and explicit goals that will allow us to prioritize the basis on which we want to grow. We have more

than enough assets to make the biosciences a driving force for the economy in Catalonia, but we have to think as a whole. We have to believe it. We need a daring strategy, for the middle and long term, because we must rethink many of the things we do and how we do them. We need incentives to align our goals and encourage investment, mobilizing existing resources. We need a vision that doesn't penalize risk, and that facilitates individual decision-making, by entrepreneurs and business people, managers and politicians. We must analyze each process and each situation, identifying the optimal goal, which must be to generate value.



I.
THE BIOREGION OF CATALONIA 2011-2013
EXECUTIVE SUMMARY

THE BIOREGION OF CATALONIA 2011-2013

Adela Farré
Managing editor of the *2013 Biocat Report*

Over the period covered by this report (June 2011-June 2013) many key indicators for the BioRegion showed positive evolution: there was a slight increase in employment in companies in the sector (biotechnology, pharmaceutical, medical technology, and specialized providers and service companies); the amount of private funding for business projects rose significantly (through venture capital managers and the Spanish Alternative Stock Market, MAB); Catalan leadership in life sciences research in Spain was consolidated, as was the area's international competitiveness (with indicators like the number of publications, number of centers with the "Severo Ochoa" seal of excellence, grants from the European Research Council, and breakthroughs achieved by numerous research projects in areas like cancer, malaria, AIDS and diabetes, among many others); and the number and size of public-private partnerships has also grown (with companies, research centers and hospitals involved).

However, there are also indicators for this period that should serve as a serious warning: from January 2012 to June 2013, the number of companies destroyed in the BioRegion surpassed those created for the first since the biocluster was created; 2011 saw the end of the upward trend in turnover posted by companies in the sector that had lasted since 2007; and the availability of public funding for start-ups and R&D-intensive companies, which have a long time to market, fell between 50% and 75%. This data demands appropriate measures be taken and structured through a resolute policy to promote the sector, as highlighted in the introductory article by the CEO of Biocat.

To do so requires having detailed information on the various **players** working in the life sciences in Catalonia; identifying the system's strengths and weaknesses in **research, transfer and innovation** —as well as the overarching global trends framing the present and future state of the BioRegion—; knowing what **funding** is available to these projects, with information as to both the resources invested and the characteristics of those who manage them; and, finally, exploring the opportunities available in the various life sciences **markets** —health, agrifood, energy, etc.—, knowing how Catalan companies and organizations are taking advantage of them and how they are tackling much-needed **internationalization** in a sector that is, by definition, global.

To this end, the contents of the *2013 Biocat Report* have been structured into four chapters, with a selection of the most relevant data outlined in this summary.

PLAYERS IN THE BIOREGION OF CATALONIA

- There are 512 **companies** in the BioRegion of Catalonia: 194 biotechnology businesses, 40 pharmaceutical corporations, 54 medical technology companies, 105 suppliers and engineering firms, 96 professional services and consultancy companies and 23 investors.

- Catalonia has **56 research centers** with activity in the life sciences or related disciplines (nanotechnology, photonics, etc.), **17 university hospitals**, and **11 universities** that offer degrees in the life sciences (of a total of 12). There are also **two large-scale research facilities** —the Barcelona Supercomputing Center (BSC-CNS) and the ALBA-CELLS Synchrotron—, **118 scientific and technological platforms**, **12 technology centers** and **16 science and technology parks** with activity in biosciences (11 of which are home to companies in the sector).

- The **194 biotechnology companies** focus on researching and developing therapeutics and diagnostics (48), providing R&D services (73), and various areas —that often overlap— like veterinary (35), agrifood (31), cosmetics (9), industrial biotechnology (9) and the environment (5).

- **20% of the companies that carry out R&D in biotechnology** in Spain are found in Catalonia, with the main application of their research being in human health.

- Diseases of the **central nervous system** (27%), **oncology** (22%) and **cardiovascular diseases** (19%) are the focus of R&D in pharmaceutical companies and biotechnology firms that develop drugs and diagnostics.

- In **medical technology**, the most relevant subsectors are the production of **reusable medical instruments** and **surgical implants**, both *active* (pacemakers and other similar products) and *non-active* (surgical prosthesis, dental implants, etc.). Half of all suppliers and engineering firms (52) carry out activities in medical technology (distribution, laboratory equipment, instruments, electronics and software).

- The **23 specialized investors** in the life sciences include 10 venture capital funds, 7 networks of business angels and half a dozen corporate funds and investment banks, which in 2012 managed transactions valued at more than €37 millions.

- More than **80% of the companies in the BioRegion of Catalonia are SMEs**. 43% of all companies are microenterprises, with fewer than 10 workers and turnover under €2 millions per year. There are 60 large companies in the BioRegion, which are mostly national and international biopharmaceutical companies. 61 companies are subsidiaries of multinational corporations (12% of the total).

- As a whole, companies in the BioRegion posted **operating revenue of €11,527 millions** in 2011, down 3.74% from 2010. Pharmaceutical corpora-

tions saw turnover of €6,240 millions, biotechnology firms, €2,426 millions, and medical technology companies, €1,555 millions.

- Companies in the life sciences sector contribute **5.8% of Catalonia's GDP**. The volume of business generated by biotechnology (biotechnology companies and those that use biotechnology) is estimated at €5,000 millions, making up 2.5% of the Catalan GDP.

- Companies in the BioRegion employ **a total of 33,689 workers** (2011), 8,169 working in biotechnology firms, 14,427 in pharmaceutical corporations and 5,884 in medical technology companies. A total of 2,493 people carry out R&D activities in biotechnology (1,455 researchers and 1,038 technicians and aides). The 56 research centers have a joint staff of **7,200 people**, 4,500 of which are researchers, and the 17 Catalan university hospitals have more than 3,500 researchers devoted to biomedical research.

- Catalan **biotechnology companies** devoted **€154.8 millions in internal expenditure to R&D** (2011), 28.8% of all R&D spending by biotech companies in Spain. This investment was basically covered with funds from within the company (71%), while the government contributed only 14%.

- **Between 2000 and 2013, the number of companies in the BioRegion practically doubled**: in 1999 there were 261 companies and in 2013, 512. Over this period, 59 companies were destroyed (closing down, being acquired by another company or moving out of the region).

- Biotechnology and pharmaceutical companies in the BioRegion of Catalonia have a pipeline of **227 therapeutic and diagnostic products** for human health and **122 medical technology products**.

- In 2011, 9.1% of all Catalan companies active in **biotechnology** applied for a total of **140 patents**.

- The 56 Catalan research centers working in the life sciences have a joint budget of more than **€380 millions** per year and have **more than 900 active research groups** and more than 360 research projects; their work is noteworthy in the areas of **bioinformatics**, **genetics/genomics** and **nanotechnology** and in the therapeutic areas of **cancer** and **neurodegenerative diseases**.

- More than **30,000 students** enrolled in life sciences and health degrees in the 2011-2012 academic year at **11 Catalan universities**: 9,595 undergraduate students in the life sciences, 17,377 undergraduate students in health sciences, and 3,163 students in 90 masters degrees.

- 24% of the companies in the BioRegion are located in science and technology parks. **Barcelona and its metropolitan area concentrate 90% of the sector** and, more specifically, the Catalan capital is home to 51.6% of companies (264) and half of all research centers (27).

RESEARCH, TRANSFER AND INNOVATION

Human health is the main area in which biotechnology is applied around the world, and also in Catalonia. But, due to internal and external pressures, this arena is undergoing a profound transformation that is leading to new models in several areas: research management, collaboration among the stakeholders involved, convergence of technology, patient participation, valorization and reimbursement for products, etc. This chapter frames Catalonia's assets in research, technology transfer and innovation within overarching global trends.

- The **percentage of the Catalan GDP devoted to R&D (1.55%)** is clearly above that of Spain as a whole (1.33%), but still far from the average of the EU-27 (2.03%).

- **Internal R&D expenditure in Catalonia in 2011 was €3,104 millions**, 21.9% of all that in Spain, surpassed only by Madrid (26.5%).

- **Investment by Catalan companies in R&D** (€1,733 M in 2011) **is above the Spanish average**, but still far from the levels of private investment seen in the most innovative countries in Europe.

- Through 2012, Catalan **research bodies** had received a total of **€660 millions through the EU's 7th Framework Program** (7FP), 28.7% of all these funds received in Spain.

- In Spain as a whole, companies receive the most 7FP funds for R&D (33.2%), but **in Catalonia companies only received 18.3% of funds** through this program, an indicator that must clearly be improved.

- Catalonia received **52% of the research grants from the European Research Council** (ERC) awarded in Spain (2007-2012).

- In total, the **102 ERC grants** received by scientists working in Catalonia over the 2007-2012 period **awarded €189.87 millions**, €53.22 millions of which went to 32 projects in the life sciences. 54 of the 102 researchers that received these grants belong to the ICREA program.

- **Internal expenditure in R&D in the life sciences** in Catalonia is more than **€850 millions per year**, making up 26% of all internal R&D expenditure in Catalonia (€3,104 M in 2011).

- Catalonia stands out for its **strengths and capacities in oncology research**, which cover the whole value chain from basic research in epigenetics and cell modifications through marketing diagnostic tests and drug-delivery systems. This has led to a unique, groundbreaking initiative for the application of personalized medicine in cancer, the **Barcelona Patient Cancer Platform** (BPCP).

- Catalonia produced 19,750 scientific publications in 2012, which is **2.9% of all those in Europe** and **0.79% of global scientific production**.

- Recognition of **six Catalan research centers** as **"Severo Ochoa" centers of excellence**, of a total of 13 in Spain, is a positive indicator of the level and impact of the Catalan research system.

- **54 spin-offs in the life sciences arena** were created in Catalonia between 2000 and 2013 (universities, 29; research centers, 9; hospitals, 6; joint initiatives, 10).

- Between 1997 and 2011, 19,152 patent applications were submitted in Spain for pharmaceutical inventions, biological products and medical technology products (approximately 1,300 per year). **Catalonia generates 20% of all patent applications in the life sciences**, a percentage below its weight in research.

- **Companies** generate the most IP in this sector, with **51% of all patent applications in 2011** and **56%** of those in **2012**.

- There has been growing interest in **public-private partnerships (PPP)**. In 2012, four significant agreements were signed involving research centers, hospitals and companies: CRG-Sanofi; Hospital Clínic-CSIC-Histocell; Hospital Clínic-Olympus; and IRB Barcelona-Novo Nordisk-EFSD.

The conclusions drawn in this chapter show that the **global paradigm shift** in the biopharmaceutical industry **is also arriving to Catalonia**: with strategic research agreements and large national pharmaceutical companies joining the shareholders of small biotech companies; with growing interest in rare diseases (Catalan companies have **10 EMA orphan drug designations**, out of the 15 in Spain) and with the opening up of emerging markets, etc.

However, with an inefficient knowledge-transfer system and most companies being very weak financially and facing difficulties in accessing resources and the market, we must make a concerted effort to align strategies, identify strengths and find the right partners to compete internationally, with sights set on Europe, which is emerging as the only alternative to the political and economic weakening of the Spanish research and innovation system.

FUNDING

Over the period covered by the *2013 Biocat Report,* private capitalization in the life sciences sector in Catalonia grew significantly, at the same time as public grants were cut drastically. Investment is growing at the Catalan life sciences sector, despite the shrinking venture capital and private equity markets in both Europe and Spain, in line with the determined commitment global markets are making to biotechnology and innovative medical technology.

- Between 2009 and 2013, **venture capital** investment in companies in the BioRegion **grew five-fold**. In 2012, companies attracted more than €18.08 millions in VC and €5 million on the MAB (Spanish Alternative Stock Market). From January to September 2013, they obtained €25.6 million in VC and €3.62 million on the MAB.

- The **€17 million investment** in medical technology company **STAT-Diagnostica**, led by Ysios Capital, is the largest to date in the BioRegion.

- In December 2012, **InKemia IUCT Group** became the second Catalan company in the sector to be traded publicly on the Spanish **Alternative Stock Market**. In July 2013, they successfully closed a €2.5 million capital increase, which will go to fund their international expansion and the **IUCT Emprèn** knowledge capital fund.

- Large companies in the sector are beginning to play an active role in capitalization: **Almirall** joined the equity holders of **AB-Biotics** —which is also traded on the MAB— in a capital increase the biotech firm closed in December 2012. And **Grífols** holds a majority stake in **Nanotherapix** and **VCN Biosciences** —in addition to investment in Spanish and foreign companies like **Araclon**, **Progenika** and **Aradigm**.

- Catalan networks of **business angels invested €2.5 millions** in the health and life sciences in 2011 and 2012.

- Over the 2011-2012 period, Catalan **VC management funds** carried out **23 transactions outside of Catalonia** (out of 47 made in the life sciences sector). **36% of all transactions** involved **medical technology companies**.

- The **most active investment funds in Catalonia** in the life sciences sector have joint resources of more than **€136 million**.

The growth of private investment over the past two years is a positive sign of the sector's maturity and that of its business projects. However, new entrepreneurial projects will need proper support in order to maintain and increase interest from national and international investors. In the coming years it will be a key point that business growth allows solid return of investment for early stage investors, fostering the flow of reinvestment. In this regard, IPOs on the MAB are becoming an interesting option for capitalization of companies in the BioRegion.

MARKETS AND INTERNATIONALIZATION

Knowledge generated through biotechnology research can be applied in many areas and, as a result, in many *markets*. That of human health carries the most weight in Catalonia, but there are great opportunities in areas like animal health, agriculture, food and energy. On the other hand, the degree of internationalization of Catalan companies in the sector is significant, with a slight tendency towards the European and US markets among a highly diversified group of countries where emerging markets are an option for the future yet to be explored.

- If we can align the interests of industry with capacities in public and private research, the **€370 millions the pharmaceutical industry invests in R&D in Catalonia** can play a significant role in the growth of the life sciences sector.

- Despite the opportunities available in the **biosimilars** market for biotech companies, pharmaceutical corporations looking to incorporate these into their pipeline, and R&D service companies (CRO and CMO), companies in the BioRegion have minimal presence in this arena.

- The **35 Catalan companies** working in **biotechnology for animal health** posted joint turnover of €400 millions in 2012 and employ 1,300 workers.

- In 2013, companies began to market foods made with ***Tritordeum***, the first **newly created cereal** for human consumption, developed in Catalonia.

- Spain is the third largest European producer of **biodiesel** and the fifth of **bioethanol**, but **Catalonia's participation in this market is merely anecdotal**, despite having been a pioneer in introducing biofuels in the nation.

- The EU aims to boost production and use of **3rd generation biofuels** (made with waste materials, fats and algae), which opens up new opportunities for Catalan companies and research bodies.

- **65% of all biotech, pharma and medtech companies** in the BioRegion sell products on **international markets**. Most of the companies that don't have products on the market have signed scientific or technological collaboration agreements with international partners.

- **France**, **Germany**, **the United States** and **Italy** are the priorities for international activity (sales and collaborations) among companies in the BioRegion, although efforts are geographically quite scattered.

- The BRIC countries —**Brazil**, the **Russian Federation**, **India** and **China**— and the **USA** are the countries most companies in the BioRegion are interested in for expanding their internationalization activities.

- **38% of companies in the BioRegion with products on the market** see more than 50% of their turnover from international markets.

II. STAKEHOLDERS IN THE CATALAN LIFE SCIENCES SECTOR

STAKEHOLDERS IN THE CATALAN LIFE SCIENCES SECTOR

The BioRegion of Catalonia constitutes a complex ecosystem of nearly one thousand organizations associated with the biotechnology and health arenas, from basic research through market. The bulk of the data compiled in this chapter comes from the **Biocat Directory**[1], which has a total of **1,403 entries**. These correspond, on one hand, to **830 organizations**, including **companies** (biotechnology, pharmaceutical, medical technology and service firms, in addition to suppliers and investors), **research centers, hospitals, universities, science parks, technology centers, scientific and technology platforms** and various **support bodies**. On the other hand, the Directory also has a specific search engine for the **573 research groups** working at research centers and institutes, universities and hospitals.

The statistics and graphs in this chapter are based on the classification of the organizations in the Biocat Directory. Companies are categorized by their main sector and the rest of the organizations fall under the category Public / Non-Profit Organization / Medical Facility, and are then classified by subsector (Foundation, Governmental Organization, Hospital, Industry Association, Institute, Private Clinic, Research Facility, Science / Technology Park, University, Other). The ongoing process of keeping this database up to date and the fact that the subsector field allows for multiple answers may lead to small differences in the total number of organizations listed in this report and the figure given in the Directory search engine. If not otherwise noted, all data from the Biocat Directory was collected on 30/6/2013.

Beyond the Biocat Directory, the data provided in the following text on each category of stakeholders has been compared with benchmark external databases and studies or taken from them. In particular, data for 2011 on the companies in Catalonia has been taken from the Biotechnology Survey carried out each year by the Spanish National Statistics Institute (INE), as well as the Survey on Technological Innovation in companies. Another key source for the economic and employment data was the SABI database (Iberian Balance-sheet Analysis System), which compiles financial and economic information on more than one million companies in Spain and Portugal. In this chapter, and those that follow, the source of the data is noted in each case, as well as the specific selection and validation criteria where necessary.

1. The Biocat Directory underwent a complete overhaul in late 2012, adopting a new classification system based on the main international database in the life sciences sector, BiotechGate (www.biotechgate.com), owned by the company Venture Valuation, with which Biocat has a collaboration agreement. It is a certified classification system used by the main international stakeholders, which facilitates, among other things, comparison of the BioRegion of Catalonia with other benchmark clusters. Thanks to this agreement, pipeline and financial data on the companies has been added to the Biocat Directory, which was previously unavailable. Additionally, taking advantage of this revision of the data to be integrated with that of BiotechGate, a decision was made to create a separate search engine for research groups working at Catalan universities, hospitals and research centers.

A. COMPANIES

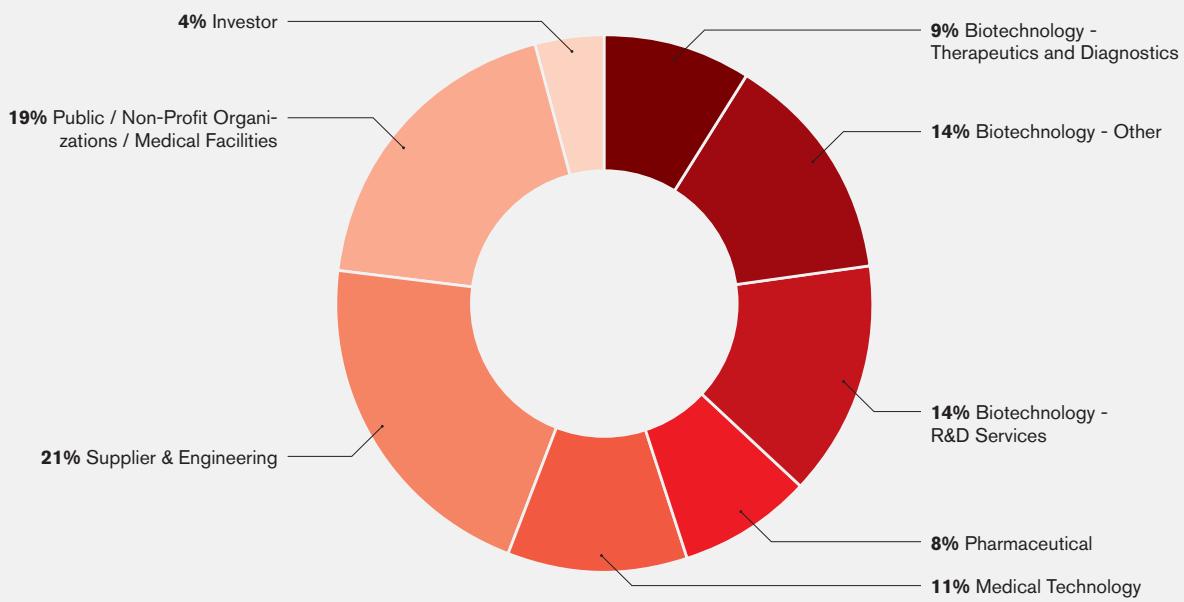
A total of **512 companies** work in the life sciences sector in Catalonia, and can be broken down into the following categories:

Table1 **Number of companies in the BioRegion by main sector**

Biotechnology – Therapeutics and Diagnostics	48
Biotechnology – Other	73
Biotechnology – R&D Services	73
Total biotechnology firms	194
Pharmaceuticals	40
Medical technology	54
Supplier & engineering	105
Professional services and consulting	96
Investors	23

Font: Directori Biocat

Graph 1 **Percentage of companies in the BioRegion by main sector**

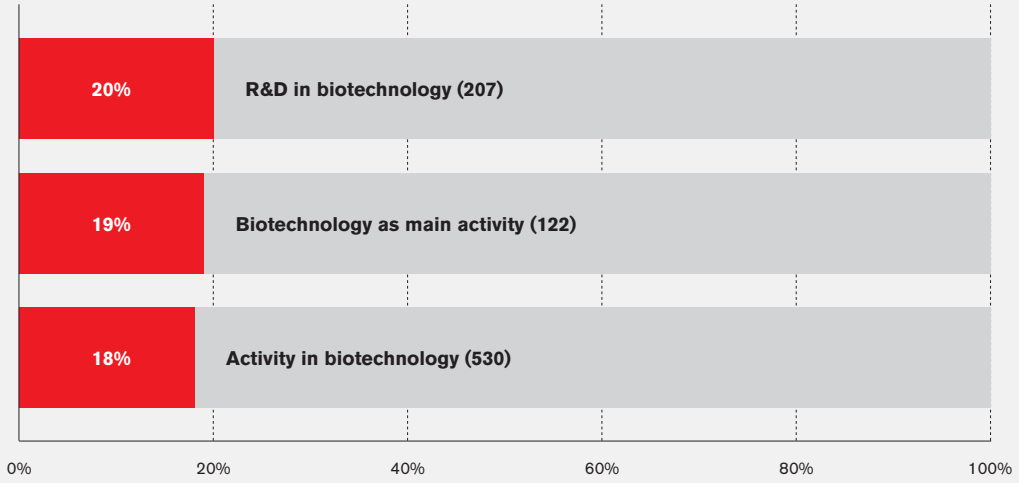


Source: Biocat Directory

Regarding **biotechnology companies**, the data from the Biocat Directory (194 companies, including those in therapeutics and diagnostics [48], other areas [73] and R&D services [73]) is consistent with the information collected through the innovation survey carried out each year by the Spanish National Statistics Institute (INE). According to the data from the INE on Catalonia for 2011,[2] the region has 530 companies that work in biotechnology, 207 of which carry out R&D activities in biotechnology.

According to the INE survey, biotechnology is the main or only sector of activity for 122 Catalan companies, for 111 companies it is a secondary line of action, and for 297 it is only a tool necessary for production. The INE data, which is also used for the Asebio Report,[3] ranks Catalan biotechnology companies first in the country with regards to number of companies with some activity in biotechnology (17.52%, ahead of Andalusia [10.89%] and Madrid [6.71%]), to those whose main sector of activity is biotechnology (18.54% in Catalonia, followed by Madrid [15.49%] and Andalusia [13.05%]), and to those companies who carry out R&D in biotechnology (207 in Catalonia of a national total of 1,041, accounting for 19.88%).

Graph 2 **Catalonia as percentage of Spanish total regarding companies with…**

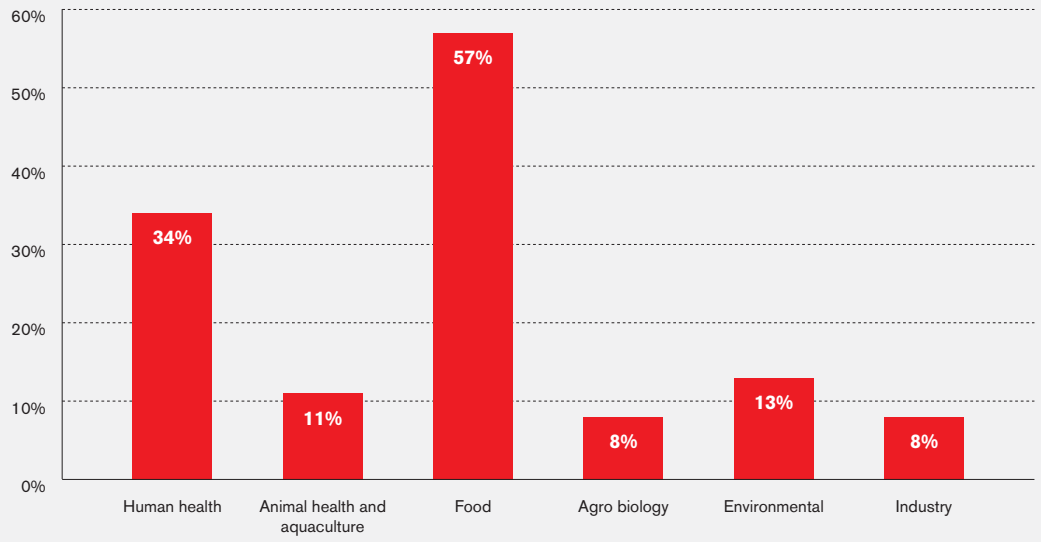


Font: INE. Statistics on Biotechnology Use 2011.

2. The INE innovation survey is censual in nature and is sent to all companies in the country. It includes a section on biotechnology sent to companies listed in the corresponding INE directory (409 in Catalonia in 2011) and, later, to any additional companies that list use of biotechnology on the general innovation survey. Both the general innovation survey and the specific one on biotechnology included under the National Statistics Plan and must be filled out by companies. The latest data available is from the 2011 fiscal year, analysis of which was finished in December 2012.
3. Informe Asebio 2012, Asociación Española de Bioempresas, Madrid, July 2013 (http://www.asebio.com/es/documents/Asebio_2012_web.pdf)

The most important sector in terms of use of biotechnology is food, a sector comprised of 46% of the companies that list themselves as users on the INE survey but don't carry out R&D activities (a percentage that is closer to 57% if we include both users and those that do research). However, human health is the main sector of activity of companies that carry out R&D in biotechnology, as highlighted both in the data compiled from the INE survey and that from the list of biotechnology firms in the Biocat Directory.

Graph 3 **Percentage of companies (R&D and users) by sector of application of biotechnology**

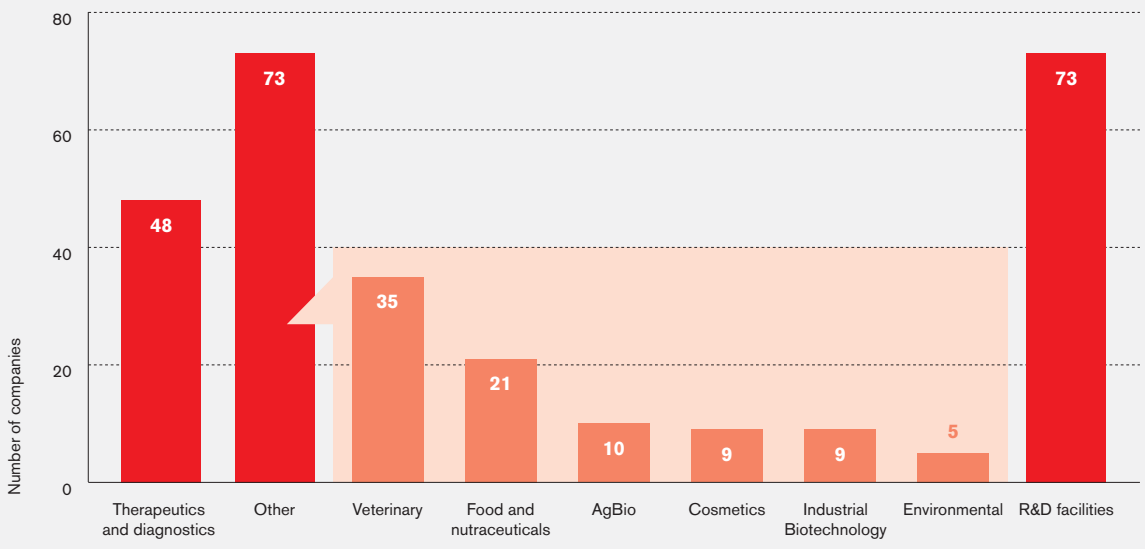


Source: INE. Survey on use of biotechnology 2011. Segmentation of data for Catalonia.

The Biocat Directory lists 194 biotechnology companies (table 1). The main activity of 48 of these (25%) is research and development of new therapeutic and diagnostic products, 73 (37.5%) work mainly in the areas of green and white biotechnology, and the other 73 companies (37.5%) focus on the provision of R&D services. 58% of the listed biotech firms carry out R&D on new products and services.

More specifically, the 73 companies in the Biotechnology – Other category (graph 4) carry out activities in the areas of veterinary (35), food and nutraceutics (21), agrobiotechnology (10), cosmetics (9), industrial biotechnology (9) and the environment (5).

Graph 4 **Primary therapeutic areas of Catalan biotechnology companies***



* Each company may choose more than one category of Biotechnology – Others

Source: Biocat Directory

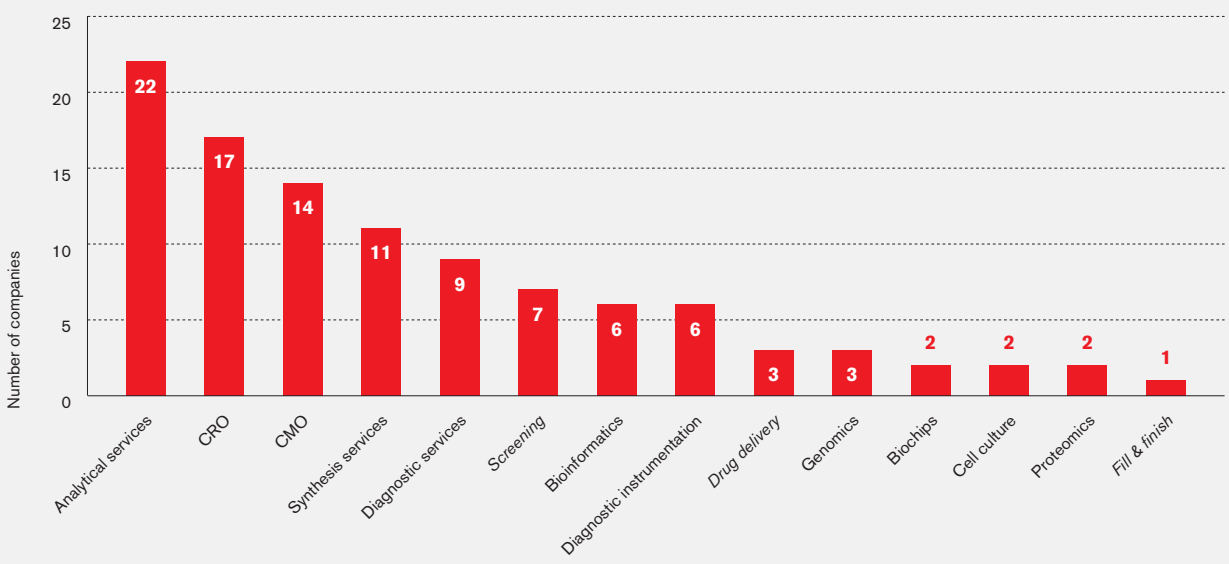
The activities carried out by Catalan biotech firms that offer R&D services for third parties vary widely (graph 5) and, moreover, most of these companies (75%) have two or three services in their portfolio.

Analytical services, mostly geared towards the medical-hospital setting and clinical research, and contract manufacturing organizations (CMO) and contract research organizations (CRO) are the main activities of this segment of biotechnology companies.

Therapeutics and diagnostics

Graph 6 gives an overview of the activity of biotechnology companies devoted to developing new drugs and therapeutic products in the BioRegion of Catalonia. 50 of the 88 companies that make up this group research or produce compounds based on either synthetic or biological small molecules, which are the base of most drugs. No other area of activity particularly stands out, with an average of 12-15 companies in each of the areas of antibodies, anti-infectives, drug delivery, molecular diagnostics, peptides and proteins. The relatively small number of these companies working in cell and gene therapies is noteworthy, and only one company works in biosimilars. Most companies work in 2 or 3 areas, but the large pharmaceutical companies —Novartis, Bayer, Sanofi, Boehringer, etc.— do so in at least 6 or 7.

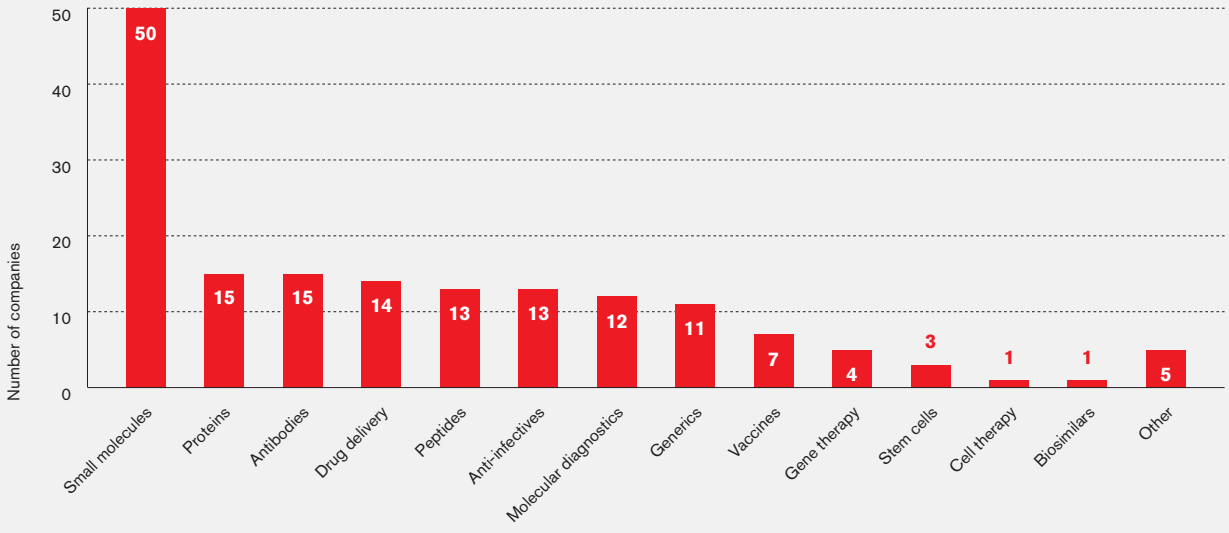
Graph 5 **Areas of activity of biotechnology companies that offer R&D services***



* Each company may choose more than one category

Source: Biocat Directory

Graph 6 **Areas of activity of companies working in therapeutics and diagnostics (biotech and pharma)***

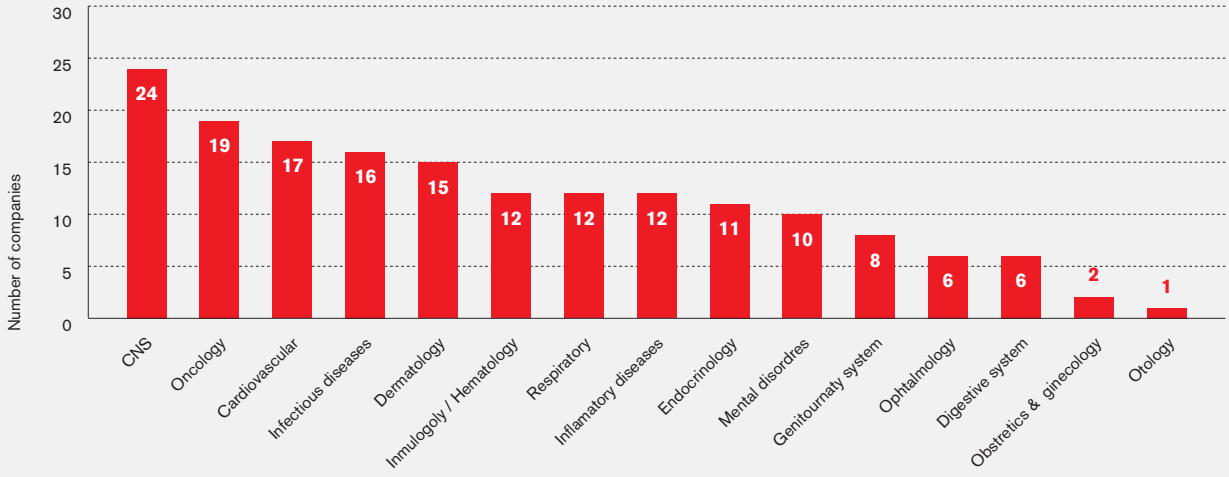


*Each company may choose more than one category.

Source: Biocat Directory

Pharmaceutical and biotechnology companies devoted to the production of drugs and diagnostics mainly focus their R&D on diseases of the central nervous system (CNS) —Alzheimer, Parkinson, multiple sclerosis, etc.— (27%), oncology (22%) and cardiovascular diseases (19%), as shown in graph 7. As analyzed in the following chapter, R&D in cancer is one of the great strengths of the BioRegion of Catalonia, which has significant assets throughout the value chain, from basic research through highly specialized companies, with hospitals playing an important role in translational and clinical research. In terms of companies, research and production of gene-based diagnostic kits and research of new drug-delivery systems is particularly significant.

Graph 7 **Therapeutic areas of pharmaceutical and biotechnology companies in the BioRegion***



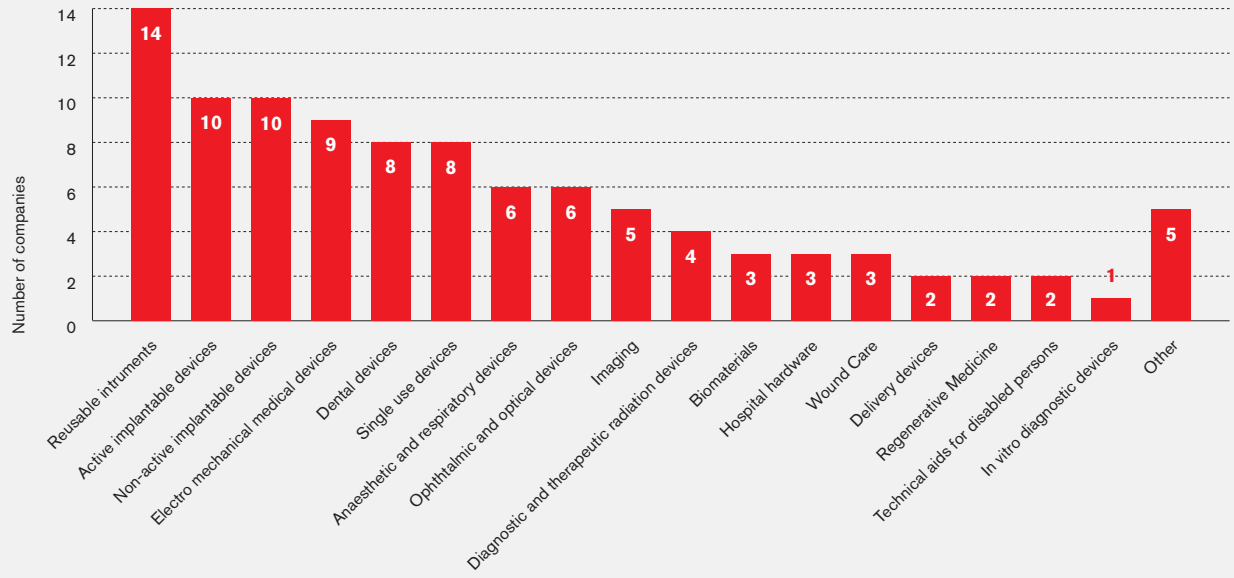
*Each company may choose more than one category.

Source: Biocat Directory

Medical technology

The BioRegion of Catalonia Directory lists **54 medical technology companies**, whose activities are broken down in graph 8. The two most relevant subsectors are production of reusable medical instruments —a highly varied category that ranges from surgical instruments (scalpels, clamps, forceps, etc.) to furniture specifically for medical use and innovative devices for endoscopy, for example— and products for surgical implants, both *active* (pacemakers and similar) and *non-active* (surgical prostheses, dental implants, etc.). 55% of these companies carry out activities included in two or more categories, which are normally related. Thus, for example, companies that produce non-active implants also make all of the reusable instruments needed for implants, or those that produce electro-mechanical devices, for respiratory control and treatment for example, also produce the single-use items they require.

Graph 8 **Areas of activity of medical technology companies***



*Each company may choose more than one category.

Source: Biocat Directory

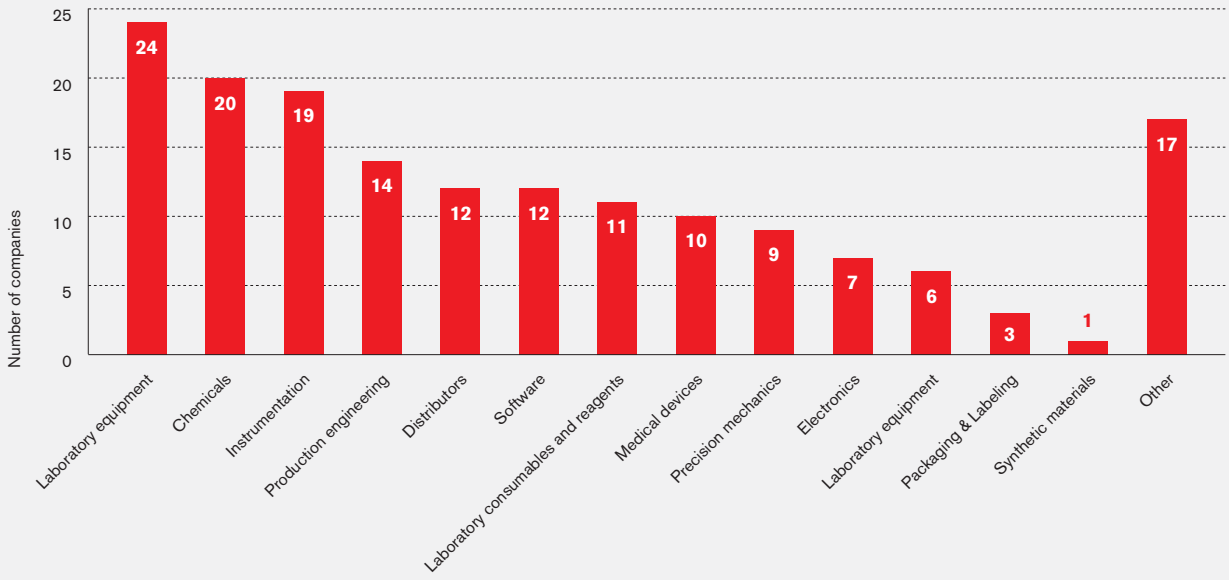
This group includes some of the companies that have come out of initiatives like BioEmprenedor XXI,[4] which is jointly promoted by Biocat, la Caixa and Barcelona Activa: companies like Better Care, a spin-off of Hospital Universitari Parc Taulí in Sabadell, and Transmural Technologies, a spin-off of Hospital Clínic, both from the 2008 edition, or Endoasic Technologies, a spin-off of the University of Barcelona that was a finalist in the 2011 edition, and Regenear, the winner of that edition created by two researchers from Institut Químic de Sarrià (IQS).

Under the classification used in the Biocat Directory, companies with links to the medical technology arena that focus on distributing and marketing medical devices or manufacturing instruments for hospital laboratories are listed under the heading **Supplier & Engineering**. As shown in graph 9, the bulk of the companies in this group distributes **medical devices** (10) or produces and distributes **laboratory equipment** (24) or **instruments** (18). Furthermore, the medical technology category also includes part of the companies classified under the headings Electronics, Software and Other, which offer products like computer software to control clinical processes related with nutrition, oncology or pediatrics, telemedicine products (remote follow-up and self-control of health indicators), products for animal health (chips, scanners, etc.), for treatment and for management of medical imaging, etc. In total there are **52 companies** in addition to the 54 mentioned previously that research and produce medical technology.

4. Of the 34 companies created through the BioEmprenedor XXI program (see Report 2007-2012. BioEmprenedor XXI on http://www.biocat.cat/sites/default/files/Memoria_BioEmprenedorXXI_2012_v1_cat.pdf) 31 are currently active, working in the fields of Biotechnology – Therapeutics and Diagnostics (10); Biotechnology – Other (3); Biotechnology – R&D Services (10); Medical technology (6); and Supplier & engineering (2).

Thus, we have more than one hundred technology companies (106) that work in the health services sector, which has great potential for growth due to the paradigm shift underway. As mentioned in the following chapter, we are moving from disease-focused medicine to that geared towards people and prevention, in which patients take control of their health. To do this, medical technology is key, as are new image diagnostic techniques, minimally invasive surgery and telemedicine.

Graph 9 **Areas of activity of supplier & engineering***



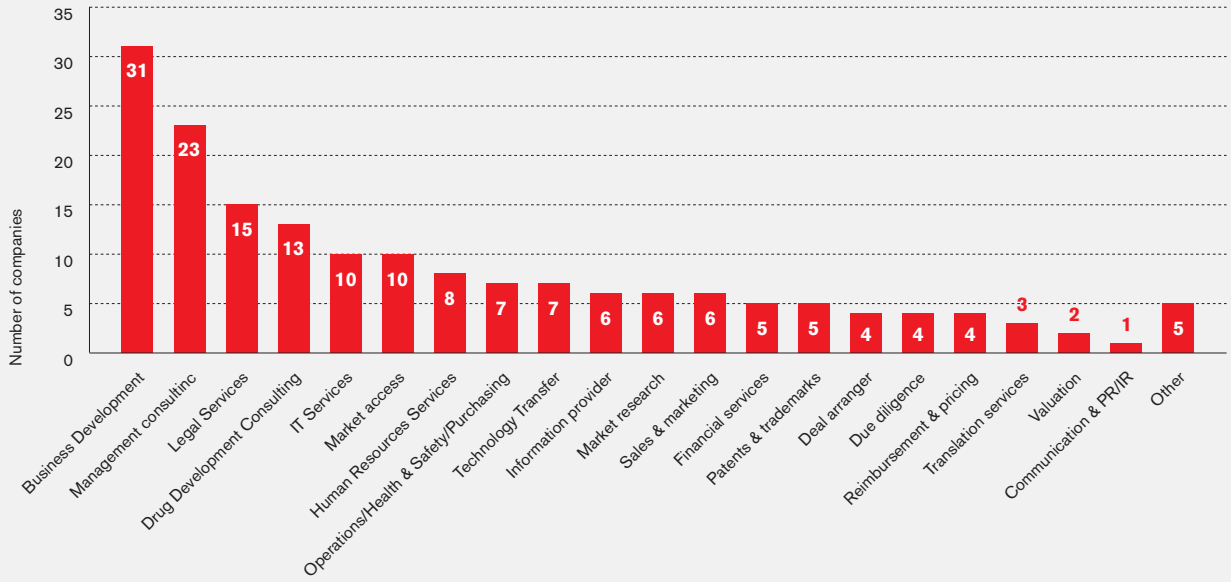
* Each company may fall into more than one category

Source: Biocat Directory

The companies in the BioRegion also include those providing **professional services and consulting** (graph 10) and another group made up of 23 specialized investors. In this case, most companies also offer a wide variety of services —above all those in the business development and management consulting categories, which basically act as full-service agencies to guide new biotech and med-tech companies through all the stages of development— and the areas of human resources, legal services and information technology services show higher specialization among the companies included therein.

Regarding **investors**, the BioRegion has companies that manage venture capital funds, 7 networks of business angels and half a dozen corporate and investment-bank funds. Chapter IV of this report analyzes the activity of these stakeholders that, as a whole, managed operations valued at €37 millions in the biotechnology and biomedicine sector in 2012.

Graph 10 **Areas of activity of professional services and consulting***



* Each company may fall into more than one category

Source: Biocat Directory

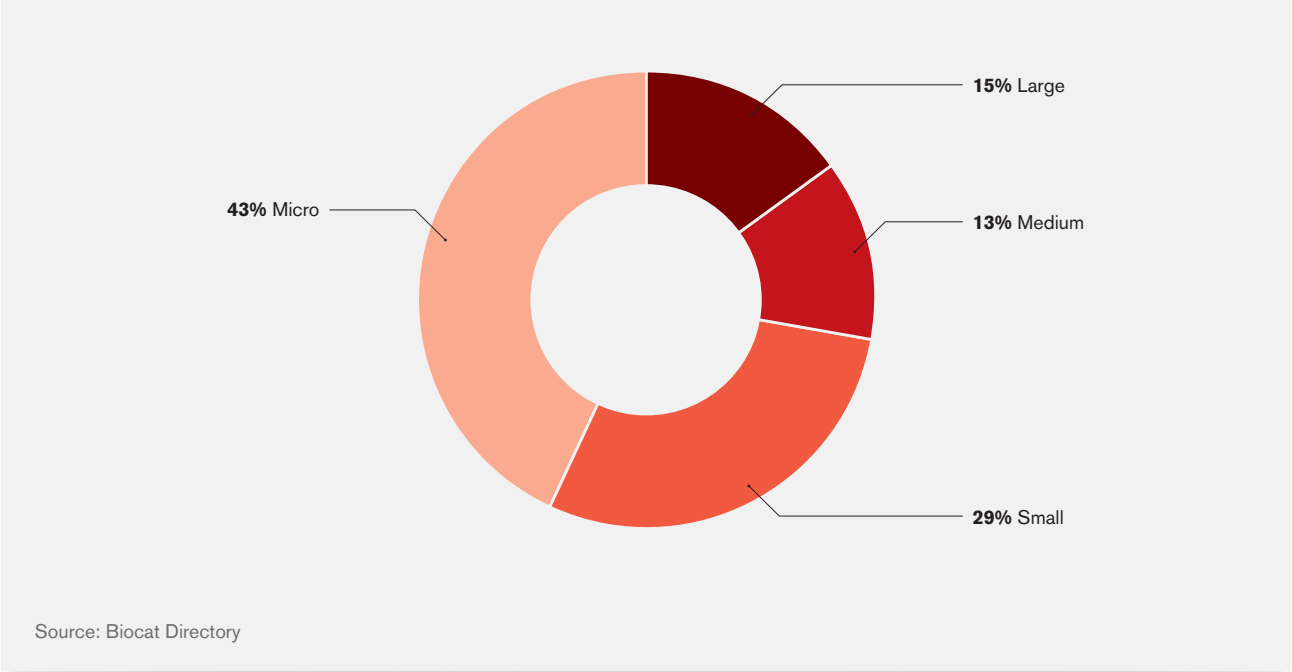
Size and resources[5]

More than 80% of companies in the BioRegion of Catalonia are SMEs, meaning they have fewer than 250 employees and turnover under €50 millions per year. Specifically, **351 companies** (85% of those for which economic data is available) belong to this category. Furthermore, nearly half of the 100 companies for which detailed economic information is not available are biotechnology or medical technology companies created in the past 5 years, leading us to put the percentage of small and medium-sized companies at 81.84% of all those in the BioRegion.

5. All of the economic data in this chapter is from the SABI (Iberian Balance-sheet Analysis System) database, which compiles information from balance sheets companies submit to the trade registry. When not otherwise indicated, the data refers to the 2011 fiscal year. We have financial reports for 412 companies (80.31% of the 512 listed in the Biocat Directory). None of the companies provide information on 100% of the indicators in a balance sheet and, as a result, each one has a different number of responses, but all cover more than 75% of the entries in the segment analyzed, so we consider the information to be highly reliable.

As shown in graph 11, most of these SMEs are **microenterprises** (with a staff of 10 or fewer workers and revenue of less than €2 millions per year), which accounts for **43% of all the companies** in the Catalan biocluster, while small companies (between 10 and 50 workers and annual turnover under €10 millions) make up 29% of all companies. The number of medium-sized companies (between 50 and 250 employees and annual sales under €50 millions) is 55 (13%), while the BioRegion has **60 large companies** (15%), a category mainly made up of national and international biopharmaceutical companies (Almirall, Bioibérica, Esteve, Ferrer, Grífols, Amgen, Boehringer Ingelheim, Novartis, Sanofi, Zoetis [Pfizer], etc.), but which also includes large R&D or medical-technology services companies, both in research and production as well as distribution (Roche Diagnostics, GE Healthcare, B Braun Medical, Isaza, Telstar, Palex Medical, etc.).

Graph 11 **Percentage of companies in the BioRegion by size (revenue and workers)**

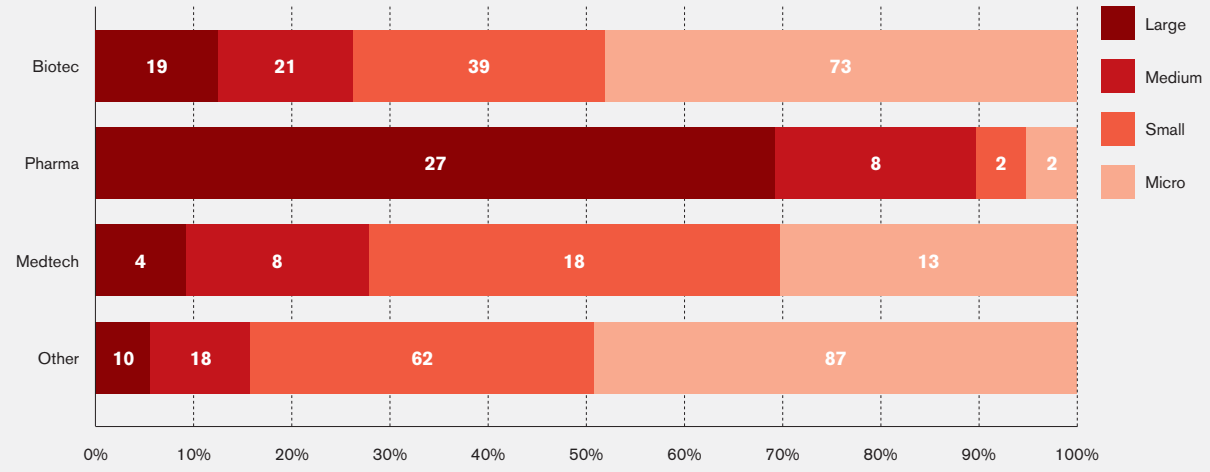


Source: Biocat Directory

By sector of activity, the absolute number and relative weight of SMEs is much higher among biotechnology companies, where most fall into the microenterprise segment (38% of biotech firms). These also make up a very large proportion of consulting and professional-services firms, with an abundance of highly specialized microenterprises (legal consultancy, patent management, human resources, business advisory, etc.). As we mentioned previously, the largest companies are found in the pharmaceutical segment (graph 12).

It must be said that, in the BioRegion, **61 companies are subsidiaries of multinational corporations**, which accounts for 12% of the total. This group includes the largest companies in the sector, both from abroad (Amgen, B. Braun, Boehringer Ingelheim, Novartis, Sanofi, etc.) and Catalan companies that have been acquired by large foreign groups, like Telstar, which has joined Japanese corporation Azbil.

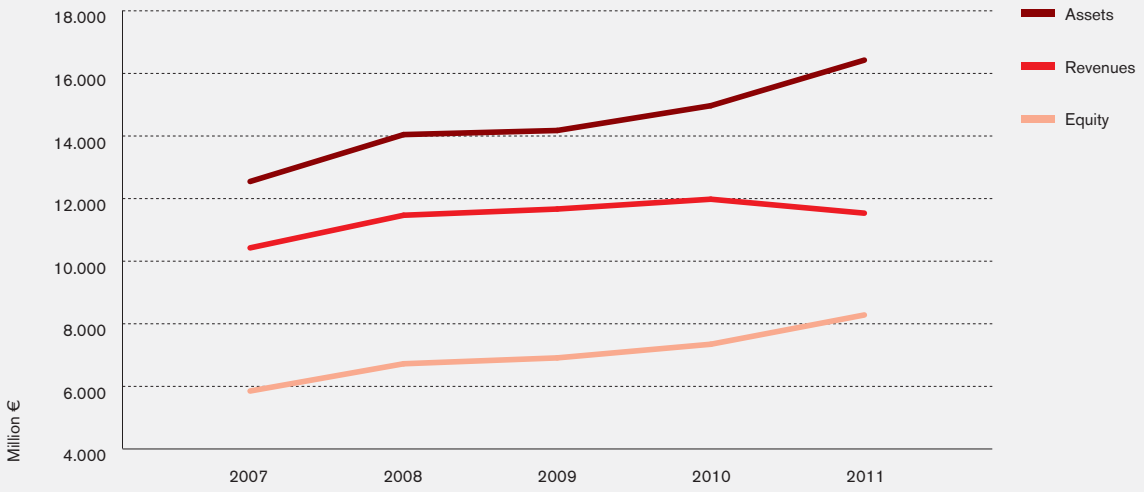
Graph 12 **Breakdown of companies in the BioRegion by size and subsector**



Source: Biocat Directory

As a whole, **the companies in the BioRegion saw operating revenue of €11,527 millions in 2011**. This figure is down 3.74% from that of 2010 (€11,976 M) and breaks the positive trend seen in this indicator since 2007 (graph 13). Despite this negative point, the capital position of companies in the BioRegion has been strengthened, with assets of the group as a whole reaching €16,450 millions in 2011 (up 9.79% from 2010) and equity of €8,253 millions (up 13% from 2010).

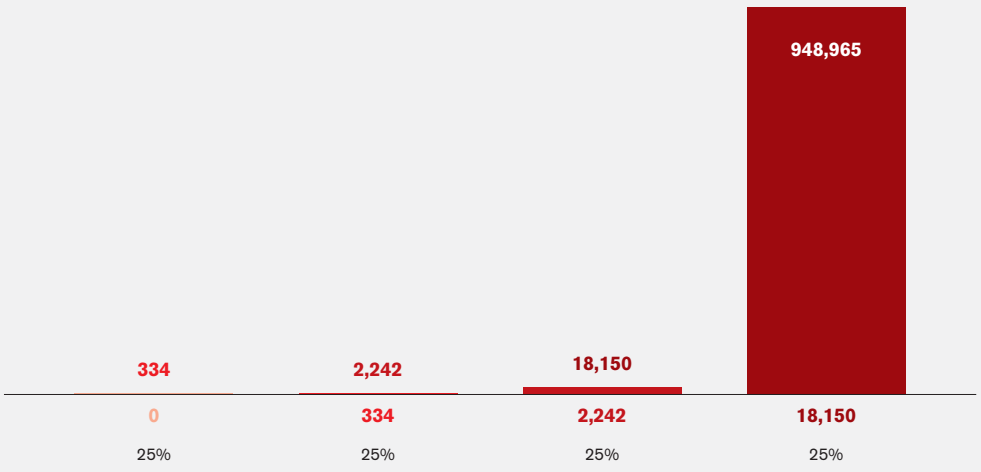
Graph 13 **Evolution of revenue and capital of companies in the BioRegion**



Source: SABI. Prepared in-house.

However the bulk of these resources, as well as revenue, is concentrated in a small group of companies. As shown in the analysis of turnover by quarter (graph 14), 50% of the companies in the BioRegion see annual turnover of less than €2.24 millions, 25% of companies are between €2.24 and €18 millions, and the other 25% is between €18 and €949 million per year.

Graph 14 **Analysis of distribution of revenue of companies in the BioRegion (in thousands of €)**



Source: SABI

If we look at the companies a little closer, we see that the joint 2011 turnover for pharmaceutical firms was €6,240 millions and for **biotechnology firms, €2,426 millions**. The turnover of the medical technology subsector —including the group of companies that carry out R&D, production and distribution— was €1,555 millions. Turnover of pharmaceutical companies makes up 54% of all revenue generated in the sector in Catalonia and it is precisely given this importance that the decrease in revenue seen in pharma companies (-6.8% from 2010) affected the sector's 2011 results. Biotechnology and medical technology companies —many with business models based on R&D, maintained through middle and long-term investment, and without products on the market— saw only a slight decrease in revenue in 2011, 0.4% and 0.6%, respectively.

According to data from Farmaindustria, public pharmaceutical expenditure on prescriptions in Spain (61% of the market) decreased 12.3% in 2012, after falling 2.4% in 2010 and 8.8% in 2011.[6] And, although the hospital market (39%) increased slightly (3.3% in 2011 and 0.6% in 2012),[7] this was far from making up for the global decrease. In Catalonia, this decrease in public expenditure on prescriptions was even more pronounced, falling 8.5% in 2011 and 14% in 2012. Forecasts for the Spanish pharmaceutical sector expect this downward trend to continue in the coming years and sales volume is expected to go from $28,000 millions in 2011 to $19,200 millions by 2020.[8]

Faced with this situation, experts highlight, on one hand, the importance of internationalization and market diversification, with a view to emerging markets (see chapter V), and, on the other, the need for pharmaceutical companies to include innovative products and therapies into their pipelines that can address unmet needs and offer a clear differential value over existing drugs and therapies. This entails a clear commitment to biotechnology and new ways to promote collaboration among the various stakeholders in the system (see chapter II).

Along with the fall in revenue of the pharmaceutical companies, we must also take into account the difficulties biotechnology and medical technology start-ups have experienced in recent years in their initial stages of growth. Proof of this can be seen in the fact that revenue of this segment has remained practically unchanged since 2008 (when biotech firms in the BioRegion had a turnover of €2,289 millions), with changes of less than ±1%.

The business volume generated by the group as a whole means that **companies in the life sciences sector account for 5.8% of Catalonia's GDP**.[9] If we narrow our analysis to the turnover of the biotechnology companies for which we have data (€2,426 M), direct participation in the GDP is 1.2%. In this respect, we must stress that, according to data from the INE survey on the use of biotechnology, the economic impact of this activity in Catalonia is even higher, as the business volume of the 122 companies that list biotechnology as their only or main sector of activity totaled €3,142 millions in 2011. To this amount we must add the contribution of biotechnology —at a percentage unfortunately not provided by the INE survey— to the income of companies with biotechnology as a secondary line or as a necessary tool for production. These companies (408) had a global turnover of €15,300 millions (2011), making it in no way an exaggeration to estimate the **business volume generated by biotechnology in Catalonia at more than €5,000 millions**, which puts it at roughly **2.5% of the Catalan GDP**.

In chapter II we will go back to this data and that on public investment in R&D in order to calculate the global economic impact of the sector as a whole.

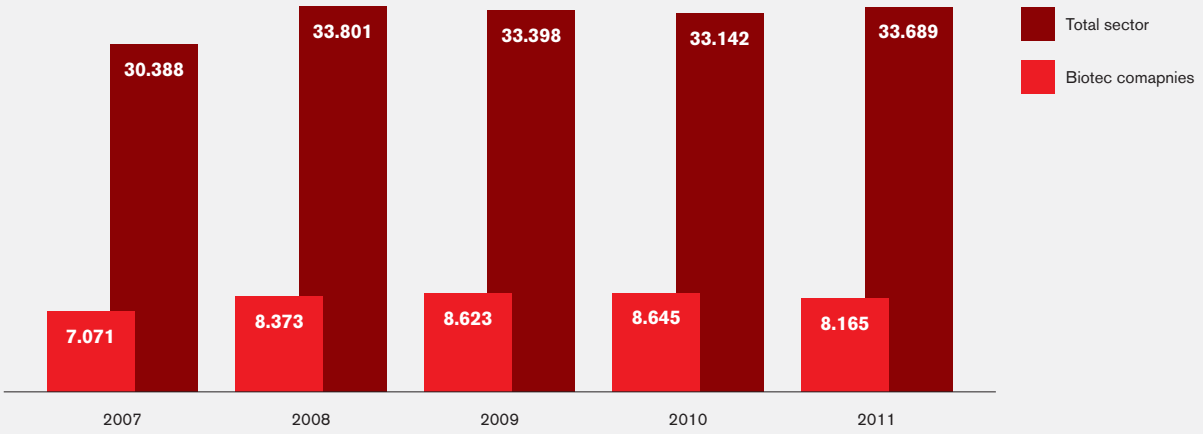
6. El mercado del medicamento en España, Boletín de Coyuntura nº 94, Farmaindustria, February 2013
7. Análisis del mercado hospitalario 2008-2012, IMS Health, 2013. (http://static.correofarmaceutico.com/docs/2013/04/23/merhos.pdf)
8. Previsions from the report From vision to decision. Phama 2020, PwC (http://download.pwc.com/ie/pubs/2012_pharma_2020.pdf), cited in Boletín de Coyuntura nº 94, Farmaindustria, February 2013.
9. Calculated from the official INE figure for 2011 (€198,908 millions).

Human resources and R&D investment

In total, **companies in the BioRegion employ 33,689 workers** (2011 data). Of these, 8,169 work for biotechnology companies, 14,427 for pharmaceutical companies, and 6,517 for companies that research, produce or distribute medical technology.[10]

In the sector as a whole, the number of workers has risen slightly, up 1.65% from 2010. Despite small year-on-year variations, graph 15 shows that employment has held steady since 2008. If we concentrate specifically on biotechnology companies, the number of workers, which had shown an upward trend since 2007, fell 5.5% in 2011 from the previous year.

Graph 15 **Evolution of global number of workers in the sector and of biotechnology firms**



Source: SABI. Prepared in-house.

According to figures collected through the 2011 INE survey on biotechnology, Catalan companies employ **3,564 people working directly on biotechnology**, 2,493 of which carry out R&D activities (**1,455 researchers** and 1,038 technicians and aides).[11] This data shows a 24.8% increase in biotechnology personnel from 2010 and the number of those devoted specifically to R&D is up 15.6%.

Of the people employed directly in biotechnology, 48% are women; a percentage that increases if we look at personnel employed to carry out R&D tasks, of which women make up 58%. The percentage is higher, however, among technicians and research aides (65% women) than researchers (53% women). Furthermore, it must be noted that **approximately one third of all R&D personnel in biotechnology are on part-time contracts** and if we calculate the full-time

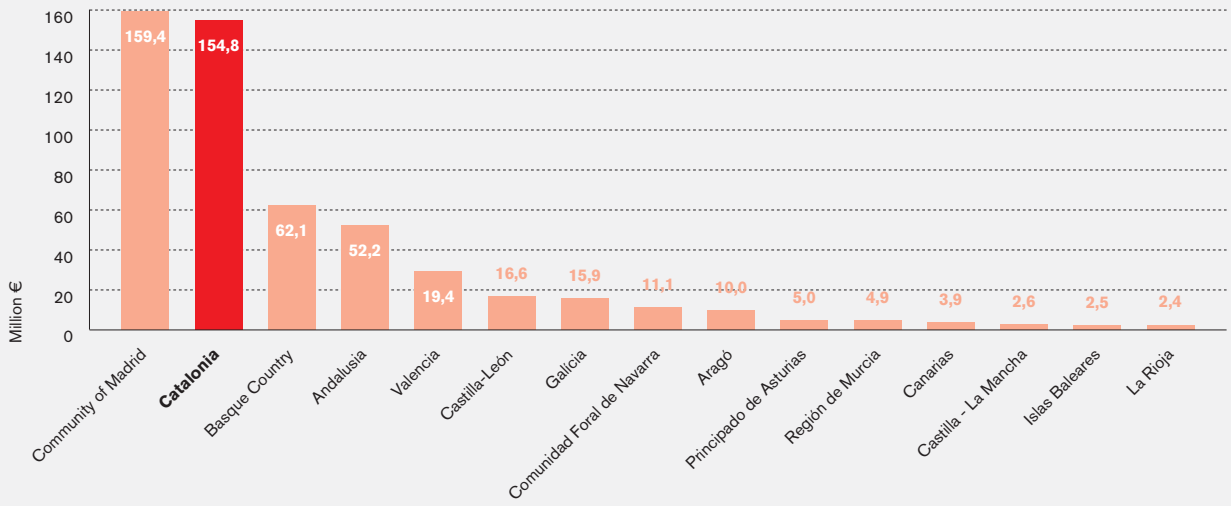
10. Data available for 68 companies listed under the headings Medical Technology and Supplier & Engineering (subsectors: Distributors, Instrumentation, Medical Devices, Electronics and Software).

11. The global number of workers at biotechnology companies listed in the Biocat Directory is higher than that given in the INE survey because companies that work in fields like veterinary or the environment, many of which provide R&D services, have other lines of business not related with biotechnology.

equivalent (FTE), the number of people employed falls to 1,941.1 (1,096.9 researchers and 871.2 technicians). In any case, this number puts Catalonia first in Spain (29.3%) in terms of R&D personnel employed in the business sector, trailed by Madrid (1,556.3 jobs in FTE) and Andalusia (760.6 jobs in FTE).

According to INE data, Catalan companies spent €243.4 millions on biotechnology in 2011, **€154.8 millions of which was in R&D expenditure**. This figure is down 12.5% from 2010 (€178 M), but is still above that of 2009 (€147.5 M). The most significant budget item is research and technical personnel, which in 2011 was €79.2 millions. Internal expenditure of Catalan biotechnology companies made up **28.8% of all R&D expenditure by biotech companies in the nation**, second by volume after Madrid (29.6%).[12]

Graph 16 **R&D investment by biotechnology companies in Spain**



Source: Survey on use of biotechnology 2011, INE. Prepared in-house.

The bulk of internal R&D investment in biotechnology, logically, comes from the 122 companies that list this as their main or only sector of activity (€108.6 M), while those that list biotechnology as a secondary activity or as a production tool invest considerably less in (€17M and €29M, respectively). Paradoxically, biotechnology R&D makes up only 17% of all R&D investment of companies that list this as a secondary business line, while it is 39% of all R&D investment in companies that use biotechnology as a production tool.

Regarding external expenditure, the most significant budget item is R&D services in biotechnology, on which Catalan companies spent a total of 43 millions in 2011, for services acquired in Spain (69%) and abroad (31%), which is up slightly from 2010 (€41.3 M).

Internal R&D expenditure on biotechnology is generally covered through

12. As a whole, the internal R&D expenditure of Spanish biotechnology companies was €537.9 millions. See chapter III for analysis of the global investment, public and private, in biotechnology R&D in Catalonia and the rest of the nation.

company equity (71%). Contributions from the general government in 2011 only covered 14% of R&D expenditure, in a marked decrease from 2010 when public contributions covered 27% of all business expenditure in biotechnology R&D. The contributions received from other companies, however, were up in 2011, covering 9.4% of expenditure while in 2010 this figure was only 4.2%.

Foreign funds —mainly from the European Union (66%)— covered only 3% of internal R&D expenditure in 2011, up slightly from 2010 (2%).

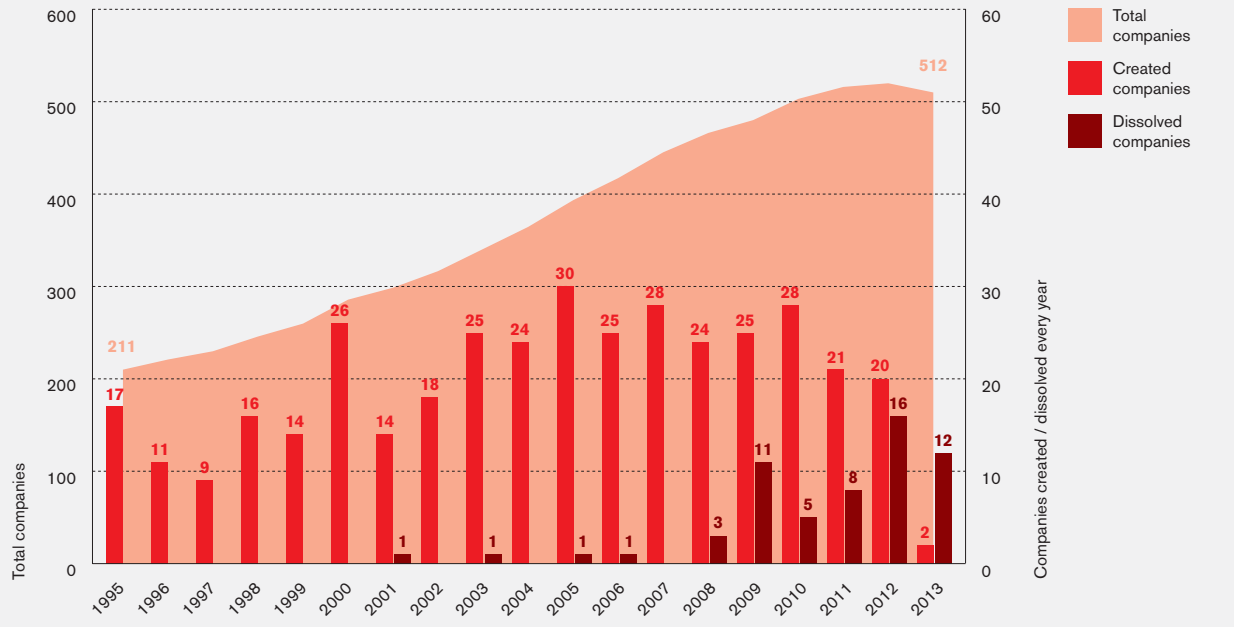
Business creation and destruction

Although the creation of biotechnology companies grew notably between 2003 and 2007, if we analyze the companies in the BioRegion as a whole, the progression has been more balanced. This is due to the fact that both pharmaceutical and medical technology companies, as well as specialized suppliers of products and services, were created in the mid 20th century. In the sector as a whole, there are many companies that have incorporated biotechnology into their research and business lines after the 1980s, some time after founding.

In any case, it is worth noting that **between 2000 and 2013, the number of companies in the BioRegion has nearly doubled**: in 1999, there were 261 companies and in 2013, 512, nearly twice as many. However, graph 17 shows that in 2013, for the first time, the number of companies closed surpasses that of those newly created. In fact, the pace at which new companies are created in the sector began to slow in 2010, along with an upward trend in number of companies destroyed that began in 2009.

It must be said that in some cases, the companies have disappeared but the business and its activity have not been destroyed. Of the 59 companies closed in the BioRegion, 12 were due to mergers with another company and 5 moved out of Catalonia. As we said previously, the bulk of business destruction has come in the period since 2009: in total, 36 companies have closed their doors since that year and 16 have disappeared in Catalonia due to a move, acquisition or merger.

Graph 17 **Business creation and destruction in the BioRegion of Catalonia 1995-2013***



*2013 data for January – June period

Source: Biocat Directory

The impact of the economic crisis on this change in trend is clear, most negatively affecting the number of new business projects. In a normal environment, these should compensate for the destruction of projects that, in the middle term, don't find their place in the market. The number of mergers and acquisitions should also make up a higher percentage of the number of destructions. What we see, however, is that for the first time in 2013 business creation doesn't compensate for destruction and the total number of companies in the BioRegion is down 1.92% from 2012.

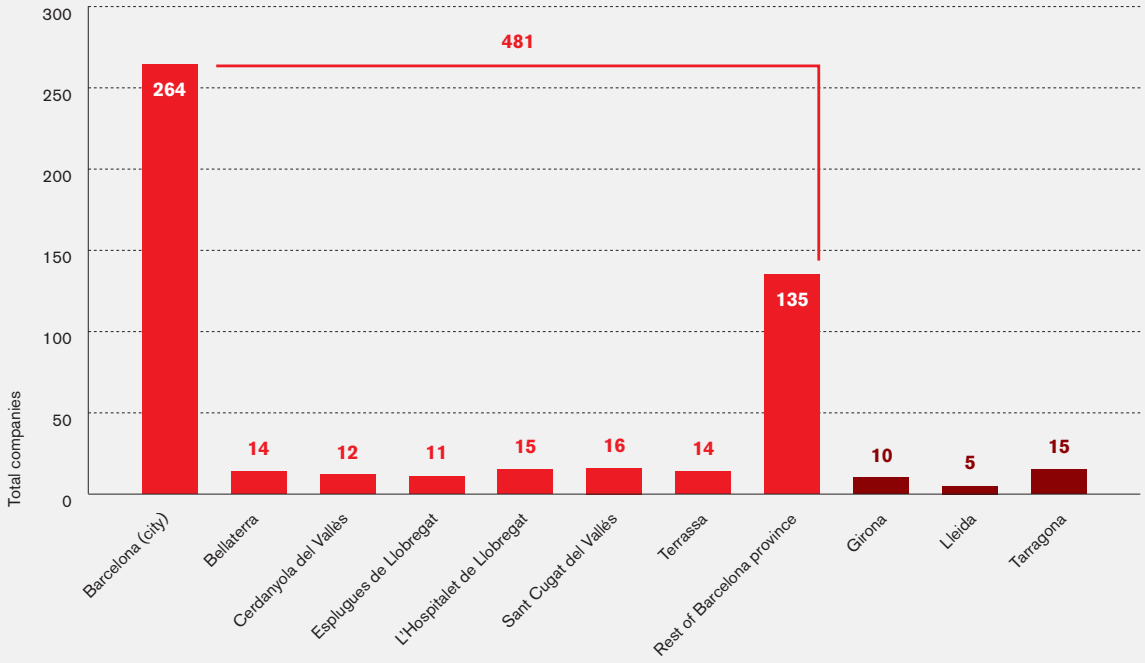
If we take into account that, according to data collected by FECYT more than 170,000 companies have disappeared in Spain since 2009, with yearly rates of between -1.9% and -1.2%,[13] the Catalan life sciences sector is weathering the crisis quite well. However, the current trend must serve as a warning and lead to implementation of measures to ensure the development of the business fabric in this sector that is strategic to our economy.

13. Indicadores del sistema español de ciencia y tecnología 2012, ICONO-Observatorio Español de I+D+I, Fundación Española para la Ciencia y la Tecnología (FECYT), Madrid, 2012

Location

Companies in the BioRegion are mainly found in the Barcelona metropolitan area. In fact, 94% of all companies are located in this province, mostly in the city of Barcelona (264, 51.6% of the total). As seen in graph 18, only six cities in the metropolitan area show small concentrations of companies; the rest are distributed fairly equally in a total of 68 towns throughout the province. The lack of critical mass of companies outside the city of Barcelona —both in this province and in those of Girona, Lleida and Tarragona— prevents us from detecting clear trends, sectorial specialization, or other specific characteristics. On the other end of the spectrum, the high concentration in the city of Barcelona, with more than half of all companies in the Catalan life sciences sector, means that there aren't any traits that differentiate this group from the sector as a whole. (See square *The life sciences in Barcelona* for more details on the specific figures for the city).

Graph 18 **Geographic distribution of companies in the BioRegion**



Source: Biocat Directory

24% of the companies in the BioRegion are located in science and technology parks. In section *g) Science and technology parks* of this chapter we provide more data on these spaces and the organizations located there.

Pipeline and patents

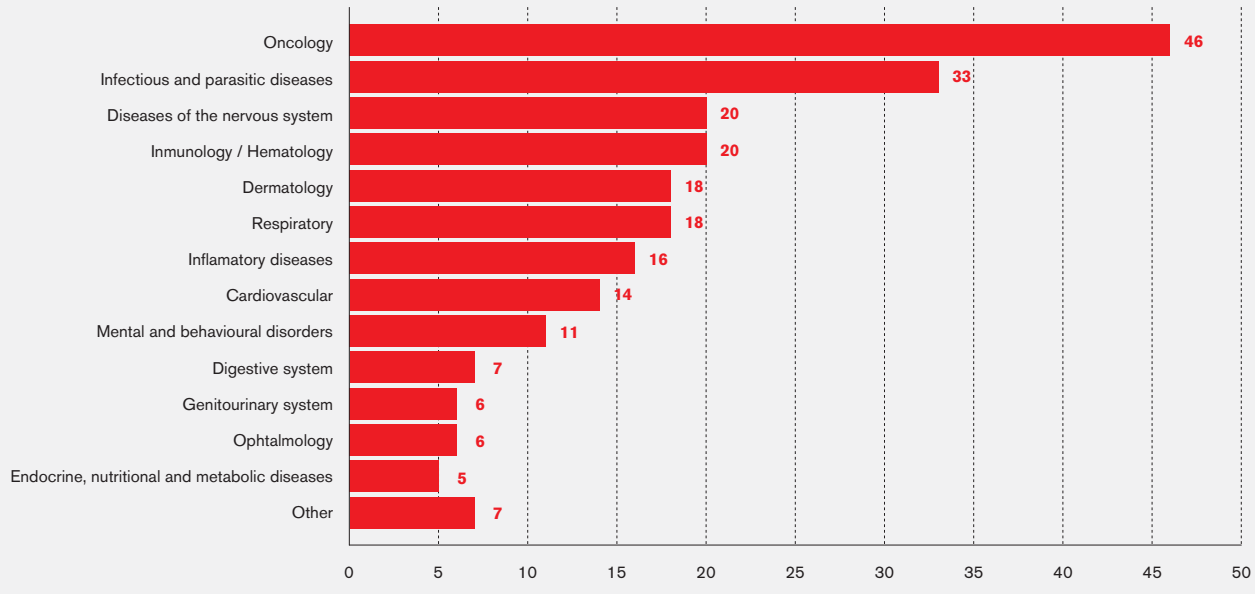
Biotechnology and pharmaceutical companies in the BioRegion of Catalonia have a pipeline of **227 therapeutic and diagnostic products** for human health. To this we must add an additional **88 products** that include **technology for drug and therapeutic research** (9), **functional foods and nutraceutics** (18), **diagnostic** (11), **veterinary** (29) and **cosmetic and plant health** (22) products.

On the other hand, the BiotechGate database lists **122 medical technology companies**, including the in vitro diagnostic devices of some biotechnology companies working in this field.

Information on these 433 products has been provided by a total of **122** biotechnology, pharmaceutical and medical technology **companies**.

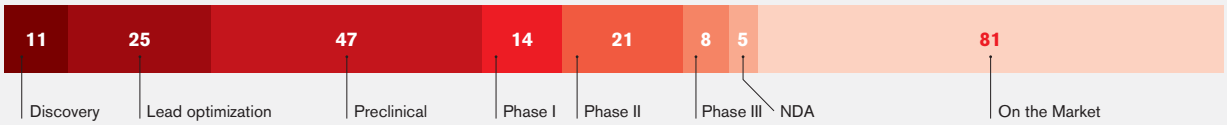
Regarding the 227 therapeutic and diagnostic products, treatment of cancer and neoplasms is the area with the most products (46), followed by infectious and parasitic diseases (33), the nervous system (20) and hematological and immunological diseases (20), as seen in graph 19.

Graph 19 **Therapeutic and diagnostic pipeline of companies in the BioRegion**



Nearly one third of this therapeutic and diagnostic pipeline (81) is already on the market, and most of the products currently in development (47) are in the preclinical trial phase (graph 20). According to data from the companies in the BioRegion, a total of 81 therapeutic and diagnostic products are available for out licensing.

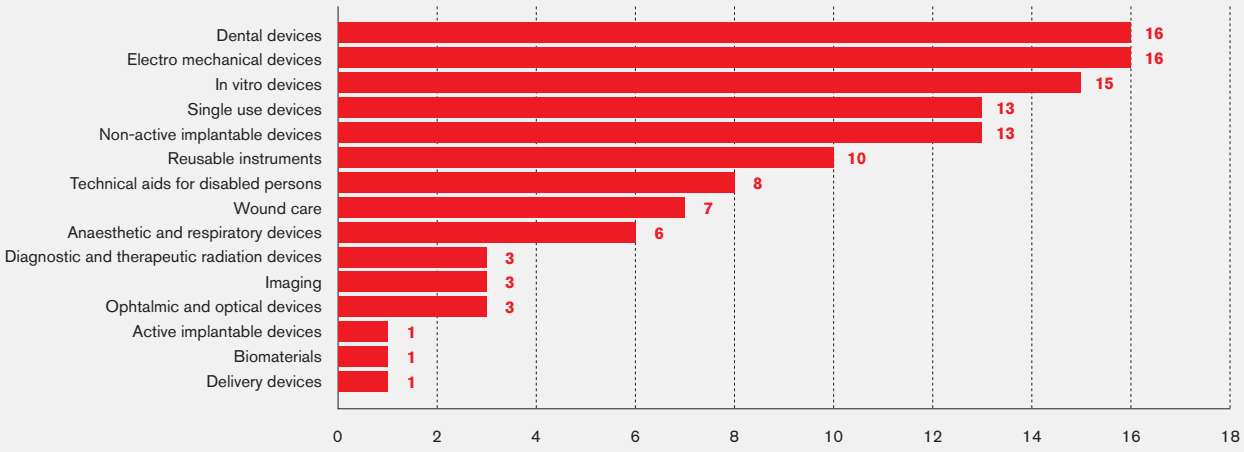
Graph 20 **Therapeutic and diagnostic products by phase of development**



Source: BiotechGate

Regarding medical technology, the number of dental and electro-mechanical devices stands out, followed by in vitro diagnostic devices (graph 21).

Graph 21 **Type of medical technology produced by companies in the BioRegion**



Source: BiotechGate

Of the 122 registered products, 103 are on the market and 19 in development. It must be noted that many of the medical technology companies listed in the Biocat Directory and on BiotechGate only provide the database with a small selection of their catalog of products, according to criteria based on interest or innovation, so the number of products marketed and in development is really much larger.

To conclude this section on the companies in the BioRegion, we must note that in 2011, according to the INE survey on use of biotechnology, 9.1% (48) of all companies active in biotechnology applied for a total of **140 patents**. Both the number of companies applying and the number of patents have dropped significantly from 2010, when 192 patents were applied for by 16% of the companies active in biotechnology (59). However the figures for Catalonia are proportionally better than those for the nation as a whole, where only 5% of companies active in biotechnology (151 out of 3,025) applied for 430 patents in 2011. Therefore, Catalonia accounts for 32.5% of all patents applied for and 32% of all applying companies, when the region is home to only 18% of all companies active in biotechnology.

LIFE SCIENCES IN BARCELONA

The city of Barcelona and its metropolitan area are home to 90% of the Catalan life sciences sector. Specifically, the Catalan capital has **264 companies** of the 512 in the BioRegion as a whole (51.6%), which are grouped by main sector of activity in graph 22.

Barcelona has **27 research centers** that work in the biosciences or related disciplines of the 56 total in Catalonia, and is also home to **4 of the 17 Catalan university hospitals** (Hospital Clínic, Hospital de la Santa Creu i Sant Pau, Vall d'Hebron University Hospital and Hospital del Mar). The province of Barcelona has 8 more university hospitals, including Bellvitge University Hospital (L'Hospitalet de Llobregat); Hospital Sant Joan de Déu (Esplugues de Llobregat); Germans Trias i Pujol University Hospital and Institut Guttmann, in Badalona; Consorci Sanitari de Terrassa and Mútua de Terrassa; Corporació Sanitària Parc Taulí in Sabadell; and Consorci Hospitalari de Vic.

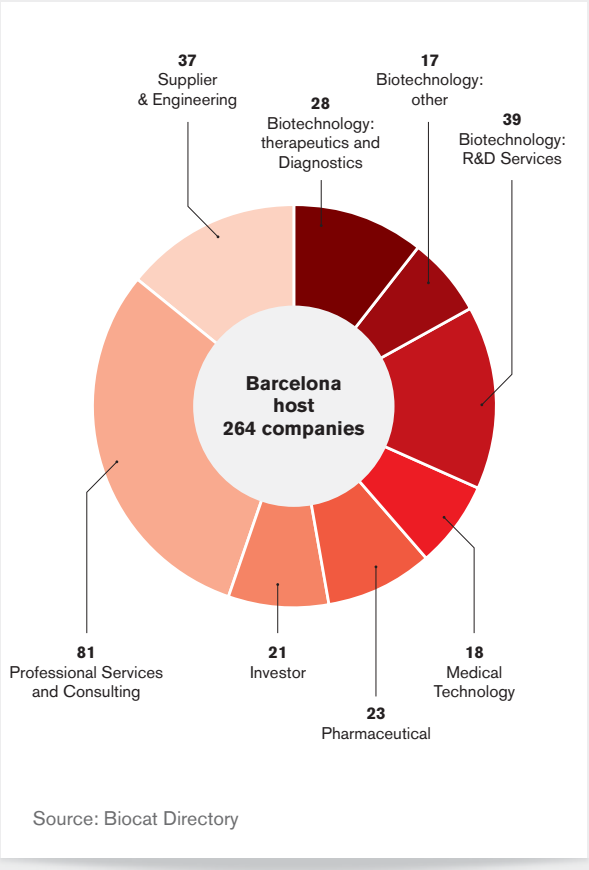
The city and province of Barcelona is also home to **7 universities** of the 11 that offer studies in the life sciences and related disciplines: including public universities UAB, UB, UPC and UPF, and private UIC, URL and UVic. The Open University of Catalonia, which given its particular characteristics can't be considered to be "in Barcelona", has more registered students from the county of Barcelona than anywhere else: 8,651 of a total of 38,213 students doing undergraduate, masters and engineering degrees.

The 264 companies in the BioRegion that are based in the city of Barcelona have a joint annual turnover of **€7,108 millions** and employ a total of **18,387 people** (2011). This means that the Catalan capital concentrates 62% of all revenue of companies in the sector and 54% of all employment. The weight of the city is lower if we only consider biotechnology companies located in Barcelona, which have a total of 3,300 workers on staff and in 2011 generated turnover of €710 millions, 29% of the revenue of all biotech firms in the BioRegion.

The concentration of biotechnology companies in the Catalan capital devoted to therapeutics and diagnostics (58% of the total) and R&D services (53%) is noteworthy, while Barcelona is home to only 23% of biotech companies in other subsectors, like agrobio or veterinary. The largest concentration of investment companies (21 of 23 registered) and professional services and consulting (84%) is also found in Barcelona. The city not only has 57.5% of all Catalan pharmaceutical companies but, logically, is also home to the central headquarters of the main national and multinational corporations, which explains the concentration of employment and revenue there.

Barcelona also has **7 science and technology parks** of the 16 parks in Catalonia with activity in the biotechnology and biomedicine arena. The Barcelona Science Park (PCB) is particularly noteworthy for the number of companies (41), research centers (3) and scientific services located there. It is followed, in number of companies, by the 22@Barcelona technology district, with 32 companies in the sector. The PRBB, Barcelona Nord Technology Park, a municipal initiative, and part of Parc UPC —with locations in various points of the province— complete the map of parks in the city (see section *g)* of this chapter).

Graph 22 **Distribution by type of companies in the life sciences sector located in Barcelona**



Source: Biocat Directory

B. RESEARCH CENTERS

The BioRegion of Catalonia has **56 research centers associated with the life sciences** given the disciplines on which research at the center focuses. Most work in the fields of biotechnology and biomedicine, but centers devoted to physical sciences (photonics, nanotechnology, etc.) and mathematics applied to research in health or food are also included in this group (see table 2). In fact, one of the salient characteristics of cutting-edge scientific research today is the importance of interdisciplinarity and how different disciplines can contribute innovative points of view and new solutions to a great number of challenges.

The bulk of these centers (33) belongs to the Government of Catalonia CERCA system, although three of them belong to two different bodies: two are also CSIC centers —the Center for Research in Agricultural Genomics (CRAG) and the Catalan Institute of Cardiovascular Sciences (ICCC-CSIC)— and the third —the Center for Research in Agrotechnology (Agrotecnio)— also belongs to the University of Lleida. The CERCA centers include the five hospital research institutes in Catalonia accredited by the Institute of Health Carlos III: IDIBAPS, IDIBELL, IIB-Sant Pau, IGTP and VHIR (see the following section *c) Hospitals* for more information).

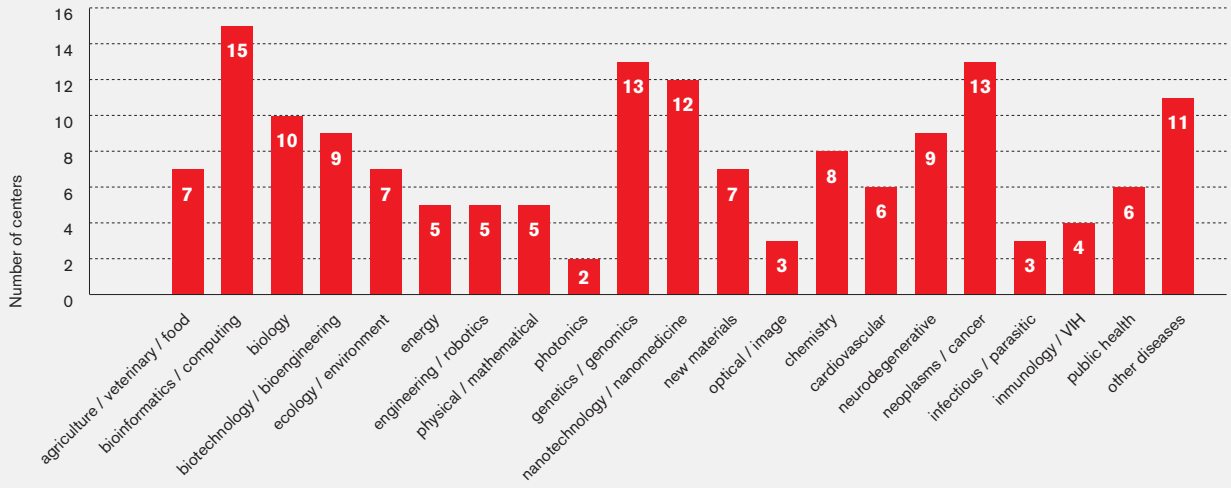
In addition to the two mentioned previously, the Spanish National Research Council (CSIC) has 10 centers in Catalonia and another —CIN2— managed jointly with the Catalan Institute of Nanotechnology (ICN). The Barcelona Supercomputing Center–Centro Nacional de Supercomputación is, like the CNAG–National Genome Analysis Center, a research center and unique scientific facility jointly managed by the national government and the Government of Catalonia.

The rest of the centers belong to various universities (Autonomous University of Barcelona, University of Barcelona, University of Girona, Polytechnic University of Catalonia and Rovira i Virgili University) and focus their research efforts on fields like biomedicine, nanotechnology, computational chemistry, and food safety.

Graph 23 sums up the main lines of research at these 56 centers. Bioinformatics, genetics/genomics and nanotechnology stand out as the most common lines of research, and cancer and degenerative diseases as the therapeutic areas on which most of the work in these centers focuses.

Table 2 shows the number of active research groups or projects at each institute, in addition to the number of groups recognized by the Government of Catalonia (2009-2013 SGR call). In the 2009 call for these AGAUR grants, 223 groups were recognized at centers working in the biosciences and related disciplines, however according to these organizations' public information, there are currently 935 active research groups and the centers that don't structure their research into groups list a total of 366 research projects underway. (See section *e) Research groups*).

Graph 23 **Lines of research at centers in the BioRegion**



Source: Biocat Directory

As a whole, research centers in the BioRegion have an annual budget of more than **€380 millions**.[14] Regarding CERCA centers, this budget was €316 millions in 2012, with more than €130 millions from the Government of Catalonia —including contributions from the Directorate-General for Research and the Department of Health—, which is supplemented, depending on the type of center, with national and international competitive projects, contributions from other levels of government, and private revenue, which may come from payment for services, donations or collaboration projects.

Both the overall budget —ranging from €1.2 to €40 millions per year— and the government's contribution —from 4.5% to 87% of the total— vary widely from one center to another. Hospital research institutes receive a smaller percentage of their budget from this source (although not necessarily less in absolute numbers) and also see the most private contributions, especially to carry out clinical trials for the pharmaceutical industry, which can make up between 20% and 25% of the yearly income of these institutes. Competitive projects, above all EU calls, are the cornerstone of the large research centers' funding —in 2011 these projects brought €13.8 millions in revenue to the CRG, €13.2 millions to IDIBELL, €12.5 millions to IDIBAPS and nearly €13 millions to VHIR.

As a whole, the 56 research centers in the BioRegion have a **staff of 7,200 workers**, **4,500 of which are researchers** (PhDs and postdocs). However, the real number of personnel and researchers is even higher if we take into account assigned personnel. The difference is particularly noteworthy at hospital research institutes, where assigned personnel hired by the hospital or other associated organizations doubles or triples the institute's staff in some cases. As

14. This figure was calculated by adding up the 2012 budget for CERCA centers provided by the Government of Catalonia Directorate-General for Research (DGR) and the budgets published in the 2011 year-end reports for the rest of the centers, where available (there is no data available for 10 of the centers). For the CSIC centers, year-end reports only provide data regarding investment in research and not global data for each center, so the global figure would be higher than calculated.

an example, we could cite IDIBELL or VHIR: there are 266 people on the payroll at IDIBELL, but the total team, including assigned personnel, is 955 people, 330 of which are researchers (706 if we include collaborators and predoctoral fellows); the VHIR has a team of 562 workers, which totals 1,259 if we include assigned personnel, including a total of 630 researchers (830 with predocs).[15]

Regarding human resources, it must be noted that, in the life sciences, Catalan research centers, both CERCA and CSIC centers, benefit from ICREA (Catalan Institution for Research and Advanced Studies) researcher hiring programs. According to the institution's year-end report, 70 of the 240 researchers hired in 2012 (29%) work in medical and biological sciences and, of these, 54 have joined research centers, while 16 have gone to various universities.

Furthermore, we must note the significant participation of Catalan researchers in the CIBER (Biomedical Research Networking Centers) system of *virtual research centers*, which manages and coordinates research efforts in research groups around the nation in lines of particular significance or interest. Specifically, there are currently 55 research groups in Catalonia participating in the following CIBER:

- Biomedical Research Networking Center for Epidemiology and Public Health (CIBERESP) [20 groups]
- Biomedical Research Networking Center for Rare Diseases (CIBERER) [18 groups]
- Biomedical Research Networking Center for Mental Health (CIBERSAM) [8 groups]
- Biomedical Research Networking Center for Respiratory Diseases (CI BERES) [13 groups]
- Biomedical Research Networking Center for Neurodegenerative Diseases (CI BERNED) [17 groups]
- Biomedical Research Networking Center for Hepatic and Digestive Diseases (CIBEREHD) [23 groups]
- Biomedical Research Networking Center Diabetes and Associated Metabolic Disorders (CIBERDEM) [15 groups]
- Biomedical Research Networking Center for Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN) [21 groups]
- Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBEROBN) [10 groups]

To conclude this section, it must be noted that, as with companies, Barcelona is home to the bulk of the 56 research centers in the life sciences. Specifically, the province of Barcelona has 82% of these bodies (46), half of which (27) are located in the city of Barcelona. Of the rest, five are in Girona, two in Lleida, two in Tarragona and one in Reus.

15. See http://www.idibell.cat/imatgesContinguts/memoria_idibell_2012_web.pdf (IDIBELL) and http://annualreport2011.vhir.org/facts-and-figures/researchers-and-technicians/ (VHIR). Also see table 4.

Table 2 **Research centers working in the life sciences or related disciplines**

Center	Association	SGR Groups 2009*	Groups / projects **
Barcelona Supercomputing Center - Centro Nacional de Supercomputación (BSC)		1	5
Center of Regenerative Medicine in Barcelona (CMRB)	CERCA		--
Center for Research in NanoEngineering (CRNE)	UPC		2
Center for Research in Agricultural Genomics (CRAG)	CSIC/CERCA	6	28
Center for Research in Agrotechnology (Agrotecnio)	CERCA/UdL		12
Biomedical Engineering Research Center (CREB)	UPC		59 p
Research Center on Engineering of Materials and micro/nanoSystems (EMaS)	URV		7
Center for Research in Environmental Epidemiology (CREAL)	CERCA	2	56 p
Barcelona Center for International Health Research (CRESIB)	CERCA	1	48 p
Centre de Recerca en Sanitat Animal (CReSA)	CERCA	2	13
Research Center for Food Safety and Control (CRESCA)	UPC		8
Centre de Recerca Matemàtica (CRM)	CERCA		3
Center for Genomic Regulation (CRG)	CERCA	18	33
Computer Vision Center (CVC)	CERCA		8
Research Center on Nanoscience and Nanotechnology (CIN2)	CSIC/ICN		14
International Center for Numerical Methods in Engineering (CIMNE)	CERCA		4 p
National Genome Analysis Center (CNAG)			17 p
National Microelectronics Center (IMB-CNM-CSIC)	CSIC	1	1
Catalan Institute of Cardiovascular Sciences (ICCC-CSIC)	CSIC/CERCA	1	40 p
Catalan Institute of Nanotechnology (ICN)	CERCA	2	15
Catalan Institute for Water Research (ICRA)	CERCA		49 p
Institute of Chemical Research of Catalonia (ICIQ)	CERCA	4	19
Institute for Bioengineering of Catalonia (IBEC)	CERCA	4	17
Institute of Evolutionary Biology (IBE-CSIC)	CSIC	2	16
Molecular Biology Institute of Barcelona (IBMB-CSIC)	CSIC	10	27
Vicent Villar Palasí Institute of Biotechnology and Biomedicine (IBB)	UAB	1	18
Institut de Ciència de Materials de Barcelona (ICMAB-CISC)	CSIC	5	18
Institute of Photonic Sciences (ICFO)	CERCA	2	25
Institute of Environmental Assessment and Water Research (IDAEA-CSIC)	CSIC	2	11
High Energy Physics Institute (IFAE)	CERCA		1
Institute of Predictive and Personalized Medicine of Cancer (IMPPC)	CERCA	1	11
Institute of Nanoscience and Nanotechnology (IN2UB)	UB		18
Neuroscience Institute (INc)	UAB		13
Institute of Advanced Chemistry of Catalonia (IQAC-CSIC)	CSIC	4	24
Institute of Computational Chemistry (IQC)	UdG		20
Institute of Theoretical and Computational Chemistry (IQTC)	UB		4
Institute for Research in Biomedicine (IRB Barcelona)	CERCA	10	22
Institut de Recerca Biomèdica de Lleida (IRB Lleida)	CERCA	1	32
Josep Carreras Leukemia Research Institute (IJC)	CERCA		--
AIDS Research Institute (Irsi-Caixa)	CERCA	1	7
Catalan Institute for Energy Research (IREC)	CERCA		3
Institute for Research and Technology in Food and Agriculture (IRTA)	CERCA	11	38
Institute of Robotics and Industrial Informatics (IRII-CSIC)	CSIC	1	43 p
Institute of Food and Agricultural Technology (INTEA)	UdG		21 p
Institute of Informatics and Applications (IIiA)	UdG		10 p
Bellvitge Biomedical Research Institute (IDIBELL)	CERCA	23	57
Girona Biomedical Research Institute (IdiBGi)	CERCA	1	16
Biomedical Research Institute Sant Pau (IIB Sant Pau)	CERCA	18	69
Health Sciences Research Institute of the "Germans Trias i Pujol" Foundation (IGTP)	CERCA	7	29
Artificial Intelligence Research Institute (IIIA)	CSIC		19 p
Institut d'Investigació Sanitària Pere Virgili (IISPV)	CERCA	4	59
August Pi i Sunyer Biomedical Research Institute (IDIBAPS)	CERCA	23	58
Institute of Biomedical Research of Barcelona (IIBB-CSIC)	CSIC	3	14
Institut Hospital del Mar d'Investigacions Mèdiques (IMIM)	CERCA	22	56
Vall d'Hebron Institute of Oncology (VHIO)	CERCA	2	19
Vall d'Hebrón Research Institute (VHIR)	CERCA	27	65

* Groups recognized by the Government of Catalonia in the 2009-2013 SGR call (consolidated and emerging). Many centers list no groups because in the resolution they were assigned to a university or hospital.

** Active research groups at the centers or number of projects (indicated with the letter 'p') when bodies are not organized into groups. This information is from the latest year-end report published or the entity's website as of 31/7/2013. In the case of centers devoted to mathematics or physical sciences, we have separated, when possible, the groups according to their links with the life sciences or lack thereof.

C. HOSPITALS

Catalonia has **17 university hospitals** out of a total of 211 establishments (65 of which are public and 146 private, according to data from the Ministry of Health, Social Services and Equality).[16] These university hospitals centralize research activity, which in most cases is carried out through associated research institutes or in collaboration with the departments at the universities with which they are associated. The teams at the hospitals and their research centers work on basic, clinical, translational and epidemiological research in various therapeutic areas, as well as developing new medical technology.

Table 3 **University hospitals in the BioRegion**

Hospital	Care personnel	Non-care personnel	Associated hospital institute
Barcelona			
Consorci Hospitalari de Vic	1.046	193	--
Consorci Sanitari de Terrassa	1.847	522	--
Corporació Sanitària Parc Taulí Sabadell	2.638	882	--
Hospital Clínic de Barcelona	3.470	908	IDIBAPS*
Hospital de la Santa Creu i Sant Pau	2.159	516	IIB-Sant Pau*
Hospital del Mar**	2.537	551	IMIM
Hospital Sant Joan de Déu	1.135	257	--
Bellvitge University Hospital	2.569	849	IDIBELL*
Germans Trias i Pujol University Hospital	1.849	479	IGTP*
Hospital Universitari Mútua de Terrassa	3.743		--
Vall d'Hebron University Hospital	4.638	1.725	VHIR*
Institut Guttmann - Neurorehabilitation Hospital	381	87	--
Girona			
University Hospital of Girona Doctor Josep Trueta	2.446	704	IDIBGi
Lleida			
Hospital Universitari Arnau de Vilanova	1.194	292	IRB-Lleida
Tarragona			
Hospital Universitari Joan XXIII, de Tarragona	1.917	648	IISPV
Hospital Universitari Sant Joan de Reus			IISPV
Hospital Verge de la Cinta de Tortosa	569	194	IISPV

* Hospital research centers accredited by the Institute of Health Carlos III

** Data for Parc de Salut Mar, which in addition to Hospital del Mar also includes Hospital de l'Esperança, Centre Perecamps, Centre Fòrum and Centre Emili Mira

16. http://www.msssi.gob.es/va/ciudadanos/hospitales.do?tipo=hospital

As mentioned in the previous section, five of the large Catalan hospitals have research institutes accredited as national healthcare research institutes by the Institute of Health Carlos III. Four of these institutes —IDIBAPS, IDIBELL, IGTP and VHIR— were accredited in 2009, and IIB-Sant Pau in 2011. There are a total of 18 accredited healthcare research institutes in the nation: seven in Madrid (accredited in 2010 [3], 2011 [2] and 2012 [2]); Catalonia has the five mentioned previously; the Valencian Community and Andalusia each have two; and Galicia and the Basque Country each have one.

In addition to these five accredited institutions, Barcelona is home to the Institut Hospital del Mar d'Investigacions Mèdiques and there are three others that structure the research activity of the university hospitals of Girona (Institut d'Investigació Mèdica de Girona Dr. Josep Trueta, IDIBGi), Lleida (Institut de Recerca Biomèdica, IRB-Lleida) and Tarragona (Institut d'Investigació Sanitària Pere Virgili, IISPV). Table 4 shows the main research indicators at hospital research institutes and hospitals that don't have this type of center: internal and assigned personnel devoted to research; theses, publications (indexed articles) and global and average impact factor; number of patents applied for; and clinical trials underway. To facilitate comparison, most of the information is from 2011, as this is the last year for which information is available on most of the centers. Where necessary, the origin and period to which the data pertains are noted.

These institutions and hospitals, as a whole, have more than **5,900 researchers** on staff. Regarding clinical research, according to data from the BEST project[17] from December 2012, Catalonia **coordinates 55.5% of all clinical trials** carried out in Spain (those with a Catalan Clinical Research Ethics Committee) and **leads the number of trials conducted (3,670, which is 27.5% of the total).**

At the same time, it must be noted that these hospitals and hospital institutes have created **12 spin-offs** working in the biomedicine and biotechnology arena. Specifically, five have come out of IDIBAPS/Hospital Clínic (Neurotec Pharma [2006], Bionure [2009], Transmural Biotech [2009], Linkcare [2010] and ImmunNovative Developments [2010]); one from Hospital de Bellvitge/ICO (VCN Biosciencies [2009]); one from Hospital de Sant Pau (Argon Pharma [2008]); one from VHIR/Hospital Vall d'Hebrón (Transbiomed [2007]); two from Hospital Sant Joan de Déu (BCN Innova [2006] and Cebiotex [2012]), one from Parc Taulí (Better Care [2010]) and one from Hospital del Mar/IMIM (Chemotargets [2006]. Half of these initiatives have been carried out in collaboration with various universities.

There are also spin-offs that have come out of the hospital setting, but from other centers not included in the selection of university hospitals, like for example Catfosc, which was started up in 2008 by various professionals from Hospital Moisès Broggi in Sant Joan Despí (Consorci Sanitari Integral).

Furthermore, Consorci Sanitari de Terrassa (CST) also promoted the creation of the social healthcare company called Aura Salut and in late 2012 started up, with Parc Taulí de Sabadell, the new Institut Oncològic del Vallès, which is the result of the merger between the oncology departments at the two hospitals but has a fully autonomous organizational and executive structure in order to more efficiently manage existing resources and boost creation of new services.

17. Farmaindustria / Medicamentos Innovadores. Plataforma Tecnológica Española. http://www.medicamentos-innovadores.org/es/node/12

Table 4 **Research and technology-transfer indicators for Catalan hospitals and hospital research institutes (2011)***

Institute / Hospital	Researchers			Theses	Publications	Patents	Clinical trials
	Total	Internal	Assigned				
IDIBAPS (Hospital Clínic)	461	47	326 (H) / 98 (other)	84	906	12	232
IDIBELL (Hospital de Bellvitge)	706	330	376**	22	783	7	237
IDIBGi (Hospital Dr. Josep Trueta, Girona)***	170	58	112 (H iand other)**	--	163	--	114
IGTP (Hospital Germans Trias i Pujol)	747	134	264 (H) / 349 (other)	18	562	5	176
IIB-Sant Pau (Hospital de Sant Pau)	979	206	516 (H) / 257 (other)	17	534	2	138
IISPV (Hospital Joan XXIII, Tarragona; Hospital Sant Joan, Reus; Hospital Verge de la Cinta, Tortosa)	586		23 grups HJXXIII 17 grups HSJ 3 grups HVC 16 grups (other)	22	281	--	149
IMIM (Hospital del Mar)	497	83	414 (H and other)	34	702	--	96
IRB-Lleida (Hospital Arnau de Vilanova)	278	70	208 (H i UdL)	--	209	--	113
VHIR (Hospital Vall d'Hebron)	830	372	290 (H) / 168 (other)	50	656	20	255
Consorci Hospitalari de Vic	--	--	--	--	15	--	11
Consorci Sanitari de Terrassa	--	--	14 groups	1	39	--	--
Corporació Sanitària Parc Taulí Sabadell	281	--	--	--	191	2	88
Hospital Sant Joan de Déu****	108	108	6 groups	--	215	--	66
Hospital Universitari Mútua de Terrassa	164	146	18 (collaborators)	2	77	--	--
Institut Guttmann – Hospital de Neurorehabilitació	113			--	29	2	--

* Table compiled with information from 2011 year-end reports from the centers except where expressly noted.

** Estimation.

*** The latest published report is from 2009. Data has been cross-referenced with information on the website (31/7/2013) and in the ICS 2011 Year-End Report.

**** Linked to IDIBAPS since 2004.

D. UNIVERSITIES

Teaching activity in biotechnology and the life sciences at Catalan universities has increased continually over the past five years. Currently, 11 of the 12 universities in Catalonia offer degrees in this area (all except University Abat Oliva CEU). 8 are public universities and 3 are private (see table 5). Six of the universities (UAB, UB, UdG, UdL, URV and UVic) offer a degree in biotechnology and the "classical" degrees in biology and biochemistry have been joined by more specific ones in genetics (UAB), microbiology (UAB), biomedical sciences (UAB, UB, UdL) and biomedical engineering (UB, UPC, UPF). A new degree in nanoscience and nanotechnology has also been created (UAB), which puts special emphasis on nanobiomedicine, as well as one in biological systems engineering (UPC).

In total, **9,595 students** were enrolled in undergraduate degrees in the **life sciences** for the 2011-2012 school year, including degrees in agrifood production. Additionally, **17,377 students** were enrolled in degrees in **health sciences** including medicine, nursing, odontology, pharmacy, and human nutrition and dietetics, which have direct links to the areas this report covers. Catalan universities offer **90 masters** to specialize in areas of the health and life sciences, which in 2011-2012 had a total of **3,163 students**.[18]

This group of 30,135 students accounts for 12.3% of the 245,369 undergraduate and masters students at Catalan universities in the 2011-2012 school year (12% of all undergraduates and 14.7% of masters students). Both globally and in the health sciences, 80% of all students go to the University of Barcelona (UB) or the Autonomous University of Barcelona (UAB). In the life sciences, students are more evenly distributed, with the combined weight of the UAB and UB dropping to 61%.

According to data from the Statistical Yearbook of Catalonia, 1,759 students received degrees in science and 1,452 in health sciences. That same year, 496 presented dissertations in science and 384 in health sciences. In 2011-2012, there were 495 dissertations in science and 462 in health sciences. Meaning that each year nearly one thousand new PhDs in areas of interest to the BioRegion join the job market.

As a whole, Catalan universities have **19,600 people** on their academic **teaching and research staff** (TRS). Their research in the life sciences is done through **241 consolidated and emerging research groups** (SGR 2009-2013). As seen in centers and hospitals, there are more groups active than those approved under the 2009 AGAUR call and the additional 35 groups listed in the Biocat Directory, but an exhaustive list of all the groups is currently being compiled and is beyond the scope of this report (see following section).

The 11 universities with life sciences activity have research results transfer offices (OTRI). Table 5 summarizes the main indicators of this activity, obtained through the survey conducted each year by the national association of university knowledge transfer offices, RedOTRI Universidades, the latest edition of which (2011) unfortunately didn't include data from UVic, UIC or URL.

18. Secretariat for Universities and Research. Directorate-General for Universities

According to this data, in 2011 Catalan universities received €193 millions in competitive grants, mostly (€121 M) for research projects. They managed 85 priority patent requests (nearly half from the UPC) and 80 applications for international patent extensions, and promoted the creation of 14 spin-offs. One of these, CIMAB, which is a spin-off of the UAB devoted to diagnosis and treatment of male infertility, belongs to the life sciences sector.

In total, including the one listed in the previous paragraph, the Directory of the BioRegion includes **39 university spin-offs**, although 10 of these are initiatives promoted jointly by universities and hospitals or research centers. The University of Barcelona alone accounts for 13 spin-offs in the life sciences; the UAB, 9 – one with the UPC, which itself has generated two more-; the UdG has created two spin-offs in this sector and there has been one each from the UdL, UPF and URV. These companies were created between 2000 and 2012, but most (22) have been in business for less than 5 years.

Table 5 **Selection of indicators on research and technology transfer for Catalan universities (2011)**

University	TRS	Technical staff with TT functions	Number of dissertations	Number of publications	Total amount in competitive grants (thousands of €)	Revenue from R&D and consulting contracts (thousands of €)	Revenue from public funding for col. projects with companies (thousands of €)	Revenue from services rendered (thousands of €)	Number of national priority patents	Number of international patent extensions (PCT)	Revenue from licensing (thousands of €)
Universitat Autònoma de Barcelona	3.804	12	522	2.223	44.848	15.768	7.894	5.485	14	16	112
Universitat de Barcelona*	5.247	19	593	4.068	53.303	7.662	6.150	5.234	18	22	166
Universitat de Girona	1.264	9	78	587	10.185	1.328	4.519	674	4	1	0
Universitat de Lleida	1.525	4	76	364	0	2.118	298	479	1	1	4
Universitat de Vic (UVic)	471	--	3	18	--	--	--	--	--	--	--
Universitat Internacional de Catalunya (UIC)	473	--	14	--	--	--	--	--	--	--	--
Universitat Oberta de Catalunya	775	10	12	86	2.597	157	322	0	0	0	0
Universitat Politècnica de Catalunya	2.822	10	252	1.483	29.526	18.527	13.389	2.948	41	33	180
Universitat Pompeu Fabra	556	8	143	682	27.978	4.593	--	0	4	4	35
Universitat Ramon Llull (URL)	1.110	--	57	140	--	--	--	--	--	--	--
Universitat Rovira i Virgili**	1.560	6	145	803	24.720	5.176	4.190	894	3	3	14

TRS: academic teaching and research staff

PCT: Patent Cooperation Treaty (international treaty on patent protection signed by 139 countries on 31/12/2008, which allows applicants to request protection from all the countries with a single application)

TT: Technology transfer

* Includes Bosch i Gimpera Foundation

** Includes URV Foundation, Fundació Privada Institut d'Investigació Sanitària Pere Virgili, Chemistry Technology Center of Catalonia, Technological Center of Nutrition and Health, Science and Technology Park for Tourism and Leisure, Catalan Institute of Classical Archaeology, Institute of Chemical Research of Catalonia, Catalonia Institute for Energy Research, Science and Technology Park for the Wine Industry, Costa Daurada Tourism Studies Foundation and Tarragona Science and Technology Park.

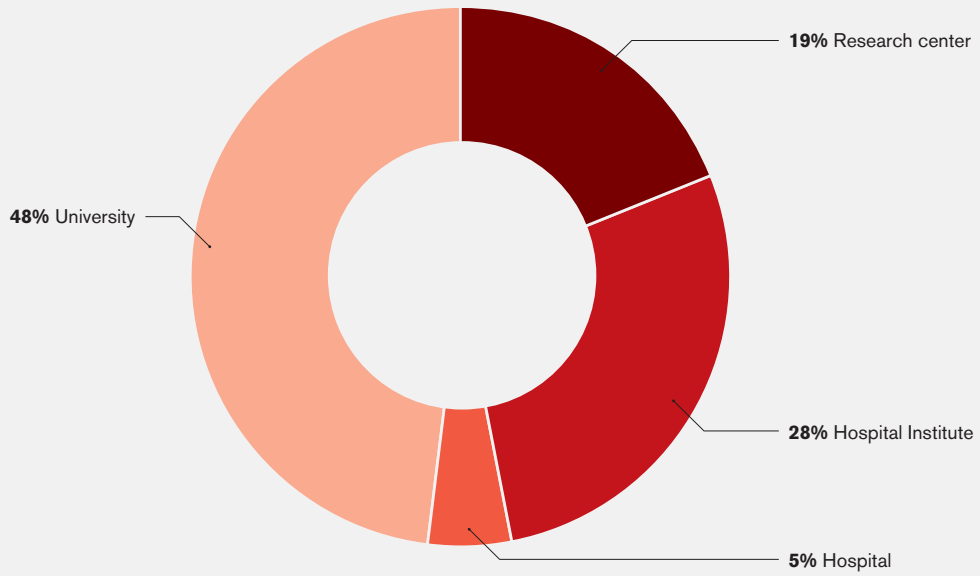
E. RESEARCH GROUPS

The Biocat Directory lists a total of **573 research groups** working in the health and life sciences or related disciplines, like nanotechnology or photonics. This figure includes, on one hand, the *consolidated research groups* (GRC) and *emerging research groups* (GRE) recognized by AGAUR in their latest call for research grants in 2009 that are active in the life sciences (485) and, on the other, all of the groups Biocat has registered of those active at universities, research centers and hospitals that didn't receive this designation because they did not yet exist or because they were still in the early stages.

However, this figure is well below the number listed on the websites and in year-end reports of Catalan research centers working in the fields this report covers, which are listed in table 2. In total, we would be looking at 935 research groups, although part of these may be included on other lists as associated with other universities or hospitals. Biocat is working to extend the list of groups in its directory. In any case, the data provided in this section is based on the 573 groups available as of 30/6/2013.

48% of the groups listed in the Biocat Directory originated in universities (276) and 47% in research centers (269), while only 5% (28) are associated with hospitals. However this figure must be clarified because, as we explained in the section on hospitals, these bodies channel their research through hospital research institutes, which are home to 163 of the registered groups (graph 24).

Graph 24 **Entity of origin of life sciences research groups**

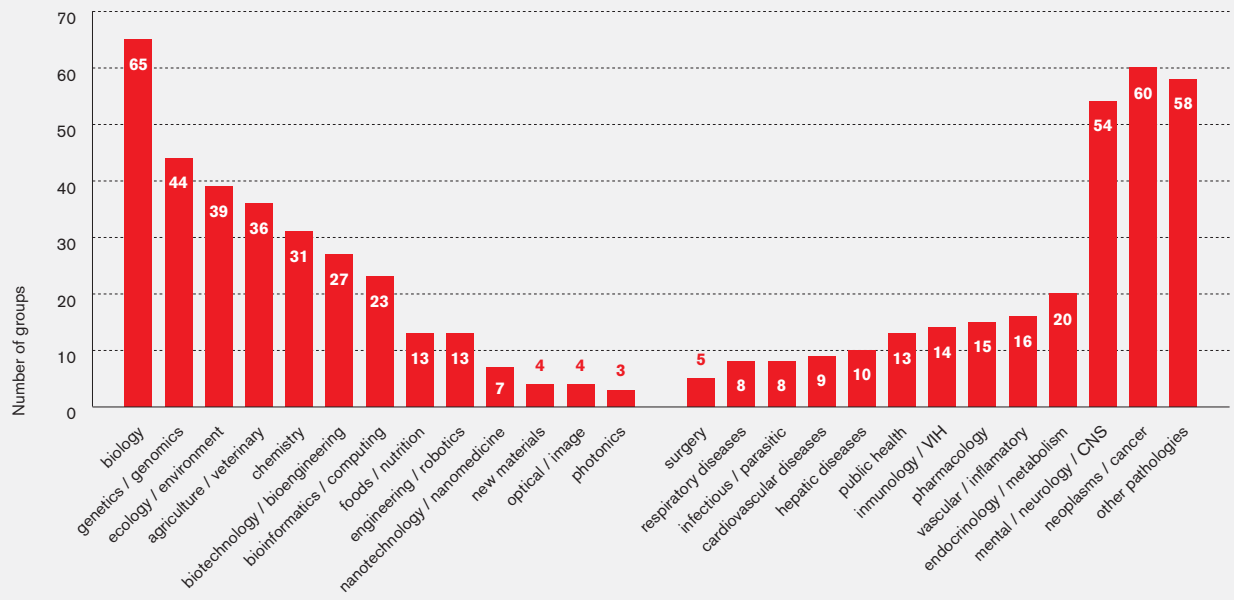


Source: Biocat Directory

Nearly 51% of the research groups in the Biocat Directory (290) carry out research into specific pathologies, noteworthy among which are cancer —the focus of 60 registered groups— and mental and neurological diseases (54 groups). At least half of the groups that work in endocrinology/metabolism focus on diabetes. The *Others* category includes various therapeutic specialties studied by one to four groups: pathologies of the digestive system, developmental studies, muscular conditions, application of nuclear magnetic resonance, osteoporosis, ageing, rheumatology, pancreatic conditions, etc.

The other half of the groups work in fields not directly related with human health therapeutics (agriculture/veterinary, food production and processing, ecology/environment, etc.) or in basic and applied research in fields like biology, bioinformatics, photonics, optics, chemistry and nanotechnology, which can have various uses (therapeutics, medical technology, industrial processes, etc.). Areas of research like genetics/genomics and engineering/robotics cross several therapeutic areas in the classification of the work of various groups (graph 25).

Graph 25 **Work areas of research groups in the BioRegion**



Source: Biocat Directory

F. RESEARCH FACILITIES, TECHNOLOGY PLATFORMS AND CENTERS

The BioRegion of Catalonia has **two large-scale research facilities**, which are the *Mare Nostrum* supercomputer at the Barcelona Supercomputing Center – Centro Nacional de Supercomputación (BSC-CNS),[19] created in 2005 through a joint initiative of the Spanish government, the Government of Catalonia and the UPC, and the ALBA-CELLS Synchrotron,[20] a project that was in the works for a long time (the first studies were commissioned in 1994, construction was carried out between 2006 and 2010, and the first beamlines went into operation in May 2012) that has just approved a new strategic plan for 2013-2016 with the aim of reaching its full potential and occupying the place it deserves as one of the great science facilities in Europe. The synchrotron was built with joint funds from the Spanish government and the Government of Catalonia and is managed by the CELLS consortium (Consortium for Construction, Equipment and Exploitation of the Synchrotron Light Laboratory).

In addition to the services offered by the BSC and ALBA Synchrotron, researchers in the biocluster have access to an additional **118 scientific and technological platforms**, including the sequencing services of the National Genome Analysis Center (CNAG).

Additionally, **12 technology centers** in various specializations offer their services to businesses, with those focusing on the agrifood, pharmaceutical and medical technology industries being particularly relevant to the scope of this report. The technology on offer is highly varied and can range from specialized analytical services through process engineering, and conceptualization and design of new products. These centers work in areas like food (quality control, packaging, preservation, etc.), electronics, materials (corrosion, wear, biomaterials, new compounds, nanomaterials, etc.), smart fabrics, toxicology and bioremediation.

Barcelona Supercomputing Center

The Mare Nostrum supercomputer housed at BSC is ranked 29th on the list of the fastest supercomputers in the world (www.top500.org). Its calculation capacity is 94.21 teraflops (94.21 billion operations per second) and, after its latest upgrade, has a main memory of 96.6 TB and a 2-PB storage disc.21 The BSC is organized into four departments, one of which is devoted to life sciences research, with five work groups researching various areas of application of computational theory and science for the study of living beings, from computational biology through bioinformatics for genomic studies. The supercomputer allows scientists to model the mechanisms of action of molecules, cells or complex organs, or the way drugs and DNA interact, for example, and is absolutely essential for processing the enormous amount of data generated by the growing capacity of genome sequencing.

Since 2011, the BSC has been certified as a *Severo Ochoa Center of Excellence*, a program of the Secretariat of State for Research, Development and Innovation that recognizes centers working in frontier research that are among the best in the world in their field. Catalonia is home to six of the 13 Severo

19. www.bsc.es

20. www.cells.es

21. A TB (terabyte) is 1012 bytes and a PB (petabyte) is 1015 bytes.

Ochoa centers in the nation (see chapter III). The BSC is also one of the 10 nodes that make up the Spanish Institute of Bioinformatics, whose mission is to provide top-notch services for the national and international scientific community in bioinformatics, and particularly in its application in fields like functional genomics, transcriptome analysis using RNA-Seq, genotyping, medical genetics, and molecular dynamics simulations. Six of the 10 nodes are groups or programs belonging to centers located in Catalonia (CRG, IRB, UPF, IMIM, CNAG and BSC).

The BSC is part of the PRACE initiative (Partnership for Advanced Computing in Europe),[22] made up of 25 elite supercomputing centers in Europe, and which the BSC leads jointly with the CINECA (Italy), GCS (Germany) and GENCI (France) supercomputers.

ALBA-CELLS Synchrotron

ALBA is a third-generation synchrotron –the newest in operation in the world— that is among the best in its class, given its technical characteristics.

There are currently 51 operational synchrotrons in the world, 18 of which are in Europe, 9 in North America, one in South America, three in the Middle East, 19 in Asia and one in Oceania. Of these, 20 are third-generation synchrotrons, four of which are high energy and the rest medium energy, which is the group to which ALBA belongs. Right now there are five new synchrotrons of this type being built around the world —in Sweden, Poland, the United States, Jordan and Taiwan— and two more are in the project stage, in Brazil and Armenia. Based on the useful photon energy produced and emittance (radiation emitted), the synchrotron in Cerdanyola is among the most efficient, just behind, although with very similar levels, the Diamond (Chilton, United Kingdom) and Soleil (Paris, France) light sources.[23]

Despite this positive competitive position on a technical level, the ALBA synchrotron is facing challenges in becoming fully competitive as a scientific facility. The first challenge posed by the ALBA team, which has been led by Dr. Caterina Biscari since July 2012, is full utilization of current resources: the two accelerators (Linac and Booster) and seven beamlines built in phase I. In this regard, the facility has proposed some technological improvements to the active beamlines and increasing the number of hours of operation of the whole facility, which in 2012 totaled 4,272 and is hoped to reach 6,000 hours of operation as of 2015. They also aim to develop scientific capacities in three specific areas: neuroimaging for nanoscience and nanotechnology; pump-and-probe (spectroscopy) to research the dynamics of chemical, physical and biological processes; and new coherent diffraction techniques.

Despite these projected developments, it must be noted that most of the operational synchrotrons in its class have more beamlines up and running. Phase I of ALBA, which began in May 2012 and ended in early 2013, put seven beamlines into operation, when the Diamond synchrotron already has 20 and 11 more under construction, Soleil has 26 operational and three under construction, and the SSRF synchrotron in China, which only has seven operational beamlines like ALBA, has 23 under construction. This issue is relevant for two reasons:

22. http://www.prace-ri.eu

23. ALBA. Strategic Plan 2013-2016, p. 40-42. http://www.cells.es/AboutUs/strategic-plans/strategic-plan-2013-2016

first, because given the technical and human resources needed to operate the accelerators, the ratio of cost to scientific production is much worse with fewer active beamlines; and second, more operational beamlines available opens up opportunities to attract more significant international scientific projects, with the positive impact that would have on local research. Given its design, the ALBA Synchrotron could have up to 31 beamlines operating simultaneously. The goal set in the Strategic Plan 2013-2016 is for seven to go into operation over this period and to begin preparations on eight more that could be operational by approximately 2020. However, the investment needed to make these projects possible has not yet been tied down; a challenge that the CELLS consortium must tackle urgently if Catalonia and Spain hope to ensure the scientific and economic competitiveness of this large-scale facility.

The ALBA Synchrotron currently has a team of 160 people and an operating budget of €32.4 millions. If the seven additional beamlines become operational, the facility expects to have a team of 204 people and annual budget of €48.7 millions in 2016.

Three of the seven beamlines in phase I of the ALBA synchrotron, given their technology, are geared towards research projects in the life sciences (MISTRAL, NCD and XALOC), as would three of the beamlines expected to become operational between 2013 and 2016. So far, ALBA has held two calls for academic users (November 2011 and September 2012), receiving in each approximately 200 proposals. The projects selected under the first call were executed in two groups, from May to December 2012 and from January to March 2013, and those from the second call are being carried out from April 2013 through March 2014. The XALOC beamline was requested the most in both the first and second calls (24.75% and 20.86% of the projects, respectively); on the other hand, the MISTRAL beamline, with more innovative technology, was the least requested (8.42% and 3.74% of the projects, respectively).

The ALBA Synchrotron has also signed agreements to carry out research for industry, specifically with multinational corporation Henkel and pharmaceutical company Almirall.

Scientific and technological platforms

The Biocat Directory lists 118 scientific and technological platforms serving researchers in the BioRegion. It must be noted, however, that some of these listings are for bodies created to jointly manage various platforms, like for example CCiTUB (University of Barcelona Science and Technology Centers), which operates the UB's 35 technological platforms grouped into eight areas: spectroscopy; mass spectrometry; microscopy and advanced characterization; nuclear magnetic resonance; radiation protection; biotechniques (cytometry, genomics, granulometry, etc.); animal facilities; and support technology, including mechanics, electronics and vacuum chamber. The CCiTUB catalog of services offers up to 17 types of technology for biotechnology research and 15 for healthcare research.[24]

Regardless of their size, 45 of the 118 registered platforms (38%) are managed by research centers (29 of these by hospital research institutes), 61 by seven universities and the other 13 by science parks (PCB and PRBB) or through mixed management models. In the case of the PRBB, it is managed by the various scientific bodies located at the park (IMIM, CRG, CMRB, CREAL, IBE-CSIC and the UPF Department of Experimental and Health Sciences) in order to jointly offer all of their platforms and services —16 in total— to the scientific community. These range from one of the most complex robotized animal facilities in Europe (PRBB) to the CRG/UPF Proteomics and Flow Cytometry units and the biobank or the IMIM-Hospital del Mar Molecular Cytogenetics Platform, among others.

The UB has 9 of the registered platforms —including the CCiT and its 35 platforms— but the fact that the 8 platforms managed by the PCB are also linked to this university must also be taken into account. The Autonomous University of Barcelona (UAB) has 21 scientific and technological platforms and the University of Lleida (UdL), 18.

These platforms specialize in a wide variety of fields and provide the scientific community working in the biosciences with services in techniques like cell cultures, chromatography, spectrometry, radiology, bioinformatics, etc. Genetic research, with more than twenty platforms devoted to both human and animal genomics and proteomics, is one of the areas with the most scientific and technological resources.

Biocat has published a guide, which is currently being updated, to the scientific and technological platforms in the BioRegion with a detailed technical description of their resources and conditions of access, which can be consulted and downloaded from the Biocat Directory (www.biocat.cat/directory).

24. http://www.ccit.ub.edu

G. SCIENCE AND TECHNOLOGY PARKS

As Pere Condom pointed out in the *2011 Biocat Report* ("Science and biotechnology parks", p. 70-97), parks have facilitated and promoted the clustering of the biosciences sector, both in Europe and the United States, acting as spaces to bring together the various stakeholders that intervene in the value chain: universities, research centers and companies, with particular attention paid to entrepreneurs and technology-based SMEs. Collaboration with local authorities has also allowed these settings that facilitate technology transfer in the bio arena to become more attractive to large national and international companies, which have also moved into parks or their surroundings, thus completing the ecosystem.

In Catalonia there are currently some twenty science and technology parks: Xpcat, the association of these parks, has 13 members and 8 associate members, but two of these 21 parks —the ones in Tarragona and Central Catalonia (Manresa)— haven't yet passed the project phase and another three specialize in sectors not related to the biosciences.[25] Over the period covered in this report, the Biopol'H consortium was dissolved (February 2013), which had been created in 2008 to start up a Health Park around Hospital de Bellvitge. Thus, there are currently **16 science and technology parks** in Catalonia with activities related to the life sciences, but only 11 are home to biotechnology, pharmaceutical, medical technology or specialized services companies registered in the BioRegion (graph 26).

Table 6 **Science and technology parks active in the life sciences**

Xpcat members
Barcelona Science Park (PCB)
Lleida Agri-food Science and Technology Park (PCiTAL)
Science and Technology Park of the University of Girona
Barcelona Biomedical Research Park (PRBB)
UAB Research Park (PRUAB)
laSalle Technova Barcelona
Parc UPC - Research and Innovation Park of the UPC
Parc Tecnològic del Vallès
TecnoCampus Mataró-Maresme (TCM)
Tecnoparc, Parc Tecnològic del Camp
22@Barcelona
Barcelona Nord Technology Park (Barcelona Activa)
Xpcat Associate Members
Esade Creàpolis
BZ Barcelona Zone Innovation
Parc de l'Alba
Science and Technology Park of Terrassa (Orbital.40)

25. b_TEC Barcelona Innovation Technology (energy and water), UPF Research Park (social sciences and humanities), and Science and Technology Park for Tourism and Leisure.

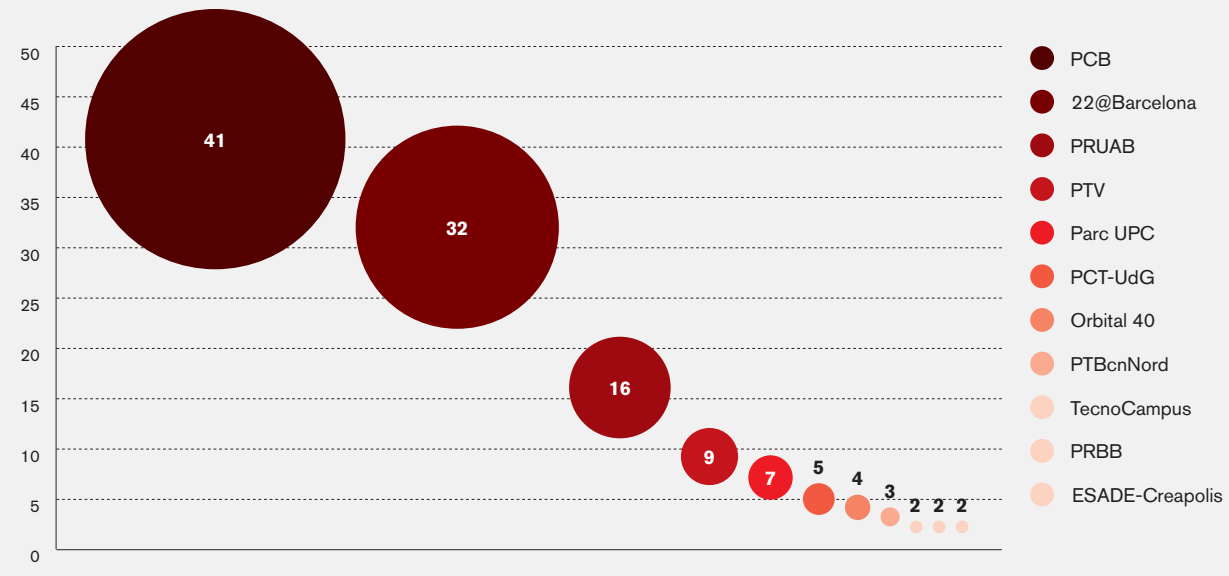
By critical mass and specialization, the PCB and PRUAB are the closest to the biopark model Condom discussed. 22@Barcelona is, in reality, a *technological district*, where municipal policies have favored the establishment of knowledge-intensive companies, especially in ICT and audiovisuals, but where economic conditions, the availability of newly built spaces and communications have attracted the corporate headquarters of large biopharmaceutical and medical technology companies.

Parc Tecnològic del Vallès was the first park in Catalonia and, along with the one in Zamudio, in the Basque Country, one of the first in the nation. However both were business projects, without connections to universities, and thus far from the model posed, although interesting as industrial parks with value-added services.

The PRBB, despite its clear specialization in bio and concentration of research centers, is limited in its ability to attract a large number of companies by its physical characteristics.

The high concentration of bio companies in the city of Barcelona makes it difficult for other initiatives to take on a critical mass of companies if not by encouraging entrepreneurial initiatives, which is now facing many difficulties. Condom also points out in the aforementioned article that the appearance and growth of parks around the world has gone hand in hand with favorable economic factors and tax incentives to encourage and attract companies, more than just availability of space or specialized services. Đ

Graph 26 **Companies in the BioRegion located in science and technology**



Source: Biocat Directory

III. RESEARCH, TECHNOLOGY TRANSFER AND INNOVATION

RESEARCH, TECHNOLOGY TRANSFER AND INNOVATION

The *2013 Biocat Report* sets out to analyze the main activities and developments in research, technology transfer and innovation as a continuum that can't be segmented, because it is precisely the flow between these three links of the value chain that provide the most significant information on the state of the sector.

This chapter, like those that follow, features an initial summary of overarching global trends, followed by the main milestones reached in Spain over the 2011-2013 period, and then moves on to analyze the evolution and status of the issue in Catalonia.

More than an exhaustive list of cold facts, we emphasize the data and activities we consider to be most significant in terms of the evolution of the sector over the past two years and carry out an initial analysis to detect the main strengths of the BioRegion and the weaknesses that should be addressed. In any case, the indicators on which this analysis is based are explicitly discussed and made available for new studies.

Before starting on the summary of overarching global trends, it is worth remembering that the *life sciences* encompasses a wide range of research, technology-transfer and innovation activities that have an impact on other economic sectors. On one hand, we have the developments derived from the application of biotechnology in the fields of health, food, agriculture and livestock, the environment, and energy. On the other, we must consider applications of biotechnology in various industrial-manufacturing processes (textiles, detergents, cosmetics, etc.). Furthermore, we must take into account —as we have seen in the chapter on stakeholders— the complementary field of medical and healthcare technology.

The biomedical arena, which encompasses, on one hand, the production of drugs and biological-based diagnostic systems, and, on the other, various medical devices and healthcare technology for prevention, diagnosis, treatment and rehabilitation, right now is undoubtedly spearheading development in the life sciences sector. Although the creation and use of productive technology from the manipulation of living materials, basically in agriculture and food production, has a centuries-long history, the *explosion* of biotechnology is linked to the development of genetics after DNA was discovered by Watson and Crick (1953). The full sequencing of the human genome, in 2003, was a turning point, accelerating and changing the focus of medical research, which concentrates on discovering the underlying causes and genetic mechanisms behind diseases in order to find new therapeutic approaches that allow us to not only to treat but also to prevent them.

By volume, the energy and agrifood sectors are clearly those that can drive the development of a global bioeconomy. However biotechnology still carries a relatively smaller weight in these sectors, although it is increasing. On the other hand, biotechnology is at the heart of all scientific and technological development in health, and is radically transforming the pharmaceutical and medical technology sectors. Therefore, throughout this chapter we will pay special attention to the biomedical sector, which is also, as we have seen in the previous section, the main activity of the majority of stakeholders in the Catalan life sciences sector. However we also include the most significant data available on other subsectors (food, agro-production, energy, etc.) for the world, Spain and Catalonia.

GLOBAL TRENDS

THE HEALTH SECTOR IS EXPERIENCING A PROFOUND TRANSFORMATION, DUE TO INTERNAL (BUSINESS MODEL) AND EXTERNAL PRESSURES (CHANGING DEMOGRAPHICS, ECONOMIC CRISIS, ETC.)

Various scientific, social, economic and political factors are bringing about a profound transformation in the health sector around the world. On one hand, despite the spectacular scientific advances in knowledge about diseases, the production of new drugs has become much more expensive and the difficulties and time required to take a new drug to market have also increased. On the other hand, healthcare systems in developed countries —currently the main market for drugs and medical technology— are being squeezed by two opposing forces: rising costs, as a result of the ageing population and increase in chronic diseases, and the pressure to lower public healthcare budgets as a result of the crisis. In emerging countries, like Brazil and China, the pressure comes from the growing middle class that is beginning to demand accessible quality social services and the obstacles are not as much due to the economy as to politics and technical issues.

These opposing forces have an impact on drug production —where biotechnology firms are gaining ground at the expense of pharmaceutical companies forced to transform— but also on medical technology, which has a growing importance in healthcare systems seeking to reduce hospital stays by promoting patient self-monitoring and remote follow-up for those suffering from chronic conditions. Genetic research gives us an immense amount of data that must allow us to develop personalized medicine —knowing more about each disease, better understanding how each individual develops it and how they react to treatment— but also brings the challenge of managing and exploiting immense databases and finding the most efficient way to apply this knowledge in clinical practice and to develop new therapeutic approaches that unite drugs with a companion diagnostic device.

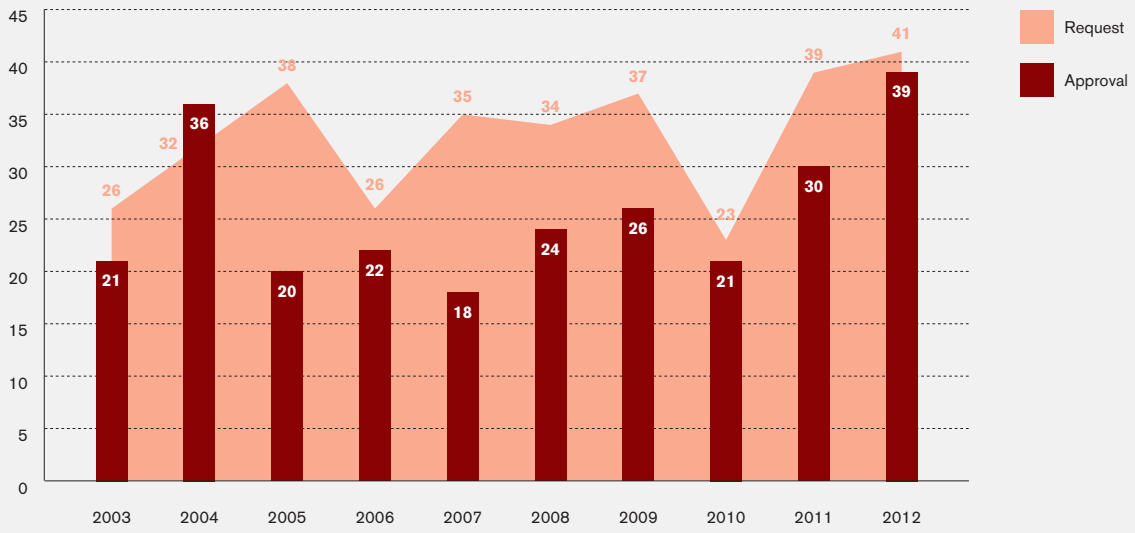
DEVELOPING A NEW DRUG CAN TAKE 15 YEARS AND COST UP TO $1,500 MILLIONS

According to data in the latest Burrill Report (April 2013), if developing a new drug in 1980, on average, took 7 years and cost $200 millions, by 2010 the average time had doubled (15 years) while the investment required had increased more than seven-fold, to $1,500 millions. The same report cites studies that believe these estimations are very modest: the InnoThink Center for Research in Biomedical Innovation calculates that, if we include R&D expenditure on projects that have had to be set aside during development, the investment required to take a new drug to market is more like $4,000 millions.[1]

1. Burrill 2013, p. 13

In 2012, the FDA (Food and Drug Administration) approved 39 new drugs (NME, new molecular entity), double the average approval rate for this US regulatory body since 2003 (graph 27). In the 1990s, the average rate was 50 new products per year, a number that fell to 21-22 products per year in the following decade. Although this increase in drugs approved improves the perspectives for the biopharmaceutical industry, it also raises many questions regarding the real return on investment each drug may have. Getting a product approved is only the first step to move into a market in which those who pay for medical treatment —mainly public health systems in Europe and private hospitals and insurance companies in the United States— demand to see the differential value of any new product before assuming higher prices for a novel therapeutic for a disease for which treatment is already available.

Graph 27 **Approval of new drugs (NME) by the FDA 2003-2012**



Source: FDA

Faced with this dilemma, large pharmaceutical and biotechnology companies channel their efforts into products with the potential to be first-in-class or best-in-class that can show an unquestionable leap forward in treating a specific ailment. But the competition for each new treatment is fierce: a report published by the PhRMA (Pharmaceutical Researchers and Manufacturers of America) in late 2012 shows that there are currently 93 potential new treatments for Alzheimer in phase I or phase II clinical trials in the United States;[2] normally only one in five drugs that reach the clinical phase get regulatory approval and in this case it is clear the proportion will probably be even lower.

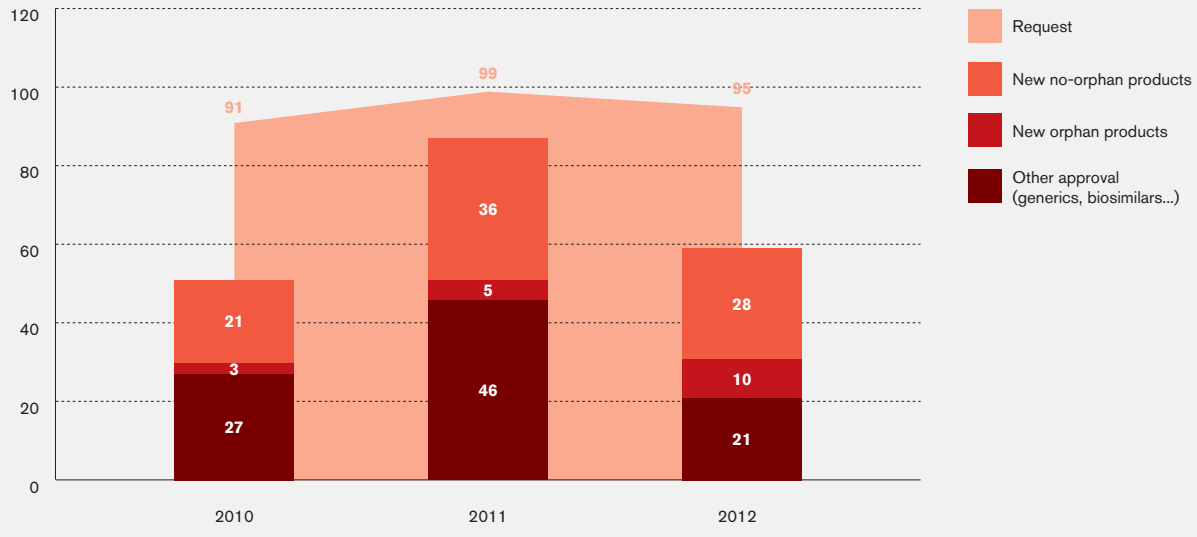
The aforementioned data on FDA approval includes only a small number of biotechnology drugs (based on complex recombinant DNA molecules); specifically only six for 2012. Each year the FDA also approves very few biological products

2. Alzheimer's Disease. 2012 Report, PhRMA (http://www.phrma.org/sites/default/files/pdf/alzheimers2012.pdf)

used in medicine that are not strictly drugs (made with proteins, nucleic acids, cells or tissues from living beings or synthesized in the laboratory using genetic-engineering techniques). However the approval figures are even lower: 10, in 2012; 8, in 2011; 7, in 2010; and 12, in 2009. And most of these biological products are vaccines. In fact, the list of biological products approved by the FDA includes 77 vaccines and 16 products derived from plasma, but only 10 cell therapies.[3] Regarding gene therapy —treatments that can modify or correct pathological alterations in a patient's genome— there is only one drug that has been approved in the world: Gyblera, the first drug to treat lipoprotein lipase deficiency, which the European Commission authorized in November 2012 after getting the green light from scientific committees at the European Medicines Agency (EMA).[4]

The EMA —which doesn't have exclusive legal authority over approval of new drugs marketed in the EU, but does have this power over those derived from the use of biotechnology, as well as those to treat rare diseases, HIV/AIDS, cancer, diabetes, neurodegenerative, autoimmune and viral diseases— approved 38 new products (orphan and non-orphan drugs) in 2012; 41 in 2011; and 24 in 2010. It must be noted, however, in assessing these figures, that large multinational corporations tend to seek approval from the FDA before submitting a product to the EMA.

Graph 28 **Approval of new drugs by the EMA 2010-2012**



Source: Compiled internally with data from the 2012 Annual Report and the EMA registry of authorized medicines.

In any case, advances in genetic medicine, which contribute to knowledge not only of the underlying causes of diseases but also to treatments to improve results in specific patient segments, have shown that the days in which a single therapeutic compound could treat a specific disease in millions of patients are

3. http://www.fda.gov/BiologicsBloodVaccines/default.htm
4. http://www.bbc.co.uk/news/health-20179561

over. The days of blockbusters —widely used drugs with turnover above $1,000 millions per year— are gone, just when the business model that had been created around them has gone into crisis.

Over the period covered in this report, the patents have expired on many blockbusters that had sustained growth and profit levels in large multinational pharmaceutical companies. This includes drugs like Lipitor (Pfizer), for cholesterol, which posted sales of nearly $10,000 millions between 2010 and 2012 in the Untied States alone; Plavix, for cardiovascular illnesses, for which Bristol-Myers Squibb returned the rights to Sanofi in January of this year after seeing $15,000 millions in turnover from sales (USA) over the time they held patent exclusivity; and Seroquel, for bipolar disorder, schizophrenia and depression, with which AstraZeneca posted turnover of nearly $10,000 millions in the North American market between 2010 and 2012, and from which they have created a new formulation (Seroquel XR) the patent to which they are currently defending in court from manufacturers of generics like Mylan around the world.[5]

In total, the patents that have expired or will expire between 2011 and 2016 —which make up between 20% and 65% of the pipeline in companies holding these patents— will entail an estimated drop in sales of more than $100,000 millions[6] for large pharmaceutical companies.

Challenges and strategies

Decreased productivity, increased research costs, a drop in revenue due to expiring patents and pressure to reduce healthcare expenditure —either through budget cuts or regulations to control pricing, or a combination of the two as seen here at home— have forced the pharmaceutical industry around the world to revise not only their short-, middle- and long-term strategies but also their overall business model.

RARE DISEASES, OPEN INNOVATION AND EMERGING MARKETS ARE THE FOCUS OF THE STRATEGIES BIOPHARMACEUTICAL COMPANIES ARE EMPLOYING TO OVERCOME ECONOMIC PRESSURES AND DECREASED PRODUCTIVITY

In response to these pressures, companies have adopted various strategies. On one hand, they have tried to identify and gear research towards unmet needs, and this has led to the emergence of **rare diseases** as a new field of growing interest. It is what some experts call the move from the blockbuster strategy towards a nichebuster strategy: the groups affected are very small, but they are highly motivated and implicated due to the lack of alternatives and devastating effects of many of these diseases. It is easy to recruit patents for clinical trials, these are cheaper because results can be validated with much fewer participants, and patients are willing to pay —or pressure public and private entities to pay— the high prices normally charged for these therapies once they reach the market.

According to a study published by PhRMA,[7] in October 2011 there were 1,795 NME (new molecular entity) being developed in the USA that were designated

5. Terry Baynes, U.S. appeals court finds Astra's Seroquel XR patent infringed, Reuters, 14-2-2013 (http://www.reuters.com/article/2013/02/15/us-astrazeneca-seroquel-idUSBRE91E02D20130215)
6. Pharmaceutical Industry Bracing for Record Patent Expiries, EvaluatePharma Data Reveals, PR Newswire, Londres, 2/2/2011 (http://pharma.about.com/gi/o.htm?zi=1/XJ&zTi=1&sdn=pharma&cdn=b2b&tm=91&f=00&tt=2&bt=5&bts=5&zu=http%3A//www.prnewswire.com/news-releases/pharmaceutical-industry-bracing-for-record-patent-expiries-evaluatepharma-data-reveals-115099789.html). Vegeu també: Biotech 2012: Innovating in the new austerity. Burrill 26th Annual Report, Burrill & Company, San Francisco (CA, EUA), 2012, p. 4.
7. Innovation in the Biopharmaceutical Pipeline: A Multidimensional View, 2013, http://phrma.org/sites/default/files/pdf/2013innovationinthebiopharmaceuticalpipeline-analysisgroupfinal.pdf

for orphan diseases, and 30% of all drugs approved by the FDA over the last five years were orphan drugs. The EMA (European Medicines Agency) has designated 962 orphan drugs since 2000, only 75 of which have been approved for market sales.[8] The 20 rare diseases with the most designations in Europe account for 695, a list headed up by oncological diseases like acute myeloid leukemia (45 designations), non-Hodgkin lymphoma (38) and glioma (37).[9]

THE RARE-DISEASES MARKET IS VALUED AT MORE THAN $50,000 MILLIONS AND GROWS 20% PER YEAR

Each of the approximately 7,000 rare diseases identified affects fewer than 20,000 people, but there are a total of 25 million people in the USA alone suffering from one of them, and there is an effective, approved treatment available for only 5% of these diseases. The yearly cost per person of many treatments for orphan diseases is well over $150,000, meaning they can generate huge turnover. A recent article in The Wall Street Journal stated that at least one third of all orphan drugs currently on the market generate annual sales over $1,000 millions and that, as a whole, the global sales of these drugs brings in more than $50,000 millions per year, up an average of 20% in recent years.[10]

In Catalonia, as is discussed further on in this chapter and in the article by Marc Martinell (Mynorix Therapeutics), there is growing interest in the field of orphan diseases, both from research groups and companies.

Additionally, biopharmaceutical companies are starting up new collaboration methods —between companies or enterprise-academia— that move their research towards the concept of **open innovation**. Pfizer's CTI (Centers for Therapeutic Innovation) are well known and have reached agreements with some twenty university centers to open their laboratories and compound libraries in order to accelerate and identify new candidates in areas like oncology, cardiology and infectious and inflammatory diseases. Since they were launched in 2012, Pfizer has received more than 300 proposals and has selected 20 projects to develop in their laboratories in Boston, New York, San Francisco and San Diego.[11]

In March 2012, Merck launched the California Institute for Biomedical Research (Calibr)[12] in San Diego (California) and announced they will invest $90 millions in this center over seven years. In this case, the aim is also for the center to gain access to the most innovative ideas from basic researchers, while also allowing them to use pharmacological and medical-chemistry tools not normally available to them. Although Merck's investment in this project is significant, *Nature* noted, in their article on this topic, that the company had cut its R&D budget by $600 millions between 2009 and 2012.[13] Unlike Pfizer's CTI, Calibr hasn't reached specific agreements with academic institutions, but its calls for proposals are open to any US or international researcher with an interesting project. Merck, however, reserves the right to an exclusive license to any new drug candidates that may arise as a result of the research carried out at Calibr.

8. Community register of orphan medicinal products for human, EMA: http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm
9. Marcos Domínguez, "Cáncer, protagonista de la I+D huérfana", Correo Farmacéutico – Suplemento Farmacia & Industria, 3/6/2013, p. 4.
10. Johnathan, D. Rockoff, "Drug Makers See Profit Potential in Rare Diseases", The Wall Street Journal, 31/1/2013.
11. http://www.pfizer.com/research/rd_works/centers_for_therapeutic_innovation
12. http://www.calibr.org/
13. http://blogs.nature.com/news/2012/03/merck-forms-nonprofit-research-institute-for-academic-collaborations.html

Other companies, like Janssen (Johnson & Johnson) are committed to encouraging collaboration not with academia but with biotechnology start-ups, opting for a model similar to that of the bioincubators found at our science parks. Janssen Labs offers short-term rental on office and laboratory space, in a 2,800-m^2 building adjacent to the company's own research center in San Diego. Companies are selected based on the interest of their research and the medical and market needs their products cover, and although being selected doesn't entail any sort of link with Janssen, contact with and proximity to this center can clearly lead to collaborations.[14]

Promoting the exchange of knowledge and open innovation, however, is a strategy employed not only by companies. Governments, academic institutions and research centers, as well as patients' associations and other stakeholders in society, are promoting networks aimed at accelerating biomedical research and bringing new solutions for health problems to the market, a process that is also intensifying here in Catalonia (see *Knowledge networks and open innovation*).

BIOPHARMACEUTICAL COMPANIES ARE LAUNCHING NEW COLLABORATION PROGRAMS WITH ACADEMIA AND RESEARCHERS TO ACCELERATE INNOVATION

14. Burrill 2013, p. 26

KNOWLEDGE NETWORKS AND OPEN INNOVATION

In the report *Knowledge Networks and Markets in the Life Sciences* (2012),[1] the OECD confirms that the rise of knowledge networks —public, private and mixed— is mostly due to two emerging phenomena: wide-spread acceptance of the need for open innovation strategies in order to continue advancing in the scientific arena, and a growing demand for social participation in decisions that guide research and innovation. Both of these trends have benefitted from recent advances in information technology, allowing for processing of large quantities of data and direct, real-time connections with millions of people all over the world.

The OECD report distinguishes between different types of networks, which are not necessarily mutually exclusive, as can be seen in some of the most noteworthy examples in the biosciences arena. These include a) data registries and repositories; b) platform technology and tool providers; c) research consortia and public-private partnerships; d) intellectual property pools, clearinghouses, exchanges, online auctions and brokers; and e) citizen science projects.

1. http://www.oecd.org/sti/sci-tech/knowledgenetworksandmarketsinthelifesciences.htm

Through the NIH (National Institutes of Health) US National Library of Medicine, Americans can access many world-renowned databases: of publications (Medline/PubMed), of genetic sequencing (GenBank), of genotypes (dbGaP), etc. One of the most important is than on clinical trials (**ClinicalTrials.gov**), which was launched in 2000. Registration is a requirement for any drug hoping to be marketed in the US as well as for publication in indexed medical journals. Since 2008, study record details have been available online. There is growing social pressure for access to additional data (full reports) and that it be open to all researchers. In this regard it must be noted that the **European Medicines Agency** (EMA) is preparing new regulations on dissemination of clinical-trial data that is expected to go into force in 2014.

One of the key registries in the health and biomedical research arena is that of patient records in any health system. To treat individuals, it is key to advance standards and interoperability, which must allow access to patient records from within their own healthcare network but also when they are elsewhere, especially for chronic patients. To this end, the EU 7FP is funding the **DECIPHER program** (Distributed European Community Individual Patient Healthcare Electronic Record), in which Catalonia is participating through the **Agency for Health Quality and As-**

sessment of Catalonia (AQUAS). This project aims to promote the design and implementation of mobile technology to allow patients —or those caring for them— to access their medical records throughout Europe. In Catalonia, this program is part of a more wide-reaching AQUAS plan to make medical data, in a joint, anonymous format, available to researchers and society as a whole.

Falling somewhere between a data repository and a technology platform, the OECD cites examples like caBIG® (Cancer Biomedical Informatics Grid), which began as a registry of data collected by the US National Cancer Institute and has recently been transformed, under the name **National Cancer Informatics Program** (NCIP),[2] into a collaboration platform to develop IT applications for biomedical research into cancer.

The exponential growth of data for biomedical research resulting from the advancement of genomic sequencing has made it more necessary than ever to crate repositories and collaboration programs to exploit data. One of these is the **EGA** (**European Genome-phenome Archive**), created by the European Bioinformatics Institute (EBI) with research and management collaboration from CRG researchers (see details in the article by Dr. Arcadi Navarro, *Impact of genomics on clinical research*).

One of the fields in which open innovation is most necessary, and quite possibly most fruitful, is that of the conceptualization, design and production of new medical technology, which combines the interests and knowledge of engineers, scientists, medical professionals and business entrepreneurs. One example of a public-private partnership and collaboration network in this field is the **CIMIT** (**Center for Integration of Medicine and Innovative Technology**), promoted by Boston University, Northeastern University, the Harvard School of Medicine, MIT and six private and public hospitals from the Boston area (Massachusetts). CIMIT aims to encourage the emergence of initiatives and the development of innovation projects by members of participating entities, while also, through their Office of Technology Implementation, favoring collaboration with industry and institutions outside of the network.

Closer to home, there is a growing number of **themed networks** aimed at boosting research and academia-hospital-industry transfer in specific therapeutics or areas of knowledge. In late September 2013, the **Barcelona Respiratory Network** (BRN)[3] was launched as a foundation with a board of trustees comprised of pulmonologists and researchers from Catalan university hospitals and research centers (H. Clínic, H. de Bellvitge, H. del Mar, H. de Sant Pau, H. Germans Trias i Pujol, CREAL), pharmaceutical and healthcare-technology companies (Aldo-Unión, Almirall, Esteve, Ferrer, Leti, Linde) and social organizations, like the Catalan Pulmonology Foundation. The main objective is to promote research and accelerate innovation in respiratory health, and as such they set out to promote activities to generate resources for research, hold specialized international events in respiratory medicine, boost training in research in this area and provide guidance for companies and institutions. BRN thus joins the **BioNanoMed** alliance, made up of research groups and companies working in bionanomedicine, and the **Oncocat** network, which brings together companies and research institutions working on cancer.[4]

In this setting of open networks promoting biomedical research and innovation, patients and patients' associations play an increasingly important role. Traditionally, these organizations were geared towards attracting financial resources —above all in the USA— and defending the interests of the group before the government —above all in Europe— but they are now playing other roles that range from exploring new models to coordinate research and getting involved in recruiting patients for clinical trials to attracting intellectual property and creating their own registries and data repositories, which they make available to researchers.

Various organizations that represent those affected by rare diseases in the USA have been particularly active in this regard. Thus, the **Myelin Repair Foundation** (MRF) of Saratoga (California) has not only raised $45 millions for research, with which it has funded the work of eight groups of excellence, but also opened its own Translational Medicine Center in January 2012, where any research center or company working on myelin repair can carry out trials on drug candidates. The MRF also covers the cost of registering any university patents that may be of in-

2. http://cbiit.nci.nih.gov/ncip

3. www.brn.cat

4. See www.bionanomedcat.org and www.oncocat.org

terest in research on myelin and run the risk of getting pushed aside for lack of resources at academic institutions.[5]

These entities incentivize research and drug development in areas that are not very attractive for pharmaceutical companies —for example, the **Cystic Fibrosis Foundation** of Bethesda (Maryland) has invested $145 millions to develop new drugs at Vertex Pharmaceuticals, one of which, Kalydeco, was approved by the FDA in January 2012— but also call into question current models of translational research and clinical development and work to change them.[6]

Several voices are questioning the efficacy of research, above all in the clinical arena, and of healthcare protocols, calling for increased patient participation in changes considered necessary. A recent editorial in *The Lancet*[7] quoted Iain Chalmers and Paul Glasziou's estimation that 85% of biomedical research —on which $160,000 millions is spent each year around the world— is wasteful or inefficient either because it isn't relevant for clinicians or patients, doesn't use the appropriate design and methods, isn't unbiased or isn't clinically meaningful. Focusing on clinical trials, Tomasz Sablinski, director of **Transparency Life Sciences**[8] —a company that defines itself as "patient-centered" and that develops drugs for chronic diseases— affirms that "clinical trials are 80% too expensive; 80% are trials that no one wants; and they all use technology from the 80s."[9] The company has created a network of doctors, patients and researchers and designs its clinical trials through crowdsourcing, while providing free access to data from throughout the development process. They currently have three projects underway to evaluate candidates for Parkinson, multiple sclerosis and Chron's disease.

In Catalonia, where there are approximately 160 patients' associations[10] with noteworthy weight of those for the relatives of mental patients and those with neurodegenerative diseases like Alzheimer, the patent revolution recently vindicated in an editorial in the *British Medical Journal*[11] is yet to arrive. Engaging patients is key not only because it "will reduce healthcare costs through the avoidance of unnecessary investigation and treatment," affirms the BMJ, but also because "expertise in health and illness lies outside as much as inside medical circles and that working alongside patients, their families, local communities, civil society organizations, and experts in other sectors is essential to improving health."

5. "Patient Power", Nature Biotechnology, Vol. 30, Issue 9, September 2012.
6. Idem.
7. www.thelancet.com, Vol. 381, 2/2/2013
8. transparencyls.com
9. The Burrill Report, Vol. 3, Issue 1, January 2013.
10. www.somospacientes.com
11. Let the patient revolution begin, BMJ 2013;346:f2614 (14/5/2013), http://www.bmj.com/content/346/bmj.f2614

The third overarching trend identified by experts as a strategy to tackle the pressures of productivity and profits of the biopharmaceutical industry is increasing focus on **emerging markets**. The growth rate seen in the health market in countries like Brazil, Russia, India and China —the BRIC countries— has put them in the spotlight for expansion plans in large biopharmaceutical companies. However increasing government investment in research and innovation in these markets is also attracting small and medium companies, like those from Catalonia, which believe they can find partners and collaborators to develop new products geared towards both the local and international markets.

THE BIOMEDICAL MARKET IN EMERGING ECONOMIES IS GROWING THREE TIMES FASTER THAN IN DEVELOPED ECONOMIES

As the *Pricing & Market Access Outlook 2012* study by the IMS Consulting Group points out, drug sales in *pharmerging markets* rose 16% between 2007 and 2011, but only 5% in developed markets.[15] Experts agree on the opportunities to be had in the Brazilian and Chinese markets, not only in terms of drug production and sales, but also for medical technology, alongside the growing middle class, which demands quality healthcare services. However, they also warn of the difficulties of moving into highly protectionist markets, with strong local generics markets, and where it is difficult to get optimum compensation for highly specialized products, which is where portfolios in developed markets are headed.[16]

In this complex setting, biotechnology companies —which saw profits up 37% in 2012 according to the Ernst & Young *Beyond borders* report— are achieving better results and higher profits than pharmaceutical companies. However, experts warn that most of them have done so as a result of saving and cutting R&D investment, which implies risks in an industry based on knowledge. It may be true that *Big Biotech* has a much higher growth rate than *Big Pharma*, which between 2009 and 2012 allowed them to increase investment in R&D by 38%, but this effort must also be sustained over time and the 2012 data seems to question whether this trend will continue.[17]

15. Pricing & Market Access Outlook, IMS Consulting Group, 2012, p. 17. The study covers the following countries: Argentina, Brazil, Egypt, India, Indonesia, Mexico, Pakistan, Poland, South Africa, Romania, Russia, Thailand, Turkey, Ukraine, Venezuela, Vietnam and China. The developed markets covered in the study are: the United States, Canada, the United Kingdom, Germany, France, Italy and Spain.

16. See Pricing & Market Access Outlook 2012, IMS Consulting Group, p. 17-20. For more information on the Brazilian and Chinese markets: http://bioxclusters.eu/docs-resources-2/

17. See Beyond borders: Matters of evidence, Ernst & Young, 2013, p. 23; Meg Tirrell, Biotechnology Draws Record Profit as Research Money Slows, Bloomberg, 23/4/2013, http://www.bloomberg.com/news/2013-04-23/biotechnology-draws-record-profit-as-research-money-slows.html; and Big Biotech outpaces Big Pharma, Burrill & Company says, press release, 16/4/2013, http://www.burrillandco.com/content/news/PR-BIO-2013-4-16-13-final.pdf.

BIOTECH INNOVATION BEYOND THE RESEARCH LAB: NEW PARTNERSHIPS AND NEW SOLUTIONS FOR SUSTAINABLE HEALTH CARE

Roland Wandeler
General Manager, Amgen Spain & Portugal

In tough economic times, we can sometimes overlook positive and promising developments. Biotechnology is one such example. In Spain, and particularly in Catalonia, biotechnology is emerging as a sector of immense value – as a driver of medical innovation and economic growth, but also as a source of new collaborations and new health care solutions.

Over the past decade, biotech has grown steadily, and today employs more than 20,000 people in Spain. These are the kind of highly-educated, high-value jobs all countries seek to create. It is a bright spot in this country's economy, and a sector that offers unique promise for the 21st century, since technology transfer and consistent investment are breeding new start-ups every year.

Here in Catalonia the biotechnology "cluster" includes nearly 1,000 stakeholders, covering the whole value chain, from cutting-edge biomedical research firms, to large global biopharmaceutical and medical device enterprises. In addition, biotech is the most research-intensive of all industries, generating R&D investment that inspires and supports some of the top research talent in the world - at universities, hospitals and clinics across Spain.

The growth and successes achieved in biotechnology in Catalonia and elsewhere in Spain have been characterized by increasing collaboration: between public institutions and the private sector; between large and small companies; and between government and the industry itself. The establishment of Biocat, in 2006, is an excellent example of this kind of partnership with a long-term vision.

Collaborations in basic research and clinical development were an important factor for the advances that biotechnology could bring to patients in terms of new medications. But the innovation from biotechnology companies doesn't stop here: Today we are witnessing the emergence of a new kind of collaboration, addressing a different challenge: the imperative of protecting the quality of care patients receive, while ensuring the sustainability of the health care system.

New initiatives supported by Amgen and other companies are striving to answer two key questions. First, is it possible to maintain – or even improve – quality of care, while at the same time reducing health costs? And second, can biotech companies contribute innovation beyond the research lab, and deliver solutions beyond just new medicines?

From my perspective, the answer to both these questions is "Yes.".

One example I am particularly proud of is currently underway at centers in Catalonia and elsewhere in Spain, benefiting patients with chronic kidney disease, a notoriously complicated and serious condition. As a biotech company that provides advanced medicines for these patients, we took the opportunity at Amgen to partner with leading kidney specialists and payors to develop PAR (Programa de Atención Renal - Kidney Attention Programme) a disease management program specifically tailored for the context of our health care system.

Early data from PAR show that an intelligent, intensive approach to renal care – including the sensible use of advanced medicines and improved patient compliance – can delay the progression of kidney disease and thus postpone the need for patients to begin dialysis for as much as six months. This not only improves

the quality of life for these patients, but also delivers important savings to our healthcare system.

Moving beyond simply delivering medicines, and taking our place as a source of comprehensive solutions in health care, is a smart thing for biotech companies to do. It's in the interests of patients, providers, payers and governments. And it's also in our own business interest.

At a time when the economy is suffering, we must maintain our commitment and investment, and continue building the economy of the future. And in a time when health budgets are strained, we must prove the economic value of our medicines, and of our companies as true collaborators and partners.

The reality Amgen and other biotech companies are facing is that our futures are inextricably entwined with those of our partners. Extending our capabilities and innovation to new areas is allowing us to demonstrate that sustainability in health care does not require sacrificing quality in health care. This is consistent with a long-term vision, as well as something more: an acceptance of common stewardship of the health care system.

Medical technology

Research and development in medical technology is also under significant pressure, both in the United States and in Europe. Although development time and time to market for products are, in general, shorter than for drugs, increasing FDA requirements for Class III products (for example, active implantable devices, like pacemakers, and biomaterials, for example), which must undergo clinical trials, can lengthen time to market to up to 10 years, which is a hurdle in attracting funding for R&D.

As a recent article by US expert Steve Blank points out, *"the financing of innovation in medical devices has collapsed even further with most Class III devices simply unfundable. Companies must pay a medical-device excise tax of 2.3% on medical device revenues, regardless of profitability delays or cash-flow breakeven…[Furthermore,] under ObamaCare the government's role in reimbursing for medical technology will increase. Yet two-thirds of all requests for reimbursement are denied today, and what gets reimbursed, for how much, and in what timeframe, are big unknowns for new device companies."*[18]

THE COMPLICATED AUTHORIZATION PROCESS FOR MEDICAL DEVICES IN THE USA IS A HURDLE FOR R&D FUNDING

Producers have also repeatedly demanded changes to the FDA's 501(k) procedure that applies to all medical devices not required to undergo clinical trials, as it is slow and unpredictable. Although the reform was passed in December 2012, after 4 years of work with the sector, it isn't clear that this will speed up the approval process. Additionally, it has also added stricter requirements for diagnostic devices based on collecting and processing patients' medical data to be used to make medical decisions.

The **slow approval process** for medical devices in the USA has often led US manufacturers to seek approval for their products first in Europe. However, the European stage is also changing. The EU is reviewing three directives to regu-

18. Steve Blank, Reinventing Life Science Startups – Medical Devices and Digital Health, steveblank.com, 20/8/2013, http://steveblank.com/2013/08/20/reinventing-life-science-startups-medical-devices-and-digital-health/

late medical technology in the Union[19] and one of the most controversial debates underway is that regarding granting the EMA a similar role in approving medical technology as the one it plays as the main entity for approval of drugs, like that of the FDA in the USA.

The biggest criticism of the European system is the **lack of standardization** of the approval process from one member state to another. Not only must medical technology be approved individually in each country, but the lack of standard criteria established by the bodies in charge of carrying out technical and clinical trials on the products and the regulatory differences between countries make access for producers to the EU market slower and more difficult.

ONE OF THE MOST CONTROVERSIAL PROPOSALS IN EUROPE IS FOR THE EMA TO CENTRALIZE APPROVAL FOR NEW MEDICAL TECHNOLOGY

Personalized medicine and new drugs geared towards individuals or segments of the population for which genetic diagnostic tools have been used to find mutations that explain an existing pathology or predisposition to developing one have led to many innovative drugs to be developed alongside a companion diagnostic. One of the issues currently on the table in regulatory agencies is how to efficiently manage clinical trials and authorization for two connected products, to which very different procedures apply, above all in Europe, if more effective personalized medicine is to be developed based on innovative products.

Another challenge for the future in the field of medical technology is the **convergence** of what has been called **Health-IT**, information technology for health, and consumer **personal electronic devices**, like tablets and smartphones. This, on one hand, allows health indicators to be collected systematically and exhaustively from individuals, and puts control over their health in their own hands, as it is the patient who decides how and with whom to share this data; on the other hand, by cross-referencing data from millions of patients, new devices provide information that is highly valuable for both research and clinical practice.[20]

The exponential growth of this flow of personal data, in addition to information from medical practice and hospitals (reports, medical images, analyses, diagnoses, etc.) and that generated through genetic research puts biomedical innovation at the epicenter of **big data** technology, which are IT tools that can process millions of millions of operations in a reasonable time in order to obtain information that is useful and, in this field, applicable to clinical practice. Catalonia, with one of the most powerful supercomputers in Europe located in Barcelona and several global benchmark genetics centers, is set to play an important role in this area, as we discuss further on and as highlighted in the article by Dr. Arcadi Navarro.

19. Directive 90/385/EEC regarding active implantable devices; directive 93/42/EEC concerning medical devices; and directive 98/79/EC on in vitro diagnostic devices. See also: European Diagnostic Clusters Alliance declares position on new European directive for in vitro diagnostic products, 31/7/2013, www.biocat.cat/noticies.

20. "Power to patients", Pulse of the industry. Medical technology report 2012, Ernst & Young, p. 2-12

IMPACT OF GENOMICS ON CLINICAL RESEARCH

Arcadi Navarro
ICREA Research Professor. Professor of Genetics at the UPF and director of EGA at the CRG

The cost of genome sequencing has dropped six orders of magnitude. What cost €1 million a decade ago can now be done by one researcher alone for pennies. This has led to an explosion of information on the genomes of many species, including ours. Genomics has become a fashionable field of science and the success of large international projects resulting from this, in many cases led from Catalonia, has kept the field in a permanent state of revolution.

The most significant challenge to be tackled now is integrating genomic information with clinical knowledge to understand the causes of cancer, hereditary diseases or differential response to drugs. And beyond understanding, these discoveries must also have a positive impact on our health and, why not, the economy of our countries, allowing for advanced diagnostics and cheaper, more efficient treatments.

However there are still obstacles that impede the complete fulfillment of this ideal. Today we have genomic information on thousands, or millions, of patients but this information is fragmented: data is collected and stored in isolation, by institution, by diseases or, even, by country. It is very difficult, technically speaking, to share such enormous amounts of information that, additionally, are stored in different formats and systems. In addition to these technical problems, there are also ethical issues. Participants in genomic studies tend to do so under the condition that their data, which could reveal their familial links or risk of falling ill, not be distributed (for example on Facebook, as some volunteers do). However, the current situation isn't acceptable either: most of the studies have been carried out with public funds and it is an obligation to open them up to the scientific community.

In order to resolve this situation, the European Bioinformatics Institute (EBI) created the European Genome-phenome Archive (EGA, http://www.ebi.ac.uk/ega/), a database for both safe, permanent storage and controlled distribution of all sorts of personally identifiable genetic data. The EGA, located in Cambridge (United Kingdom), is governed by the strictest security profiles. Institutions that contribute their results know that the data is properly encrypted and protected (allowing them to save on costs associated with these tasks). It also ensures that the data will only be shared after rigorous analysis of each request and only with researchers from non-profit research centers. The EGA, which already has data from more than 100 studies, has grown quickly to become a strategic resource for biomedical exploitation of genomic breakthroughs.

Both the growing size of the EGA and the enormous complexity of the analysis required to include data and make it more useful have led the EBI to share management and development responsibilities for the EGA, for which it has turned to Catalan researchers. Under the auspices of the Government of Catalonia, an initial agreement reached between the EBI and the CRG (Center for Genomic Regulation), which receives support from the BSC (Barcelona Supercomputing Center) and other institutions, allowed for work on the EGA to begin here at home in Spring 2013. In the middle term, this collaboration will allow our researchers to contribute to the analysis of data sets that previously had to be dealt with individually and, in the meantime, Catalonia is providing a crucial service to the global scientific community. This is a step forward in not only maintaining Catalonia's leadership in biomedicine, but also consolidating and strengthening this position.

Bioeconomy

Beyond the healthcare sector, the application of biotechnology in sectors like agrifood and energy has also seen significant growth in the past two years. According to data from the ISAAA (International Service for the Acquisition of Agro-Biotech Applications), the total land devoted to **biological crops** around the world reached a record-breaking 170 million hectares in 2012 and, for the first time, that in developing countries, making up 52% of the total, surpassed that in industrial countries. This figure is up 6% from 2011 and the total farmed area has increased one-hundred-fold since transgenic seeds were first used in 1996, when they were only planted on 1.7 million Ha.

Despite the intense debate regarding genetically modified organisms (GMO) in many western countries, especially in the EU, governments and agricultural organizations in a growing number of countries in Latin America and Asia are in favor of GMO and see them as positive in terms of improvements to agricultural yield and the resulting improvement to income level among rural populations. In addition to growing use, countries in Africa, Asia and Latin America are also taking on a greater role in GMO research: the media recently reported that Nigerian researchers have developed a transgenic cowpea seed resistant to pests endemic to that country, and trials are underway in various Asian countries on a strain of transgenic rice —called *Golden Rice*— developed in Chinese laboratories and enriched with vitamin A, which populations in that region have a deficiency of.[21]

THERE ARE MORE THAN 170 MILLION HECTARES OF GMO CROPS, MORE THAN HALF IN DEVELOPING COUNTRIES

Nevertheless, the main producer of biological crops in the world continues to be the United States, with 69.5 million hectares, followed by Brazil (36.6 M Ha), Argentina (23.9 M Ha) and Canada (11.6 M Ha). India and China, ranked 5th and 6th with 10.8 million hectares and 4 million hectares respectively, have huge potential for growth. Spain is ranked 17th, with 100,000 hectares of GMO crops (mainly corn), among the only 28 countries in the world that plant biological crops.

The most common biological crops are soybeans (80 M Ha) and corn, with just under 50 million hectares. 81% of all soybeans planted around the world are transgenic, as is 81% of all cotton, 35% of all corn and 30% of all canola. Canola oil and soy oil are used for biodiesel, which along with bioethanol (produced from corn and sugar cane) are the main **biofuels**, the industrial application of biotechnology with the most potential for growth.

Although biofuels currently make up a relatively small percentage of the market (only 0.7% of global energy consumption), this industry contributes $277,000 millions to the global economy and employs more than one million people around the world. In the EU alone, the production of biofuels accounts for annual investment valued at €17,000 millions and worldwide production of biofuels is growing 17% per year (27% for biodiesel). The International Energy Agency predicts that the use of biofuels and other renewable energy sources will continue to grow, but only if current subsidy level are maintained or increased. In this regard, it must be noted that the production of fossil fuels receives $523,000 millions per year in subsidies while the production of renewable energies, as a whole, receives $88,000 millions.[22]

BIOFUELS MAKE UP ONLY 0.7% OF GLOBAL ENERGY CONSUMPTION AND HAVE EXTRAORDINARY POTENTIAL FOR GROWTH

21. Javier Sampedro, "Los transgénicos 'made in China' esquivan los tópicos", El País, 3/6/2013, p- 30-31.

22. Burrill 2013, p. 207-208.

Energy production is not the only industrial application for biotechnology, which has a great capacity to create substitute products —that are less contaminating— for petrochemical derivatives, like plastics, or to replace chemical industrial processes with biological ones. This is an opportunity for many of our companies, as explained in greater detail in chapter V.

EUROPEAN AND NATIONAL CONTEXT

The research arena in Europe is being transformed, not just due to the change of model and new research and commercial strategies of big European players in the biopharmaceutical sector (Novartis, GSK, Roche, Sanofi, etc.), but also due to the changes that will go into force in 2014 to the EU funding system for research and innovation, with the Horizon 2020 program.

The European Union wants its investment in research to have a greater impact on productive innovation and, in short, for it to contribute effectively to making European industry more competitive. The Horizon 2020 program, with a global budget of more than €80,000 millions for 2014-2020, brings under a single instrument what before was included in the Framework Programs for Research and Technological Development (the latest was the 7FP for 2007-2013), the Competitiveness and Innovation Framework Program (CIP) and the European Institute for Innovation and Technology (EIT).[23]

This new budgetary framework, which is still being negotiated in Brussels, is expected to devote nearly 32% of resources (expected to be more than €27,000 M) to *research of excellence*, which includes a 77% rise in the budget of the European Research Council (ERC), previously nearly €13,300 millions. This entity, created in 2007 and highly valued by the scientific community, awards grants to researchers working in the EU based solely on quality. Catalan researchers have received a significant number of ERC grants (see graph 22), both in the category for young scientists and that for consolidated researchers.

HORIZON 2020 WILL DEVOTE MORE THAN Đ27,000 MILLIONS TO RESEARCH OF EXCELLENCE AND Đ20,000 MILLIONS TO LEADERSHIP IN INDUSTRIAL INNOVATION

The bulk of the budget for the Horizon 2020 program (38.53%, which could be more than €35,000 M) will go to projects addressing the six large-scale social challenges that have been identified as the main concerns of European citizens: mitigating the effects of climate change, improving access to renewable energy sources, developing sustainable transport and mobility, ensuring food safety with sustainable agriculture, ensuring the wellbeing of an increasingly ageing population, and building safe, inclusive societies. The focal point on health and ageing, with 9.7% of the funds, has the largest portion of the budget.

22.09% of the budget (roughly €20,000 M) will go to programs to promote leadership in industrial innovation. It is worth noting that the Horizon 2020 budget that is being discussed expects to devote specific funds to promoting innovation in biotechnology (more than €500 M); photonics and nanoelectronics (€1,600 M); and nanotechnology and advanced materials (€3,800 M), areas in which, as we have seen, many companies in the BioRegion work.

The Horizon 2020 budget earmarks 3.52% of the available funds for the EIT. The Institute, which is structured through knowledge and innovation communi-

23. http://eit.europa.eu/

ties (KIC), already has three consortia focusing, respectively, on climate change (Climate-KIC), information society (EIT ICT Labs) and clean energy (KIC InnoEnergy). The last has a co-location center in Barcelona, in which institutions like UPC, Esade and IREC, and companies like Gas Natural Fenosa and Iberdrola are participating.

In 2014, the EIT expects to launch a new call for KIC in health and active ageing (Innovation for Healthy Living and Active Aging) and raw materials (Raw materials – sustainable exploration, extraction, processing and recycling). The call for a KIC in food (Food4Future – sustainable supply chain from resources to consumers), initially scheduled for 2014, has been postponed until 2016. Since 2008, Biocat has coordinated the work carried out in Catalonia to allow organizations and companies from the country to be active members of the KIC in health and food. In 2012, two work groups of Catalan entities were created, one from each area, and, through Biocat, each has become a European consortium that will present a bid for each of the respective KIC.

CATALONIA IS WORKING TO PARTICIPATE IN THE EIT CALL FOR THE KIC IN HEALTH AND ACTIVE AGEING (2014) AND THE KIC IN FOOD (2016)

The Work Group for the *InnoLife* (healthy living and active ageing) bid is headed up by the Health University Barcelona Campus (HUBc) and Biocat, with participation from the IESE business school and the "la Caixa" Foundation. In 2012, this group joined a European consortium with nodes in the United Kingdom, Belgium, Sweden and Germany, which includes prestigious entities like Imperial College London, University of Oxford, the Karolinska Institutet, the Max Plank Institute, the BioRN cluster and the University of Leuven, among others.

The Work Group for the *Food4Future* bid is headed up by the Institute for Research and Technology in Food (IRTA) and Biocat, with participation from the University of Lleida (UdL), Rovira i Virgili University (URV) and organizations from other regions of Spain.

RIS3CAT Strategy

In order to access Horizon 2020 funds, the EU has required national and regional governments around Europe to draft research and innovation strategies for smart specialization (RIS3), with the aim of making investment in research and innovation more coherent and optimizing its impact on economic and social development. In Catalonia, the government, with support from a group of experts in research and innovation, has drafted a work document for smart specialization (RIS3CAT) that, at the time this report was published, has been opened up for public consultation in order to collect opinions from companies, research centers, universities and institutions with links to R&D&i.

RIS3CAT is structured into four focal points: leading sectors, emerging clusters, transversal facilitative technology and improving the innovation arena. The leading sectors focal point includes food, energy and health industries, among others, and transversal facilitative technology, ICT, nanotechnology, biotechnology, photonics, materials and advanced manufacturing.[24]

FOOD, ENERGY AND HEALTH ARE STRATEGIC SECTORS IN CATALONIA'S SMART SPECIALIZATION STRATEGY (RIS3)

The kick off of the new European research and innovation strategy echoes numerous changes that have also come about in the national research system since publication of the *2011 Biocat Report*. Over these two years, a new government has taken power; the Ministry of Science and Innovation has been elimi-

24. The work document is available at: http://www20.gencat.cat/docs/economia/70_Economia_Catalana/arxius/RIS3CAT_201307.pdf

nated, leaving coordination and promotion of the national research and innovation system in the hands of the Secretary of State for R&D&i under the Ministry of the Economy and Competitiveness; and the Spanish Science, Technology and Innovation Strategy 2013-2020 has been approved, as has the resulting National Plan for Scientific and Technical Research and Innovation 2013-2016 (February 2013).

The national strategy is laid out as a framework for action encompassing the activity of all stakeholders —the central and autonomic governments, research bodies, universities and the business sector— and must allow for the structuring of national and regional (RIS3) strategies with Europe, focusing on issues like promoting research of excellence, recognizing talent and employment, business leadership in R&D&i and appropriate response to social challenges, with clear alignment with the Horizon 2020 program. The Plan defines the actions and programs of the central government in science, technology and innovation.

Biotechnology appears in the national strategy as one of the *essential facilitative technologies* for the research and innovation system, and is highlighted as one of the strategic areas in which the country stands out for its scientific leadership. However it is also true that neither the strategy nor the national plan include specific measures to promote the sector and over the period studied, some sectorial instruments have been eliminated, like the Genoma España Foundation, which offered lines of credit and support programs for biotech SMEs. These included the Innocash program, the latest edition of which, in 2011, awarded grants for a total of €12 millions for technology transfer and business valorization projects.

RESOURCES FOR RESEARCH AND INNOVATION UNDER THE GENERAL NATIONAL BUDGETS HAVE BEEN CUT 39% FROM 2009 TO 2013

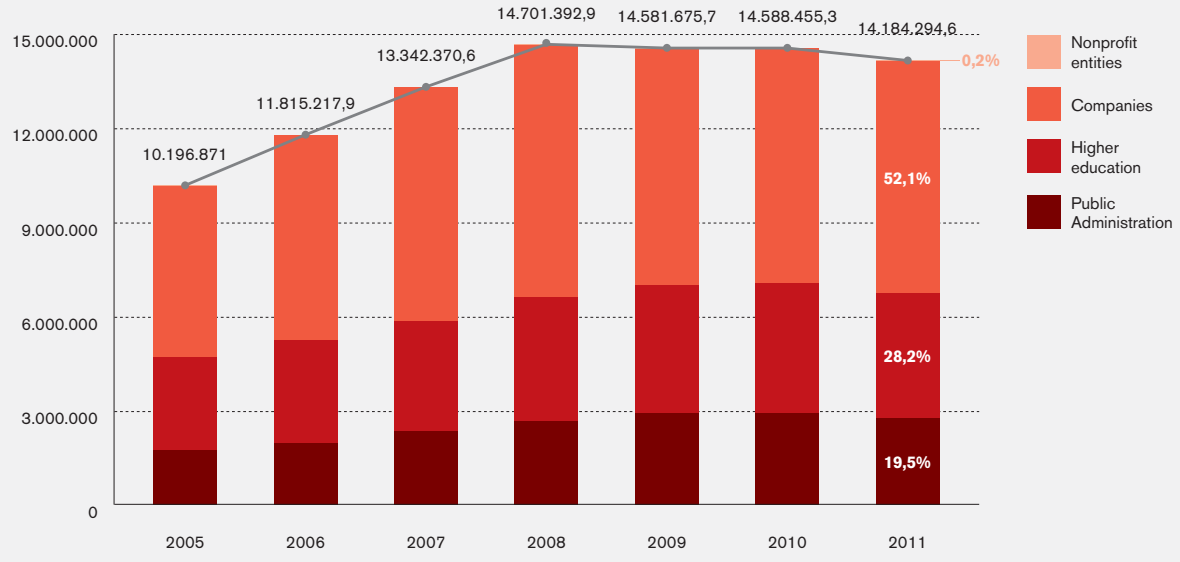
The national strategy and plan have been kicked off in a restrictive economic framework and, beyond the objectives in these documents —which commit to reaching 1.48% of the GDP in R&D&i funds by 2016 and 2% by 2020— the truth is that resources for research and innovation in the General National Budgets (PGE – *Presupuesto General del Estado*) have been cut continuously since 2009, when they peaked at €9,673 millions. In 2013, allocations for research and innovation under the PGE totaled only €5,932 millions, down 39% in four years. The cutbacks are even more dramatic if we only compare financial allocations (part of the budget is for lines of credit) for civil research, which have dropped from €3,867 millions in 2009 to €2,121 millions in 2013, down 45%. The most significant cuts came in 2012, with the new government, when the national R&D&i budget was slashed 25.5%.[25] Beyond the financial crisis, which has affected all of Europe, it is clear that political will is a key factor in ensuring investment in research and innovation.

The impact of these budget cuts is beginning to be seen in the National Statistics Institute (INE) statistics on R&D expenditure, although the latest information available is for 2011 and it is to be expected that these statistics will portray an even more negative situation in coming years (graph 29).

As a whole, internal national expenditure on R&D in 2011 totaled €14,184 millions, down 2.77% from 2010 (€14,588 M). However the decrease in government spending on R&D was even greater, 5.7%, down from €2,930 millions in 2010 to €2,762 millions in 2011. Internal R&D expenditure of higher education institutions was €4,002 millions, down 2.9% from 2010, and that of companies was €7,396 millions, down 1.5% from the previous year.

25. For a more detailed analysis on R&D&i investment in the general national budget, see the yearly reports of the Confederation of Spanish Scientific Societies (COSCE) on http://www.cosce.org/informes.htm

Graph 29 **Evolution of internal R&D expenditure in Spain 2005-2012 (in thousands of euros)**



Source: INE

From 2008 to 2010, contributions from the national government to Catalonia for research and innovation increased, in both absolute and relative terms. According to the *Memòria socioeconòmica i laboral de Catalunya 2012* (Catalonia socioeconomic and employment report 2012), in 2008 the central government's contribution was €430.9 millions, 13.1% of all R&D expenditure in Catalonia, which went up to €556.5 millions in 2010 (17.2% of the total).[26] Given the significant decrease in resources for R&D&i under the PGE, a decrease in contributions for the 2011-2013 period is expected although difficult to estimate given the wide variety of instruments through which these contributions reach the region: jointly funded facilities, competitive funds for research centers, universities and companies, support in hiring research personnel, etc.

26. Memòria socioeconòmica i laboral 2012. Capítol II: Societat del coneixement, Consell de Treball Econòmic i Social de Catalunya, 2012, p. 18. http://www.ctescat.cat/msil/

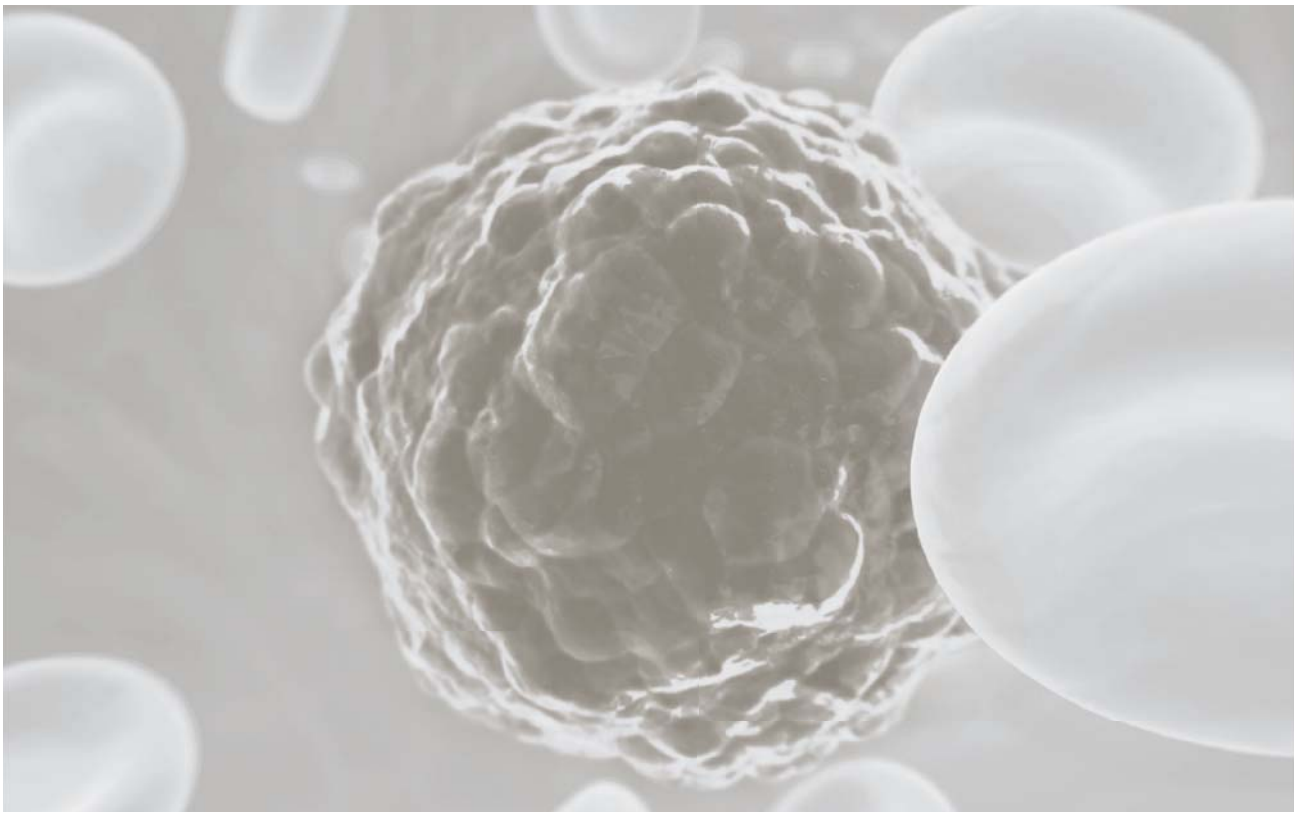
Changes to the patent system

SPAIN HAS EXCLUDED ITSELF FROM THE UNITARY EUROPEAN PATENT, AN INSTRUMENT DESIGNED TO FACILITATE COMPANIES' ACCESS TO THE WHOLE EU MARKET

To conclude this review of the European and Spanish context and its impact on the Catalan biosciences sector, we must mention the possible roll out of the new **unitary European patent** in 2014, which, despite the fact that Spain has excluded itself from the system, will affect any company or research body that wants to protect an invention throughout the EU.[27] This new system aims to promote innovation and dynamize the interior EU market while reducing the administrative burden and bureaucracy in protecting new inventions. In addition to the new unitary European patent, the agreement signed by member states creates a Unified Patent Court with exclusive jurisdiction over any disputes that may arise as a result of the unitary European patent. The new court will also have jurisdiction —although not exclusive for a period of at least seven years— over current European patents, subject to the European Patent Convention (EPC) and the Patent Cooperation Treaty (PCT).

The launch of this new system in Europe has coincided with the reform of the America Invents Act (AIA), which after being called for by companies and investors for many years went into force in March 2013. Among other changes, explained in the article by Gemma Campabadal, the AIA includes a 42% discount on fees for "micro-entity inventors" —which substitute the previous small entity inventors. This fee cut will benefit universities and researchers obliged to cede inventions to these institutions, as both fall under the micro-entity category.

27. The new system has the support of all the members of the EU-27, except for Spain and Italy.



UNITARY EUROPEAN PATENT AND AMERICA INVENTS ACT: IMPACT OF NEW IP PROTECTION SYSTEMS ON CATALAN R&D

Gemma Campabadal i Monfà
European Patent Attorney, degree in Pharmacy (UB) and Law (UOC)

After 40 years of roadblocks, the unitary European patent is beginning to see the light in order to become an effective legal instrument for a market of 500 million inhabitants, which is also the leading global market.

The current patent system is highly fragmented, has prohibitive costs and a high degree of legal insecurity and incongruence. After the European patent granting procedure, users face national validations that require translations and official maintenance fees leading to further delays and expenses. The purview of national courts regarding patents results in conflicting sentences and multiplied costs: all of these expenses and hurdles particularly affect SMEs, which are the majority in Catalonia.

The unitary patent will be a third protection instrument on top of the already existing national and European tools. Users can choose between these three options, although dual protection under the European and unitary patents is not allowed; users must choose one or the other. However a European patent may be converted into a unitary patent. The European Patent Office (EPO) will be in charge of examining, granting and validating applications following the same procedures and substantive principles applied for the European patent. The official languages will be English, French and German, however the EPO will provide an online machine translation into all official EU languages free of charge, though it is not legally binding. In the event of a dispute, the patent holder will provide an official translation into the language of the alleged infringer's country of residence, or the language of the country in which the infringement takes place.

Along with the unitary patent, a Unified Patent Court will also be created with exclusive jurisdiction for litigation relating to European and unitary patents. This court will be comprised of a Court of First Instance with its central division in Paris and two sections in London and Munich, as well as local and regional divisions; a Court of Appeal, in Luxemburg; and a Registry.

Regarding the America Invents Act (AIA), the most significant US patent reform since 1952, the main change is to allow a patent to be granted to the first person to apply. This is called first-inventor-to-file, similar to the European first-to-file, which replaces the prior first-to-invent that led to so many problems in determining who was the first inventor. This new temporal order eliminates costly interference proceedings. Laboratory Notebooks will continue to be important as proof of the inventors' identity. Another substantial change under the AIA is the introduction of the post-grant review procedure, similar to European opposition, which will be more affordable than the corresponding invalidation lawsuits in American civil courts.

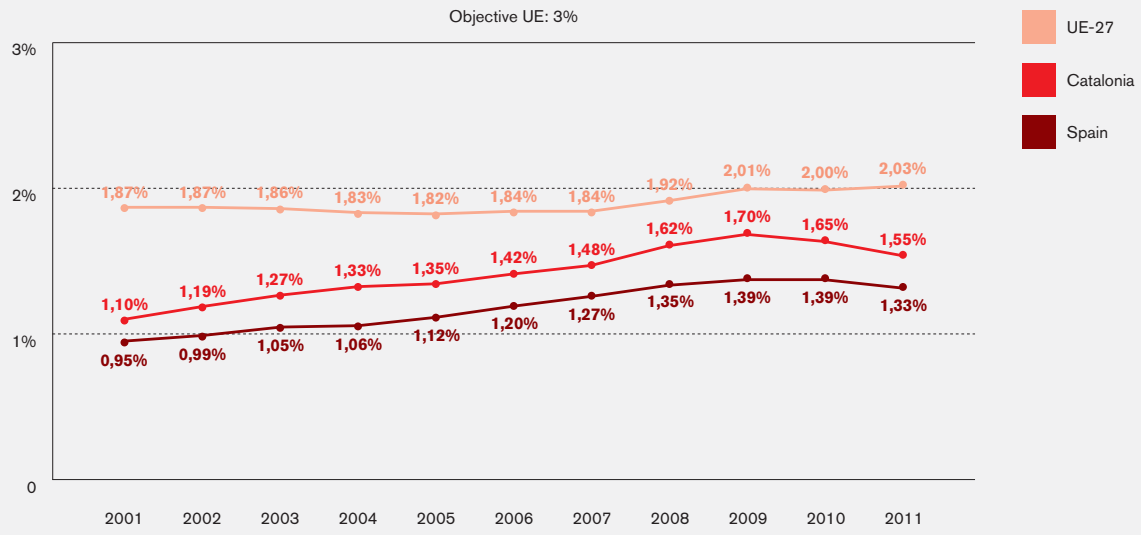
These regulatory changes in Europe and the US, both profound and close together in time, reflect market competition and the prevailing need for governments and legislators to establish tools that favor competitiveness and innovation in their territories. Although Spain and Italy have excluded themselves from the unitary patent, Catalan companies may still apply and have access to the corresponding courts. For protection in Spain, a Spanish national patent must be requested, which will probably make Spain a less attractive destination for marketing and exploiting inventions. Although in the initial stages the introduction of the unitary patent creates some additional complexities, the use industry makes of this option will determine its success and the probable disappearance of national and European patents. Only time will tell.

CATALONIA IN THE WORLD AND IN EUROPE

Catalonia is a leader in research and innovation in Spain and particularly stands out in the fields covered by this report: biotechnology, biomedicine and medical technology. This is the result of the country's clear commitment, which has been consistent since 2000, to building a strong research system that can sustain a knowledge-based economy.

The first indicator demonstrating this fact is the percentage of the Catalan GDP devoted to R&D, which is well above the joint national expenditure although still far from the EU-27 average and the 3% goal established in the Horizon 2020 project, which only three countries have achieved (Finland, Sweden and Denmark), although Germany and Austria are very close (graph 30).

Graph 30 **Percentage of GDP invested in R&D (%)**



Source: Eurostat and INE (2001-2008, GDP in market prices based on 2001. 2009-2011, GDPmp 2008).

Internal yearly R&D expenditure in Catalonia has been more than €3,000 millions since 2008, although in the past three fiscal years a slight downward trend can be seen (graph 31). Specifically, internal R&D expenditure in 2011 was €3,104 millions, 20% of which was from the government, 24% from higher education institutions, 55.8% from companies and 0.2% from non-profit organizations. Catalonia accounts for 21.9% of all internal R&D expenditure in Spain, behind only Madrid (26.5%, with €3,763 M) and well above, in absolute terms, the following communities: Andalusia (€1,648 M), Basque Country (€1,397 M) and the Valencian Community (€1,044 M), although the relative weight of R&D expenditure as a percentage of the GDP is higher in the Basque country (2.1%), Navarra (2.05%) and Madrid (1.99%).[28]

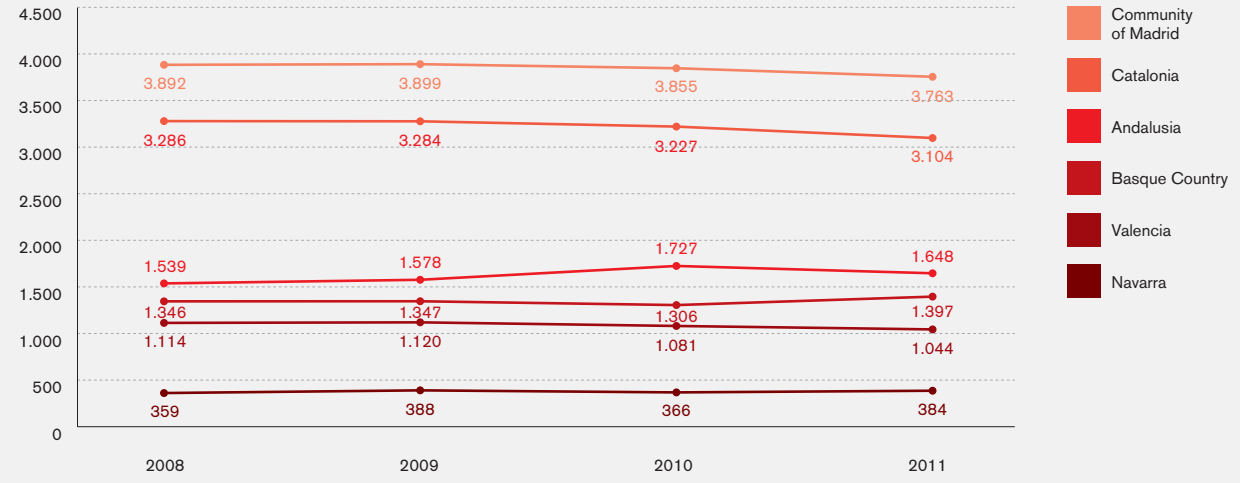
28. INE

It must be noted, however, that Catalonia is ranked first in internal R&D expenditure in the higher education arena (€736.7 M in 2011), which undoubtedly contributes to the leading position of Catalan universities in the nation in terms of indicators of scientific production.

Of all internal Catalan R&D expenditure, companies spent €1,733 millions, 55.8% of the total. As mentioned in chapter II, nearly 9% of this expenditure (€154.8 M) corresponds to R&D in biotechnology. The participation of Catalan companies in the total national business R&D expenditure, 23.4%, is higher than the joint participation of all sectors, but is even more noteworthy in the biotechnology arena, where companies in Catalonia account for 28.8% of R&D expenditure, which in Spain totals €537.9 millions.

INTERNAL R&D EXPENDITURE IN CATALONIA IN 2011 WAS Ð3,104 MILLIONS, 21.9% OF THE NATIONAL TOTAL

Graph 31 **Evolution of internal R&D expenditure in the autonomous communities that invest most in absolute or relative terms (millions of euros)**



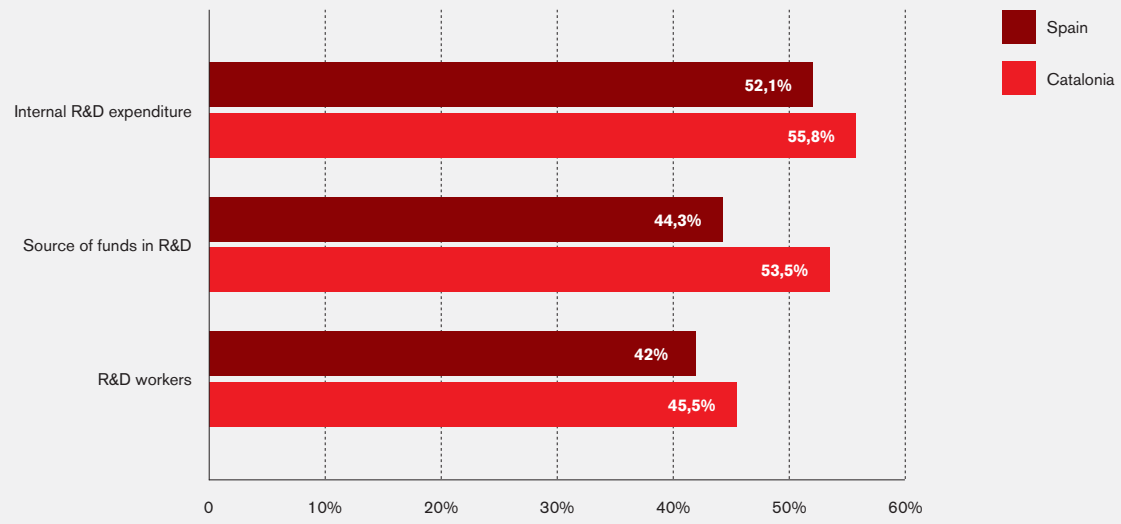
Source: INE

In general, the contribution of Catalan companies to R&D is more intense regardless of which indicator you look at: participation of companies in internal R&D expenditure nationwide is 52.1%, versus the aforementioned 55.8% from Catalan companies; nationwide, companies contribute 44.3% of all funds invested in R&D, while in Catalonia they contribute 53.5%; companies have 42% of R&D personnel nationwide, while in Catalonia companies employ 45.5% of R&D workers (graph 32). It must be taken into account that the business sector's participation in R&D is a key indicator of a country's level of innovation; thus, in the three countries that lead innovation in Europe —Sweden, Finland and Denmark— business investment in R&D is more than 2% of the GDP,[29] while in Catalonia it is only 0.86% of the GDP.

THE CONTRIBUTION OF CATALAN COMPANIES TO R&D IS ABOVE THE NATIONAL AVERAGE BUT STILL FAR OFF PRIVATE INVESTMENT LEVELS IN THE MOST INNOVATIVE COUNTRIES IN EUROPE

29. Growing Beyond. The power of simplicity. Towards a smarter and streamlined innovation policy in the EU, Ernst & Young - CEPS (Centre for European Policy Studies), 2012, p. 13.

Graph 32 **R&D investment in the business sector in Catalonia and Spain**



Source: INE

The government is responsible for 20% of internal R&D expenditure in Catalonia (€625 M in 2011), but contributes —together with higher education—40% of all these funds (€1,241 M). On the other hand, 6.5% (€200 M) of Catalan R&D expenditure comes from abroad.[30]

Specifically, the Government of Catalonia devoted a consolidated budget of €521.4 millions to R&D in 2012, up 9% from 2011 (€477.9 M). The bulk of these resources is managed by the Department of Economy and Knowledge (€274.6 M in 2012, and €272 M in 2011) and the Department of Health (€151 M in 2012 and €152 M in 2011), with significant contributions from the departments of Agriculture, Livestock, Finishing, Food and the Environment and Enterprise and Employment as well. R&D investment made up 1.2% of the total budget of the Government of Catalonia in 2011, up slightly to 1.4% in 2012.

30. Idescat

International funds

An indicator of the high level of research being carried out in Catalonia is that of the international funds attracted, both through EU framework programs and subsidies from the European Research Council (ERC) granted to researchers that work here.

Through 2012, Catalan research bodies had been granted a total of €660 millions under the EU **7th Framework Program** (7FP) covering the 2007-2013 period. This figure represents 1.3% of the €50,521 millions earmarked for the program and 28.7% of all funds granted in Spain through 2012 (€2,300.3 M).[31] Catalonia is second in the nation, behind Madrid (30.2% of all funds). Nine Catalan entities —four universities (UAB, UB, UPC and UPF) and five research centers, all of which work in the life sciences (CRG, ICFO, ICIQ, IDIBAPS and BSC)— are among the top 25 in the country in terms of funds received under the 7FP. As a whole, these nine entities have participated in 617 activities funded through the 7FP and have led 242 projects, of a total of 1,447 projects carried out by Catalan entities and companies.[32] The UPC leads the list for number of activities carried out (130), but the UAB has led the most projects (45), followed by the UB (39). Of the aforementioned research centers, the CRG leads the list, heading up 25 projects of the 43 in which it has participated.

Although universities and research centers lead the rankings in terms of funds granted under the 7FP in both Catalonia and Spain —not in vain, the Catalan Association of Public Universities (ACUP) recently pointed out that 64% of university research budgets comes from competitive funds[33]— nationwide it is companies —led by large corporations like Telefónica and Acciona— that have obtained the most funds through this EU program to fund R&D, specifically 33.2% (€763.7 M) in the 2007-2012 period, above universities (22.1%). However, the breakdown of participation of entities in the 7FP is quite different in Catalonia: CERCA lead the list, with 31.4% of all funds, and universities have obtained 27.6% of the resources, while companies have only attracted 18.3% of the European funds for research.[34] This is undoubtedly an indicator that must be improved if we aim to strengthen innovation and competitiveness in Catalan companies.

Regarding **ERC grants and subsidies**, over the 2007-2012 period Catalonia obtained funding for a total of 102 projects in various categories: 57 Starting grants, 40 Advanced grants and 5 Proof of Concept. This accounts for 52% of all grants awarded to researchers in Spain (194) over this period and would put Catalonia alone 10th on the ranking of European countries, led by the United Kingdom (with 783 projects funded), Germany (488) and France (467). As it stands, Spain as a whole is ranked seventh.

As shown in graph 33, the life sciences received a total of 71 ERC grants nationwide, 32 of which (45%) went to researchers working at institutions in Catalonia. Although the biosciences makes up approximately one third of all grants received (36.5% of all grants awarded in Spain and 31% of those in Catalonia) it must be noted that at least a dozen research projects in the physical sciences

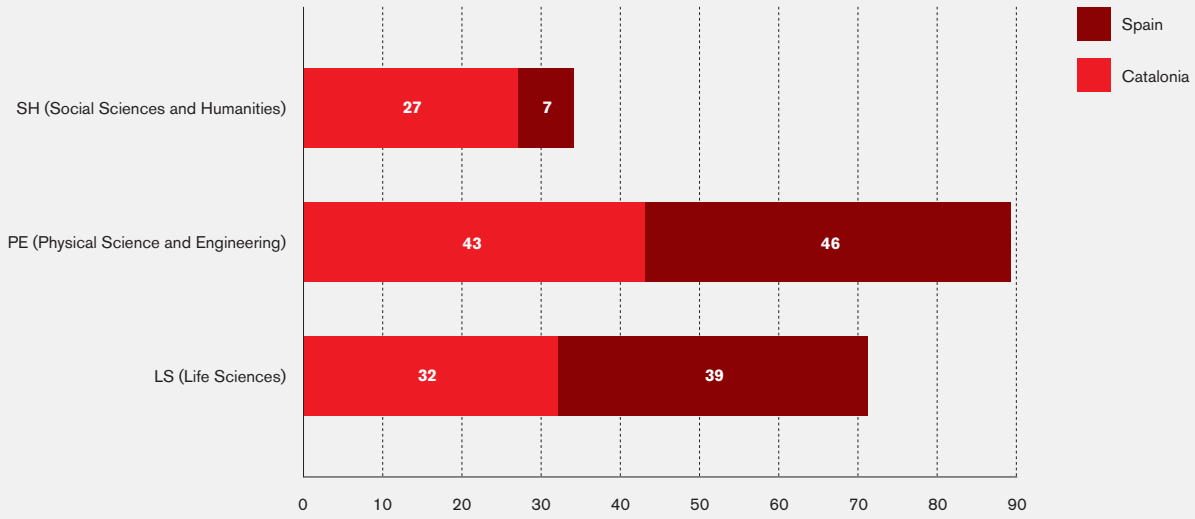
31. Participación española en el VII Programa Marco de I+D de la Unión Europea, CDTI, November 2012.

32. Més recursos de la UE per a Catalunya, Recercat 81, October 2012.

33. Indicadors de Recerca i Innovació de les Universitats Públiques Catalanes. Informe 2012, p. 9.

34. See footnote 31.

Graph 33 **Subsidies granted by the ERC by area of science (2007-2012)**



Source: ERC

and engineering have links to areas covered in this report, like photonics, nanotechnology or high computing applied to biomedical or biological research.

CATALONIA RECEIVED 52% OF ALL RESEARCH GRANTS AWARDED BY THE EUROPEAN RESEARCH COUNCIL (ERC) IN SPAIN

By entity, the Center for Genomic Regulation (CRG) stands out in the life sciences, with 11 researchers that have received ERC grants —seven Starting grants, three Advanced grants and one Proof of Concept— followed by the IRB with four projects —two in the Starting category and two in Advanced. The Institute of Photonic Sciences (ICFO) is noteworthy in the physical sciences and engineering, also with 11 projects: seven Starting grants, two Advanced grants and two Proof of Concept.

In total, the 102 ERC grants received by scientists working in Catalonia over the 2007-2012 period have brought €189.87 millions in funding for research done here at home, €53.22 millions of which has gone to 32 projects in the life sciences.

Coinciding with publication of this report, the results of the 2013 call for proposals for ERC Starting Grants and Advanced Grants were announced. Regarding the Starting Grants, 287 research grants were awarded throughout Europe, for a total value of €400 millions, 14 of which went to researchers in Spain and 6 to researchers at Catalan entities: one in the life sciences (CRG), one in social sciences and humanities (Center for Research in International Economics, CREI) and four in the physical sciences and engineering (one at ICFO and 3 at the University of Barcelona). Catalonia also received 6 Advanced Grants in the 2013 call, of the 13 that went to researchers in Spain. As a whole, this call awarded grants to 284 European projects, for a total of €660 millions. The Catalan centers with researchers that have received grants are: IRB (life sciences), ICFO (physical sciences and engineering) and, in the social sciences and humanities, two at the UPF, one at the UB and one at CREI.

Table 7 **Grants ERC 2013**

Center	Starting	Advanced
Center for Research in International Economics (CREI)	1	1
Center for Genomic Regulation (CRG)	1	
Institute of Photonic Sciences (ICFO)	1	1
Institute for Research in Biomedicne Barcelona (IRB)		1
University of Barcelona (UB)	3	1
Pompeu Fabra University (UPF)		2

International recognition of research of excellence being carried out in Catalonia through this significant number of researchers awarded ERC grants is also an indicator of the success of the **Catalan Institution for Research and Advanced Studies (ICREA)** program to attract research talent. In total, 54 of the 102 researchers that have received ERC grants in Catalonia between 2007 and 2012 are ICREA researchers. From when it was created in 2000 through the end of 2012, ICREA has hired 240 top-notch researchers, 70 (29%) in the medical and life sciences arena, 65 (27%) in experimental science and mathematics, and 40 (17%) in technology and engineering. Most of these researchers have carried out their work in Catalan universities (118 or 49%) and in centers belonging to the Government of Catalonia's CERCA system (98 or 41%).

ICREA has played a key role in attracting international talent to Catalonia: the 240 researchers in the program are from 27 different countries and, in the 2012 call offering 20 positions, more than 210 applications were received from 28 countries. But it has also been key to promoting the return of talent that had left: 55% of ICREA researchers are from Spain, but only 38% were working here when they were hired.

Possibly one of the most significant facts showing the impact ICREA has had on the Catalan research system is that projects with a head researcher from this program received a total of €56.8 millions in competitive funds in 2012, 49% of which (€26.3 M) went to projects in the medical and life sciences.[35]

35. Memoir*12, ICREA, http://www.icrea.cat/Web/files/ResearchReport2012.pdf

R&D in the life sciences

It is complicated to give an accurate global estimate of R&D expenditure in the life sciences. On one hand, we have the €154.8 millions we know Catalan companies working in biotechnology devoted to R&D in 2011; to which we must add the €380 millions managed each year by research centers in this arena (see chapter II). On the other hand, we have the internal R&D expenditure of the Catalan pharmaceutical industry, which in 2011 was more than €275 millions and in 2012 was €280 millions (52% of all R&D expenditure in the national pharma sector).[36] To these figures we must also add R&D expenditure from medical technology and services companies in the BioRegion, spending on clinical research in hospitals that isn't included in the budgets of their research institutes, and that of university research groups working in the biosciences, which we calculate to be more than €50 millions each year.[37] Thus, we can estimate public and private research expenditure in the biosciences in Catalonia to be **approximately €850 millions per year**, which accounts for **26% of all internal R&D expenditure in Catalonia** (€3,104 M in 2011).

INTERNAL R&D EXPENDITURE IN THE LIFE SCIENCES IN CATALONIA IS MORE THAN Đ850 MILLIONS PER YEAR

As we have seen in chapter II (graph 25), more than half of the registered research groups that work in the biosciences focus their research on specific pathologies and, in particular, on oncology (60 registered groups) and mental diseases and illnesses of the central nervous system (54 groups). Cancer research is one of the areas that have the highest impact on scientific production in Catalonia, which in terms of publications focuses mainly on medicine. According to the study on Catalan scientific production over the 2003-2008 period published in 2010 by the SCImago Research Group, publications on cancer research (1,245) and oncology (1,238) were by far the most cited of all scientific production in Catalonia, with an average of 40.22 and 35.23 citations per article, respectively.[38] We can see the value of this number of citations if we take into account that over the 2003-2008 period, the average for Catalan scientific publications was 7.2 per document and that, between 2007 and 2011, the average number of citations for scientific production nationwide was 10.5 citations per document.

Additionally, in late 2012 the Catalan Foundation for Research and Innovation Research Group on Bibliometrics (BAC) analyzed 10,085 scientific papers in oncology published in the 2007-2011 period and identified 102 research groups in this field in Catalonia —31% of the 346 active in cancer research nationwide— which produced 3,807 publications.[39]

As seen in the article *Oncology in Catalonia* by Alex Casta, the strengths and capacities of the Catalan system in oncology cover the whole value chain, from basic research in areas like epigenetics or cell modifications associated with various types of cancer through companies marketing diagnostic tests or in-

36. http://www.farmaindustria.es

37. According to the 2010 Biocat Survey on which the previous report was based, the average budget for university research groups in the biosciences was approximately €200,000 per year. Taking into account that the Biocat Directory includes 276 registered research groups at universities, the calculation of the funds invested in R&D in the life sciences by this group is approximately €55 millions, although we must take into account that some groups belong to more than one center.

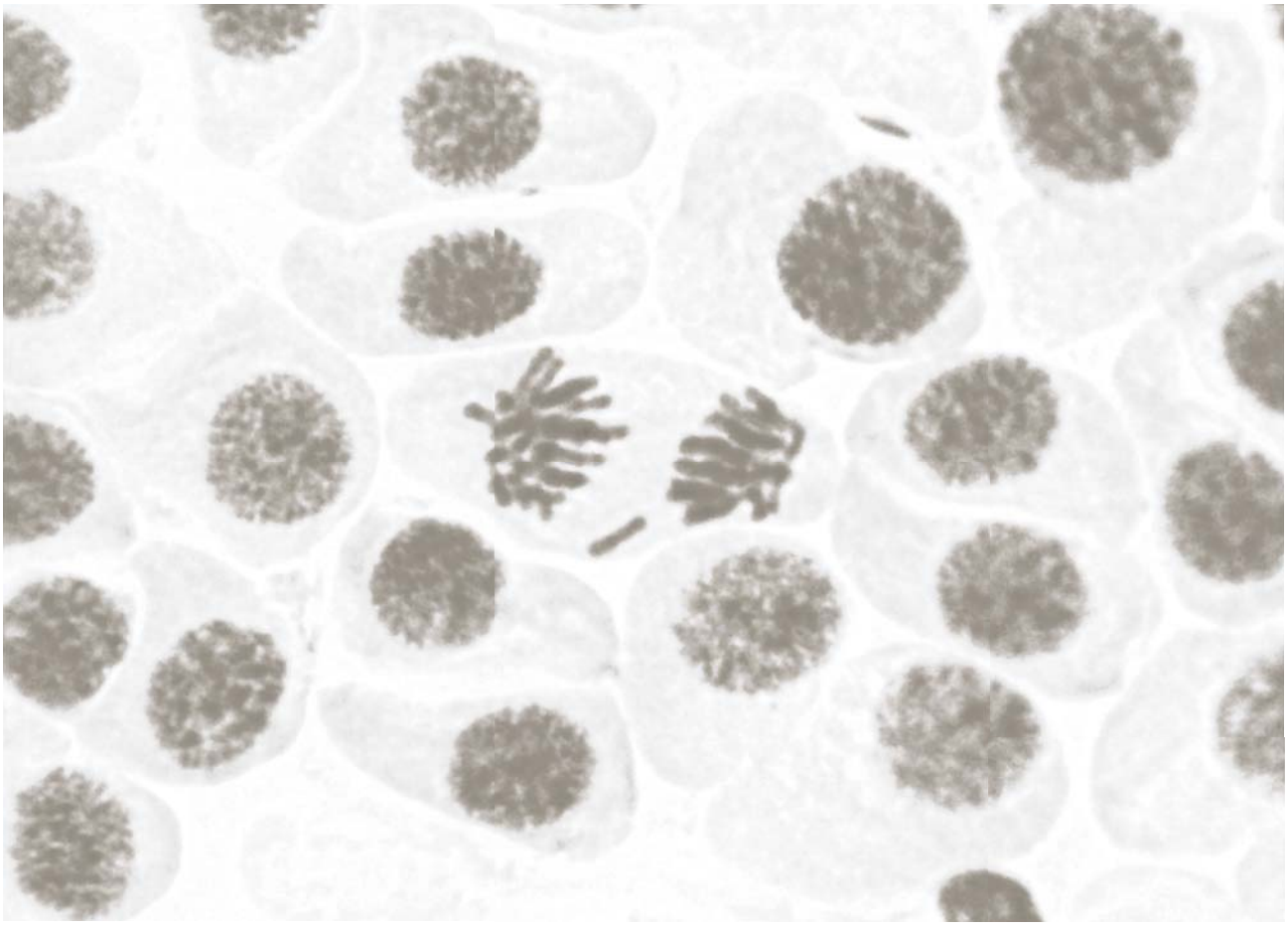
38. Félix de Moya (dir), SCImago Research Team (CSIC-Universidad Carlos III), Bibliometric Indicators for Scientific Activity in Catalonia (Scopus, 2003-2008), July 2010. A later version of the study was published by the Open University of Catalonia (UOC) and the summary can be found at http://meridia.iec.cat/ORWeb/contents/resultats/publicacions/documents/Catalunya_indicadors_bibliometrics2003-08.pdf

39. Report: http://bac.fundaciorecerca.cat/marato2012/informe

novative drug-delivery systems for oncology medications, as well as advances being made in hospitals and research institutes in diagnosis and personalized medicine for cancer patients and the various start-ups that are entering the clinical phases with innovative drugs. As noted in chapter II, in analyzing the pipeline of companies in the BioRegion, these have at least 46 therapeutic and diagnostic products in oncology (graph 19), from basic research through to market.

Additionally, cutting-edge experiences are being seen in Catalonia in applying personalized medicine to cancer, which allows for the design of specific drugs and therapies to treat the underlying genetic modifications that cause various types of cancer to be administered only to those patients with the corresponding biomarkers. In order to advance in this line, the **Barcelona Patient Cancer Platform** (BPCP) has been created, with participation from five hospitals and five benchmark research institutes in oncology (Hospital del Vall d'Hebron and the VHIO; Hospital de Bellvitge, ICO and Idibell; Hospital Clínic; Hospital de Sant Pau; Hospital del Mar and IMIM; and the Institute for Research in Biomedicine (IRB) Barcelona) and support from the Department of Health and Biocat (see article written by the researchers promoting this project).

Catalonia's strengths in research also extend to areas like genomics, bioinformatics, structural biology, bioengineering and bionanomedicine, areas from which business initiatives have also arisen in recent years that are bringing about effective technology transfer to market of the research developed at universities, hospitals and research centers.

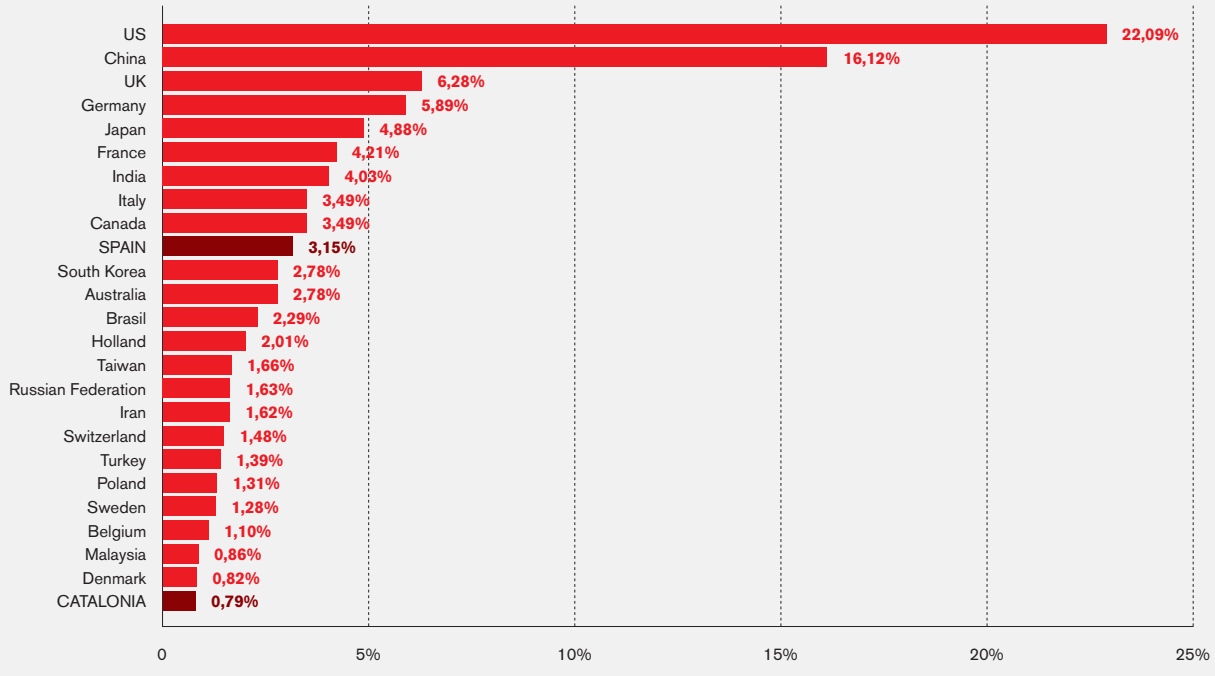


Impact of research

Analysis of the scientific publications generated shows that the impact of Catalan research is particularly noteworthy for its quality, measured by the percentage of articles an institution publishes in the most influential scientific journals in the world. Three Catalan research centers associated with the life sciences — the Center for Genomic Regulation (CRG), the Institute of Chemical Research of Catalonia (ICIQ) and the Nanoscience and Nanotechnology Research Center (CIN2)— are at the top of the SCImago ranking in terms of quality publications that come out of research institutes in Spain.[40] Moreover, the CRG is ranked 7th in Europe and 16th in the world, on a list of more than 2,700 entities. The ICIQ —which is ranked first in Spain for scientific excellence— is 16th in Europe and 29th in the world for the quality of its articles, and the CIN2 is ranked 20th (Europe) and 36th (world).

Catalonia produced more than 19,000 scientific publications in 2011 and more than 19,750 in 2012, which accounts for **2.9% of all publications in Europe and 0.79% of the global scientific production**, ranking it 25th in the world (graph 34), much higher than the position one would expect based on population (99th). It is the second autonomous community in Spain by number of scientific articles (behind Madrid), with 25.76% of all publications in the 2007-2011 period.

Graph 34 **Ranking of scientific production in 2012 (% of all publications in the world)**



Source: SCImago Journal & Country Rank

40. See the ranking and presentation of methodology on http://www.scimagoir.com/index.php.

ONCOLOGY IN CATALONIA: FROM CUTTING-EDGE RESEARCH TO BUSINESS DYNAMISM

Alex Casta
Biocat head of Technology Transfer and Innovation (2012-2013)

More than 33,000 new cases of cancer are diagnosed in Catalonia each year. This fact is more than enough to drive the work of professionals in the oncology sector in the BioRegion of Catalonia. For years now, oncology has given our country a noteworthy position on the biomedical innovation map.

La Marató de TV3, a solidary program promoted yearly by the Catalan public television channel that aims to raise funds for research, chose cancer as the focus of their 2012 edition. Thanks to donations from thousands of individuals and organizations, the program raised more than €12 millions that will go to fund scientific research projects. La Marató is a good reflection of the impact of cancer on Catalan society and the commitment of many entities, both public and private, to working to maintain the region's competitiveness in this sector.

The innovation system in the Catalan oncology sector has representatives throughout the value chain. From the most basic research through products administered daily to cancer patients, as well as service companies and healthcare centers. The current Catalan oncology stage has come about thanks in large part to research that began in Catalan universities and led to the creation of benchmark research institutes. 11 Catalan universities conduct cancer research and 13 research institutes devote teams and research to fighting this disease. Specifically, of the 573 research groups listed in the Biocat Directory, a total of 60 throughout the territory focus on oncology. Despite the current difficulties as a result of the lack of resources for quality research, all of these organizations continue to generate benchmark publications, intellectual property and professionals that develop their careers both here at home and abroad.

Researchers that work in the field of cancer in Catalonia lead key projects striving to define the foundations of this disease. To list just a few examples, we have the cancer epigenetics and biology program (PEBC) at the Bellvitge Biomedical Research Institute (**ICO/IDIBELL**) led by **Dr. Manel Esteller**; and the studies carried out by the team led by **Dr. Josep Maria Llovet** at the Pi i Sunyer Biomedical Research Institute (**IDIBAPS**), which have helped better understand liver cancer, one of the deadliest tumors. We can also highlight the research carried out in recent years at the Institut d'Investigació Biomèdica de Lleida (**IRB-Lleida**), which has discovered the molecular mechanisms involved in triple-negative breast cancer, one of the most aggressive varieties. Catalonia is also a leader in pediatric cancer research, with research groups like that coordinated by Dr. Miquel Segura at the Vall d'Hebron Research Institute (VHIR) are developing highly innovative therapies using microRNA to treat childhood neuroblastomas. To give just one more example, of the many, we have the Institute for Research in Biomedicine (**IRB**) of Barcelona, a center led by **Dr. Joan Massagué** which has an oncology program led by **Dr. Eduard Batlle** that has made breakthroughs in colorectal cancer, metastasis, controlling the cell cycle and genetic instability.

60 RESEARCH GROUPS IN CATALONIA FOCUS ON ONCOLOGY

One field in which Catalan science is particularly competitive is personalized cancer medicine, with whole institutes devoted to this task, like the Institute of Predictive and Personalized Medicine of Cancer (**IMPPC**) led by **Dr. Manuel Perucho**, which has more than 60 researchers including the renowned

Dr. Miguel Angel Peinado. High-impact genetic studies are also carried out in Catalonia at leading institutes like the Center for Genomic Regulation (**CRG**), headed up by **Dr. Roderic Guigó** and **Dr. Joan Valcárcel**. The CRG is ranked among the top 15 institutions in the world by SCImago, which ranks more than 2,500 entities in the world by the impact of their publications. This fact has not gone unnoticed by large pharmaceutical companies and Sanofi recently decided to invest €1 million in research projects at the CRG. Moreover, important translational discoveries in personalized medicine have been made in Catalonia, like those regarding HER2+ gene mutations and breast cancer, obtained by the Vall d'Hebron Institute of Oncology (**VHIO**), with teams led by **Dr. Joaquín Arribas**. Catalan groups are also leaders in hereditary cancer, with teams of excellence in this field like those led by **Dr. Gabriel Capella** at ICO/IDIBELL. As a final example in the field of personalized medicine, some of the 130 technological platforms in Catalonia are revolutionizing the study of cancer and personalized treatment of tumors, like that led by **Dr. Alberto Villanueva** at ICO/IDIBELL, a benchmark in the use of mice as avatars to develop treatments for cancer patients.

60% OF ALL CLINICAL TRIALS IN ONCOLOGY IN SPAIN ARE CONDUCTED IN CATALONIA

There are 17 university hospitals located throughout the territory that carry out translational and clinical research and are a driving force for innovation in the oncology arena. 60% of all clinical trials in oncology carried out in Spain are conducted in Catalonia. Hospital de Bellvitge and ICO/IDIBELL have a translational research program led by **Dr. Ramon Salazar** that has yielded positive results for years now in prevention, diagnosis and definition of clinical trials. The Vall d'Hebron Institute of Oncology (VHIO) applies a molecular pre-screening system to design clinical trials that is the first of its kind in the world. Important milestones have also been reached at the VHIO, like those of the team led by **Dr. Josep Tabernero**, which was the first to prove the efficacy of treating cancer patients with an innovative new therapy based on siRNA molecules. They have also improved immunotherapy-based treatments, the latest great hope in cancer treatment, led by Dr. Josep Tabernero and **Dr. José Baselga**. Finally, **Dr. Rafael Rosell**, of Hospital Germans Trias i Pujol, is a global benchmark in lung-cancer research and has made numerous contributions to translational advances in this field.

Additionally, participation of Catalan clinical teams in studies on cancer therapy resistance is noteworthy, like those conducted at **IMIM-Hospital del Mar** led by **Dr. Joan Albanell** and **Dr. Clara Montagut**, regarding a EGFR gene mutation in chemotherapy-resistant patients. Finally, Catalan hospitals are also developing vaccines for cancer. The team led by **Dr. Francesc Xavier Bosch** at ICO/IDIBELL, for example, has been working on a vaccine for the human papilloma virus for years now.

Catalan hospitals also carry out groundbreaking initiatives in molecular diagnostics, like the Colorectal Cancer Early Detection Program promoted by the Government of Catalonia and led by **Hospital Clínic** and Hospital del Mar, with renowned professionals like **Dr. Antoni Castells**. This program screens thousands of people each year between the ages of 50 and 69 in order to detect this type of cancer as early as possible.

In terms of the business fabric, roughly twenty Catalan small and medium-sized biotechnology companies focus on finding medical solutions for cancer, which as a whole make up more than 20% of all companies devoted to developing therapeutic and diagnostic systems in Catalonia. There are more than 45 drugs and diagnostic products being developed in Catalonia, which range from the initial stages of discovery through to market.

The group of small biotech firms that are leading innovation in the sector includes various success stories, like **Advancell**, which is developing a drug for chronic lymphocytic leukemia; **Ability Pharmaceuticals**, which is working on a treatment based on a new class of drugs, lipid analogs, for pancreatic and lung cancer that began the clinical phase in 2013; **Lykera Biomed**, which focuses on developing monoclonal antibodies to treat solid tumors; and **SOM Biotech**, a company devoted to repositioning and developing an active ingredient to treat glioblastoma that is in the preclinical phase.

There are also newly created start-ups working on groundbreaking therapeutics, like **VCN Biosci-**

ences, which is developing oncolytic viruses to treat cancer. Another example is **Mosaic Biomedicals**, which is working to discover drugs that attack tumor stem cells.

In addition to drug development, Catalonia also has innovative companies in the field of molecular cancer diagnostics, like **Inbiomotion**, which is developing a product to predict bone metastasis. Other examples include **Althia**, **Transbiomed** and **Pangaea Biotech**.

Nanotechnology applied to oncology is also a field with significant assets in Catalonia. One of the most noteworthy examples is **Nanotargeting**, which uses gold particles as a drug-delivery system to treat cancer.

In addition to the start-ups, there are also consolidated companies working in the field of cancer. One of them is **Oryzon**, which has been working on therapeutic and diagnostic products for various types of cancer for more than 10 years. Another example is **GP Pharm**, which is developing injectable formulas for tumor treatment from the preclinical phase through to market, combining innovation in treatment and in drug-delivery systems.

Despite the current economic difficulties, the support and traction of traditional Catalan pharmaceutical companies is also an asset to the oncology sector. The work of companies like **Ferrer**, **Almirall**, **Esteve** and **Uriach** in production and distribution, as well as in forging alliances in the development phases, is key for global success. Likewise, multinational corporations also consider the Catalan oncology stage a good benchmark and some of them, like **Amgen**, **Novartis**, **Sanofi**, **Bayer** and **Boehringer Ingelheim**, have been in Catalonia for years and participate actively in the consolidation of this sector.

Catalan governmental institutions work to align their goals with the oncology sector and maintain their strengths. The ICREA program, promoted by the Government of Catalonia in collaboration with Catalan universities and research centers, has already hired more than 70 top-notch scientists from around the world to do life sciences research in Catalonia. One third of these do so in oncology. Additionally, the creation of the CERCA institution, which monitors and facilitates the work of Catalan research centers, has a positive impact on this area. Another

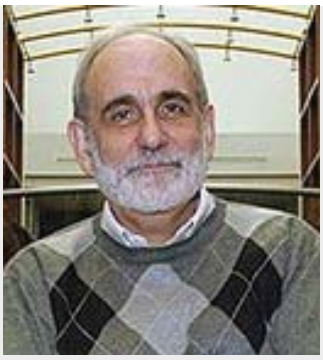
ROUGHLY TWENTY CATALAN SMALL AND MEDIUM-SIZED COMPANIES —20% OF ALL BIOTECHNOLOGY FIRMS THAT DEVELOP THERAPEUTICS AND DIAGNOSTICS— FOCUS ON FINDING MEDICAL SOLUTIONS FOR CANCER

important milestone has been the drafting and kick-off of the **Oncology Master Plan**, led by **Dr. Josep Maria Borràs**, which establishes the country's strategies for moving forward on cancer research and treatment over the coming years.

Likewise, Catalonia also has a network of private sources of funding that is in constant development. Bodies like the Botín Foundation, the "la Caixa" Foundation, the Esther Koplowitz Foundation and the Cellex Foundation are behind some of the research projects and companies in the sector, promoting projects throughout the value chain. Additionally, there are also venture capitalists specializing in the biotechnology sector that not only provide funding but also their strategic, business and management expertise. In recent years, there have been many investments made in companies in the field of oncology, like those made by **Invenready** in biotech companies Ability Pharmaceuticals and Althia, and that led by Catalan venture capital firm **Ysios** in the start-up Inbiomotion. Moreover, Catalan investors have also been involved in successful international transactions, like that of BioVex, a company in which Ysios holds a share and which develops oncolytic viruses and was acquired by Amgen in 2011 for $1,000 millions.

The Catalan oncology sector is full of talent; it is exciting, vibrant and presents countless new challenges testing cutting-edge solutions; it is home to research of excellence that, in many cases, is a global benchmark. In short, it is an area that has the potential to lead biomedical innovation and the knowledge-based economy in Catalonia, and the country has the responsibility to continue promoting this area with efficient resources and strategies.

PERSONALIZED MEDICINE AND THE BARCELONA PATIENT CANCER PLATFORM (BPCP)



Dr. George Thomas
*(ICO / IDIBELL) and the BPCP team**

* Dr. Josep Tabernero (Hospital Vall d'Hebron / VHIO); Dr. Ramon Salazar, Dr. Alberto Villanueva and Dr. Manel Esteller (Hospital de Bellvitge / ICO / IDIBELL); Dr. Antoni Castells (Hospital Clinic); Dr. Agusti Barnadas (Hospital de Sant Pau); Dr. Clara Montagut (Hospital del Mar / IMIM); Dr. Eduard Batlle (IRB); Dr. Gabriel Capella (Departament de Salut); Dr. Josep Maria Borras (Oncology Director Plan).

During the last 200 years, human life expectancy has doubled in the western world. This large increase is mostly due to the use of antibiotics in controlling infectious diseases, which overwhelmed our ancestors. However, as our life-spans grew longer, they brought with them age-related increases in chronic diseases including obesity, type 2 diabetes, arthritis, cardiovascular disease and cancer. Although science, medicine and technology are progressively reducing the burden of chronic disorders, cancer deaths have risen dramatically and have now passed cardiovascular disease as the number one killer worldwide.

The link between cancer and aging is striking in that almost 80% of newly diagnosed cases in cancer present at 55 years of age or older. Cancer, and its associated morbidities, are devastating to family members and come with a huge economic burden for the community. There is large need to improve cures in cancer.

OVER THE LAST FEW YEARS, THERE HAS BEEN A GREAT DEAL OF EXCITEMENT FOR THE APPLICATION OF NEW THERAPIES, EMPLOYING A NOVEL FAMILY OF DRUGS, WHICH BLOCK THE ACTIVITY OF THE GENES RESPONSIBLE FOR THE CANCER. THESE DRUGS ARE COLLECTIVELY REFERRED TO AS TARGETED THERAPIES.

Over the last few years, there has been a great deal of excitement for the application of new therapies, employing a novel family of drugs, which block the activity of the genes responsible for the cancer. These drugs are collectively referred to as targeted therapies. The development of targeted therapies is based on a revolution in the basic sciences led by the discovery of signaling pathways and the genes which make-up these pathways.

In layman terms, these pathways can be envisaged as a street map of a city, in which specific houses, buildings and business centers can be likened to the genes, which make-up these signaling pathways. The street map can direct tourists along specific routes, many of which intersect with one another. This is the basic map of the city and can be likened to our signaling pathways. But one can imagine the tourist moving along a route and to their surprise, there is a detour due to an accident or new construction. With time the detours will be resolved, by workers who again set the map straight. These workers can be equated with novel drugs, which are targeted to set straight a detour. Like the street map, which can vary according to different incidents, each of our maps is constantly mutating, and it is some of these mutations which lead to cancer.

Thus each of our streets maps are varying differently, but we now have the means to identify those differences and to send out the proper workers to set them straight. This has led to the development of personalized medicine platforms, which initially focused on cancer because of its horrendous impact on society, but will be applied to other chronic diseases with

time. The personalized medicine approach is critical as each of us has a variant of the master street map of the city. Moreover, we must also be conscious that despite targeted therapies having unparalleled clinical activity, resistance to these drugs eventually emerges. This is because the signaling pathways like the street map, is ever mutating. This has brought on a new challenge to the cancer community, including the oncologists, basic scientists, patients, universities, hospital staffs, advocacy groups, pharmaceutical companies, and government agencies.

To attack this issue locally, we have pooled the expertises of all the stakeholders in Barcelona to maximize our potential to cure cancer patients. In the last year, working together, we have established the Barcelona Patient Cancer Platform (BPCP) to increase the health span of the people in Catalonia and to partner with other such centers in Europe and Worldwide.

The overall goal of the BPCP initiative is to create a network of excellence in the field of personalized medicine in cancer. This platform aims to combine the molecular characterization of tumors, the use of novel drugs and the analysis of clinical progression of cancer patients in order to identify the most appropriate treatment for each individual. Barcelona, due to its prominence in the field of biomedicine, is an ideal location to build a platform involving a network of hospitals, research centers, universities, government agencies, advocacy groups, pharmaceutical companies and private donors, that will be at the cutting edge in developing the best therapies available to its cancer patients.

"THIS PLATFORM AIMS TO COMBINE THE MOLECULAR CHARACTERIZATION OF TUMORS, THE USE OF NOVEL DRUGS AND THE ANALYSIS OF CLINICAL PROGRESSION OF CANCER PATIENTS IN ORDER TO IDENTIFY THE MOST APPROPRIATE TREATMENT FOR EACH INDIVIDUAL."

According to the SCImago ranking, by number of articles, the top spots in Catalonia are occupied by the University of Barcelona (2nd in Spain, 47th in Europe and 163rd in the world), the Autonomous University of Barcelona (3rd in Spain, 66th in Europe and 202nd in the world) and Hospital Clínic Barcelona (15th in Spain, 201st in Europe and 562nd in the world).

CATALONIA PRODUCES 25.76% OF ALL SCIENTIFIC PUBLICATIONS IN SPAIN, 2.9% OF THOSE IN EUROPE AND 0.79% IN THE WORLD.

As we have already mentioned, studies available[41] show that medicine is the focus of most scientific production in Catalonia (25.8% of the articles from 2003-2008), followed by biochemistry, genetics and molecular biology (11.3% of all scientific production over the period analyzed), both above the national average (21.8% and 9.46%, respectively). No later bibliographic studies are available specifically for Catalonia, and nationwide, although the increase in scientific publications in the humanities and social sciences has decreased the relative weight of experimental sciences, medicine, on one hand, and biochemistry, genetics and molecular biology, on the other, continue to have the most articles published.

Beyond statistics regarding the number and relevance of scientific articles generated in Catalonia, some information generated by biomedical and biotechnology research in Catalonia over the past two years help give us an idea of its quality and impact. In late 2011, for example, two Catalan research projects were among the most noteworthy scientific breakthroughs published in the journal *Science*: the study on **bacterial ecosystem in the digestive tract** in which the VHIR and BSC-CNS participated, and the breakthroughs achieved in phase II of the **RTS'S malaria vaccine**, which Dr. Pedro Alonso's team at the CRESIB is working on.[42] One year later, the same journal put the ENCODE project (Encyclopedia of DNA Elements) and its efforts to discover the functions of DNA, especially the non-coding regions of our genome, as one of the breakthroughs of 2012. The Bioinformatics and Genomics team at the CRG (IMIM-UPF) headed up by Dr. Roderic Guigó has participated in this project and continues to do so.[43]

We have already discussed the quality and main lines of research in cancer. In early 2013, we saw positive results in preclinical trials of a **therapeutic HIV vaccine** developed under the Hivacat program, headed up by Dr. Josep M. Gatell of Hospital Clínic-IDIBAPS and Dr. Bonaventura Clotet of IrsiCaixa. This therapeutic vaccine can reduce the HIV load in blood by up to 90% after one year and is expected to start tests in humans in 2015, with the aim of also developing a preventative vaccine.[44]

41. See footnote 38.

42. Breakthrough of the Year, 2011", Science, 23-12-2011, Vol. 334 Issue 6063, p. 1629-1635. See also: M. Arumugam et al., "Enterotypes of the human gut microbiome," Nature 473, 174–180 (2011) and "The RTS,S Clinical Trials Partnership. First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children", N. Engl. J. Med. 365, 1863-1875 (2011).

43. See Genome Research, Vol. 22 Issue 9, September 2012.

44. http://www.hivacat.org

Also early this year, a study was published by researchers at the Institute Germans Trias i Pujol (IGTP), in collaboration with the Catalan Institute of Cardiovascular Sciences (ICCC) and the Spanish National Research Council (CSIC), showing that umbilical-cord stem cells can **regenerate tissue damaged by heart conditions**. Another team of scientists at the IGTP, in collaboration with researchers at the VHIR and the Institut de Recerca Biomèdica de Lleida (IRB Lleida), with funding from the Institute of Health Carlos III, have developed a **vaccine** to prevent **type I diabetes** in laboratory animals. Additionally, a team from the Autonomous University of Barcelona (UAB) Center for Animal Biotechnology and Gene Therapy (CBATEG) has completely cured this type of diabetes in dogs using **gene therapy**, which they hope to develop for future application in humans.[45]

Catalan research teams have also participated in high-impact international studies, like the one that analyzed the genetic burden of the most frequent **psychiatric disorders** (schizophrenia, bipolar disorder, major depression, attention deficit hyperactive disorder (ADHD) and autism) which involved 75,000 patients and 300 researchers from 250 institutions, including the VHIR, University of Barcelona and the National Genome Analysis Center,[46] and the ambitious study on **ageing** of stem cells and cell-regeneration mechanisms led by the European Molecular Biology Laboratory (EMBL) with participation from the IRB Structural Bioinformatics and Network Biology group led by Dr. Patrick Aloy.[47]

The Alfa study for early detection of **Alzheimer**, promoted by the Pasqual Maragall Foundation with support from the "la Caixa" Foundation, has attracted more than 400 volunteers related to people suffering from this neurodegenerative disease since it was launched in fall 2012. Given its size and characteristics, it is the only study of its kind in the world and can provide highly valuable data for detecting coadjuvant causes of developing the disease and helping design protocols and preventative treatments.[48]

The recognition of six Catalan centers as "Severo Ochoa" centers of excellence —of a total of 13 nationwide— by an independent international scientific committee is also a positive indicator of the quality and impact of the Catalan research system (see box).

45. "Treatment of Diabetes and Long-term Survival Following Insulin and Glucokinase Gene Therapy". Callejas D, Mann CJ, Ayuso E, Lage R, Grifoll I, Roca C, Andaluz A, Ruiz-de Gopegui R, Montane J, Munoz S, Ferre T, Haurigot V, Zhou S, Ruberte J, Mingozzi F, High K, Garcia F, Bosch F. Diabetes, 1-2-2013.

46. "Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs", Nature Genetics 45, 984–994 (2013).

47. http://systemage.eu/

48. http://www.alfaestudi.org/

SIX CATALAN RESEARCH CENTERS WITH "SEVERO OCHOA" SEAL OF EXCELLENCE

Catalonia has six research centers with the "Severo Ochoa" seal of excellence, granted by the Ministry of Economy and Competitiveness Secretary of State for Research, Development and Innovation. The first call in 2011 recognized the **Barcelona Supercomputing Center-Centre Nacional de Supercomputació** (BSC-CNS), **Institute of Photonic Sciences** (ICFO), **Institute for Research in Biomedicine Barcelona** (IRB) and **Barcelona Graduate School of Economics** (Barcelona GSE), and the 2012 call recognized the **Center for Genomic Regulation** (CRG) and the **Institute for High Energy Physics** (IFAE) at the Autonomous University of Barcelona.

The Severo Ochoa program aims to identify and support research of excellence carried out in Spain. This means that centers with this recognition carry out frontier research and are among the best in the world in their areas (life sciences and medicine; mathematics, experimental science and engineering; and social sciences and humanities). Candidates are evaluated and selected by an independent scientific committee, which in 2012 was made up of more than 70 researchers and Nobel laureates from 12 countries.

Catalonia has more "Severo Ochoa" centers than any other autonomous community, 6 out of the 13 selected in the two calls to date. Accreditation as a "Severo Ochoa" center is valid for four years and comes with a grant of €1 million per year over this period.

The 2013 call had not yet been opened when this report was published, but the Spanish government expects to do so in the final quarter of this year with a budget of €20 millions, the same as in 2012.

Research carried out by companies in the BioRegion has led to both positive results and discoveries in the preclinical phases —which are now seeking funding to begin clinical trials in humans— as well as the launch of new products to market. Over the period analyzed in this report, **Oryzon** —which launched a non-invasive biological test to detect endometrial cancer in 2011— demonstrated the efficacy of their molecules to treat leukemia in various preclinical trials and, in mid 2013, received orphan drug status for ORY-1001 to treat acute myeloid leukemia, which will soon begin phase I clinical trials. **Bionure** has successfully completed the preclinical phases with a drug candidate for multiple sclerosis and expects to begin clinical trials in late 2013. **Lykera Biomed**, a spin-off of the Leitat technological center, also expects to begin clinical trials on a new therapy for pancreatic cancer developed by the Leitat biomedical department in 2014.

VCN Biosciences, held in part by Grífols, began phase I clinical trials in 2013 on VCN-1, an antitumor adenovirus to treat pancreatic cancer. Oncology is also the focus of work being done at **Ability Pharmaceuticals**, which in early 2013 closed a €1.2-millions round of funding for clinical trials on its drug ABTL0812 for lung and pancreatic cancer. Also undergoing a multicenter trial is the prostate-cancer test developed by **Transbiomed**, a spin-off of the VHIR that merged with Valladolid-based biotechnology firm Amadix in 2013 to help launch its products to market.

Various companies have begun production or launched products developed by their R&D departments. In mid 2012, **Nanotargeting**, a spin-off of the Catalan Institute of Nanotechnology (ICN), and **Grupo Ferrer** began development of a cancer treatment using gold nanoparticles. In late 2012, **Althia** and Hospital Quiron launched a new single-dose image-guided radiotherapy treatment. In 2013, internal R&D has led to the launch of new products by **AB-Biotics** —a new probiotic, AB-Dentis, for oral conditions like gingivitis and cavities— and **Bioibèrica** —a DNA test to predict development of osteoarthritis of the knee.

Advancell has licensed a drug to treat dermatology conditions resulting from chemotherapy to Swiss group Helsinn.

Research carried out by companies in the BioRegion has also led to new products in biotechnology for food control, like the test to detect salmonella created by **iMicroQ** —a spin-off of Rovira i Virgili University— that began production in the first half of 2013, and research-support technology like the automatic inoculation system for microbiology samples produced by **NTE-Sener** and **Deltalab**. To round out this summary, we must mention the company **Specific Pig**, created in mid 2013 and the first in Europe to research, produce and market miniature pigs as animal models for biomedical research, in collaboration with IRTA, Bioemprèn and Semen Cardona.

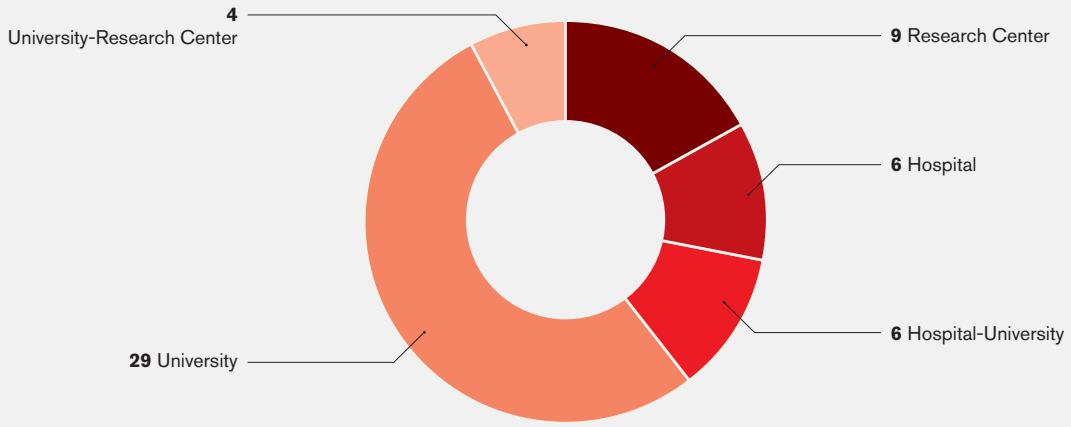
Patents and technology transfer

As seen in a good part of the examples of business R&D mentioned, technology transfer in the life sciences sector has given rise to an important number of new companies. Specifically, from 2000 through the first semester of 2013, **54 spin-offs** of hospitals, research centers and universities have been created in the BioRegion (graph 35), to which we must add the initiatives currently underway, like two projects form Catalan research centers that have received support from the Botín Foundation in 2013: Colostage (project promoted by IRB Barcelona) and Nostrum Drug Discovery (IRB and BSC). Most of these spin-offs (40) are biotechnology firms, devoted to research into new therapeutics and diagnostics (18) and specialized R&D services (14), although there are also companies working in biotechnology for food and agriculture (5), veterinary, environment and cosmetics. Half a dozen of these spin-offs produce innovative medical technology and the rest offer consultancy services or specialized software or laboratory instruments. As a whole, these companies —65% of which are less than 5 years old— have created nearly 260 new jobs, although most focus on the initial phases of research and do not generate revenue.

UNIVERSITIES, RESEARCH CENTERS AND HOSPITALS IN THE BIOREGION HAVE CREATED 54 SPIN-OFFS THAT EMPLOY NEARLY 260 WORKERS.

In addition to those mentioned in the previous section, we can also cite examples of the success of this technology transfer, like **Iproteos** (IRB/UB), which has applied for its first patent for an innovative drug to treat schizophrenia; **Advanced Nanotecnologies** (UB), which markets GraphMan-12, a graphene-based biocompatible material with applications in optics, among other products; and **qGenomics** (CRG/UPF), which produces DNA chips for diagnostic tests that are already being used in several hospitals.

Graph 35 **Number of spin-offs in the BioRegion by origin**



Source: Biocat Directory

The increase in public-private partnerships among Catalan companies and research centers in recent years is also a positive sign of technology transfer in the sector, in line with a growing international trend towards open innovation models (see box *Catalonia advances in public-private partnerships*).

CATALONIA ADVANCES IN PUBLIC-PRIVATE PARTNERSHIPS

Public-private partnerships (PPP) are one of the collaboration methods gaining steam in order to tackle the social and economic challenges in the health sector in Catalonia. Countries like Finland, Germany and the Netherlands, where this model of close collaboration between public institutions and companies to efficiently carry out R&D&i projects has been implemented for some time now, have seen satisfactory results.

In addition to funding, PPP are also important in aligning research with society's needs and speeding up the timeline to bring **solutions to patients**.

In 2012, we have seen four public-private partnerships in the biosciences in Catalonia:

Center for Genomic Regulation (CRG) and Sanofi: the CRG and the multinational pharmaceutical corporation forged a strategic alliance in March 2012, initially for a three-year period, to research new methods to assess translational medicine, from basic research through patient treatments.

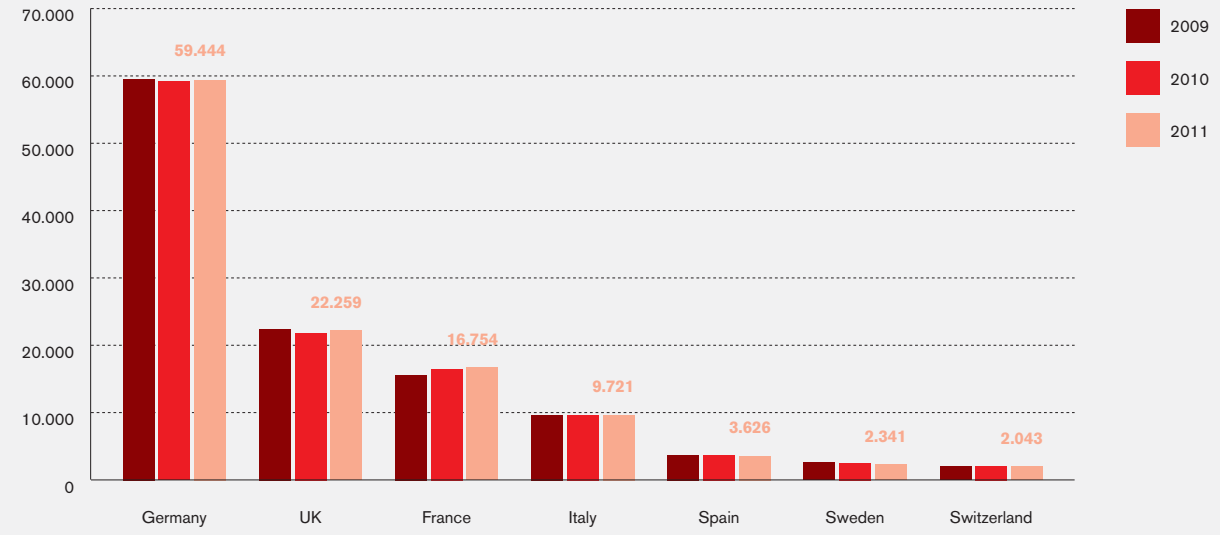
Hospital Clínic, Spanish National Research Council (CSIC) and Histocell: in January 2012, Hospital Clínic Barcelona, CSIC and Basque biotechnology firm Histocell announced that they would develop a cell medication for pulmonary fibrosis from a patent held by the CSIC and Hospital Clínic. Histocell will invest at least €3 millions.

Hospital Clínic and Olympus: these two are studying and analyzing groundbreaking optical technology for high-definition 3D laparoscopic surgery, which improves visual quality in operations and makes them safer for the patient. The technology is being developed by Olympus and Hospital Clínic is contributing their experience for possible improvements to the device.

IRB Barcelona, Novo Nordisk and European Foundation for the Study of Diabetes (EFSD): pharmaceutical company Novo Nordisk and the EFSD contributed €100,000 for a research project at the IRB Barcelona aiming to provide new options to preserve or recover glucose sensitivity in pancreatic beta cells in diabetics.

Although the rate at which new companies have been created is notable, the Catalan research system —and that of the nation as a whole— continues to generate very few patents compared to other European countries. According to figures from the WIPO database,[49] while Germany generates nearly 60,000 patent applications a year and the United Kingdom more than 22,000, Spain applies for just over 3,600 patents each year, when countries like Sweden and Switzerland, 5 or 6 times smaller than Spain, have more than 2,000 patent applications each year (graph 36).

Graph 36 **Comparison of patent applications submitted to national offices**



Source: WIPO

It must be noted, in this regard, that Europe as a whole, with 332,581 patents applications in 2011 through the national offices, trails, in absolute and relative terms, countries like Japan—which with only half the population of Europe processed more than 342,000 patent applications— the United States and China, which processed more than 500,000 patent applications each in 2011.

The type of patent applications varies widely and, if we look specifically at patents in the life sciences (biotechnology, pharmaceuticals and medical technology),[50] the numbers are considerably lower. WIPO data for 1997-2011 indicates that applicants in Spain have requested a total of 109,314 patents over this 15-year period —through the Spanish Patent and Trademark Office (OEPM) or

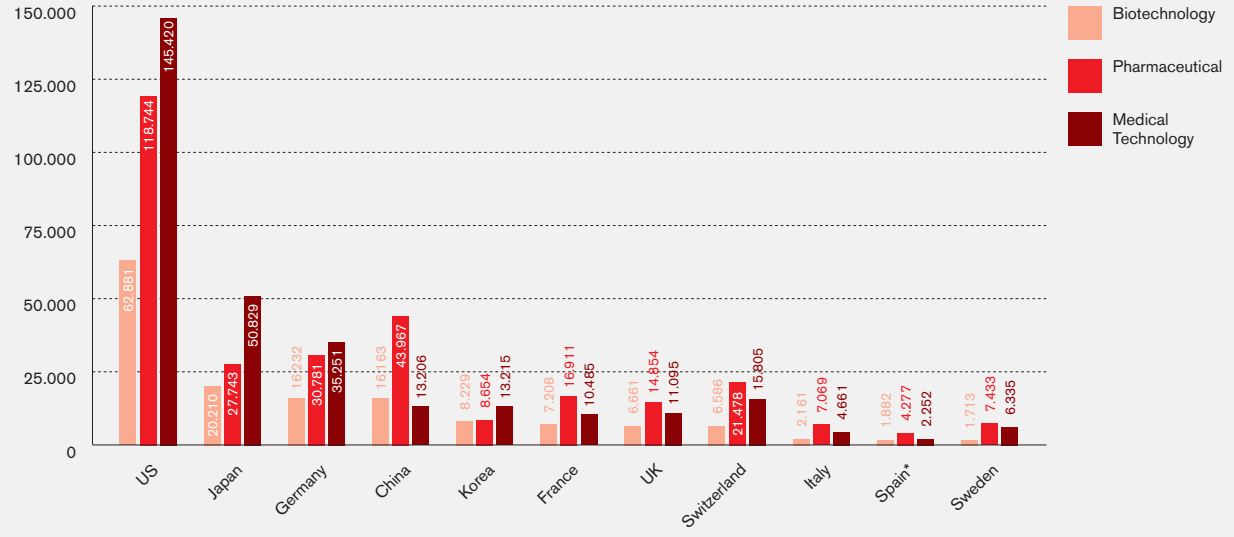
49. World Intellectual Property Organization. The data reflects the total number of applications submitted to national offices in each country.

50. The WIPO and associated offices, like the OEPM, share the same classification of technology sectors, which groups the IPC (International Patent Classification) codes established in the 1971 Strasbourg Agreement into 35 lines. This grouping, available at http://www.wipo.int/ipstats/en/statistics/technology_concordance.html, differs from that used by Clarke & Modet in the study on patents in the BioRegion included in the 2011 Biocat Report. The number of applicants included also varies (WIPO and OEPM only include the first applicant per geographic area, while Clarke & Modet also include the second and third). This is why the figures aren't directly comparable.

other international offices— 8.91% of which were for pharmaceutical inventions, 4.69% for medical technology and 3.92% for biologicals. We are looking at, thus, 19,152 patent applications nationwide in the areas covered by this report (roughly 1,300 per year), approximately 45% of which are processed by the OEPM.

Although information technology and energy are the technological sectors that generate the most patents worldwide, in Spain the top spot goes to the pharmaceutical sector, followed by civil engineering and fine chemicals. Graph 37 shows a comparison of patent applications in technological sectors of the life sciences over the 2006-2010 period.

Graph 37 **Patent applications in the life sciences 2006-2010**



* Calculated by Biocat

Source: WIPO

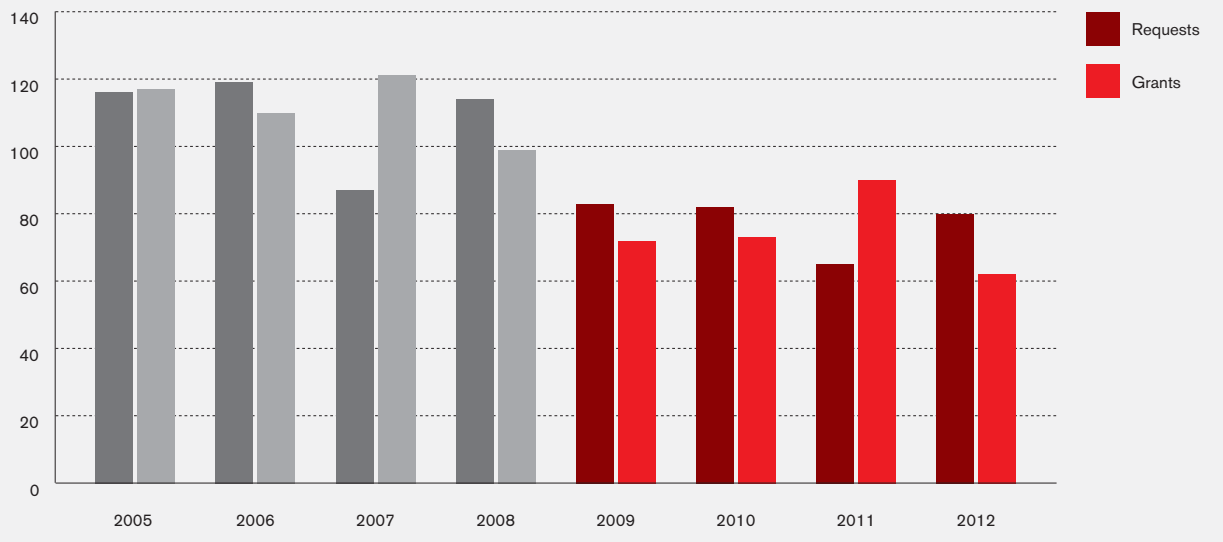
The graph —which is in no way a ranking— shows that, despite being the top sector in generating and protecting intellectual property (IP) in Spain, fewer pharmaceutical patents were applied for between 2006 and 2010 than in Sweden, which has one fifth the population and sees more IP protection in the telecommunications and digital communications sectors.

CATALONIA GENERATES 20% OF ALL PATENT APPLICATIONS IN THE LIFE SCIENCES IN SPAIN, LESS THAN ITS WEIGHT IN RESEARCH

The absolute number of patents generated in Catalonia is even lower if we compare with countries and regions of a similar size and comparable level of scientific development, and the region's contribution to patents in the life sciences generated nationwide is below its weight in research. Of the 389 applications processed in 2012 by the OEPM for biotechnology, pharmaceutical and medical technology patents, the head applicant was Catalan on 80 (20.5%), and of the 320 granted, 62 (19%) were to Catalan applicants. Graph 38 shows the evolution of biological, pharmaceutical and medical technology patents processed by the OEPM between 2005 and 2012 and those corresponding to entities, companies and individuals residing in Catalonia (head applicant).

Graph 39 shows the percentage of life sciences patent applications processed by the OEPM from each type of entity, public or private, in Catalonia. As can be seen, companies generate the most IP in this sector, with 51% of all patent applications in 2011 and 56% of those in 2012. Of the public research bodies, the relative weight of research centers in generating patents in the sector is noteworthy.

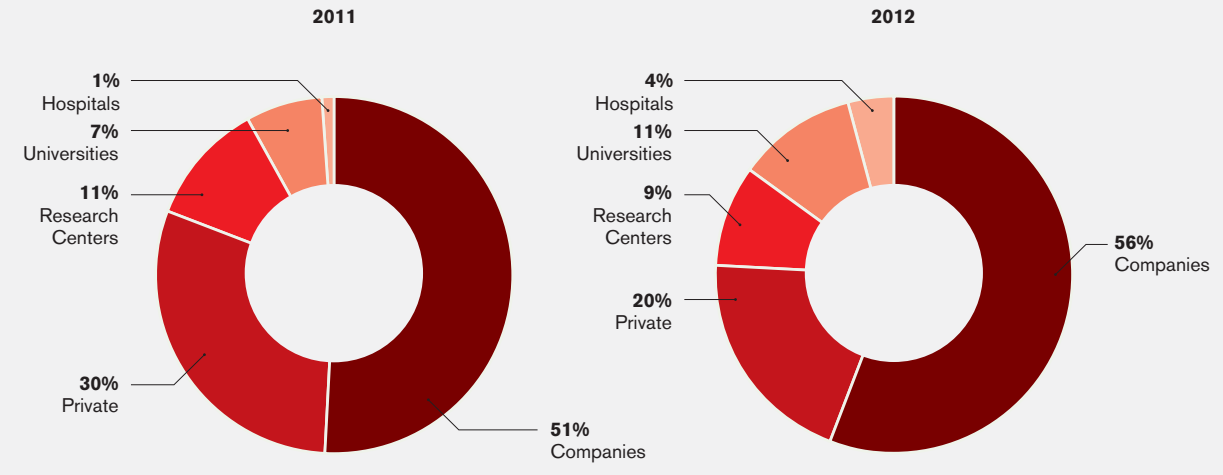
Graph 38 **Evolution of life sciences patents from applicants in Catalonia processed by the OEPM (2005-2012)***



* A different counting method is used from 2009.

Source: OEPM

Graph 39 **Percentage of patent applications processed by the OEPM by type of first applicant**



Source: OEPM

One Catalan university —the UPC— is among those with the most patents processed in 2012 nationwide, a list headed by the CSIC (with 90 applications processed) and companies Telefónica (90) and ArcelorMittal (25). The UPC is sixth on this ranking, with 21 patent applications. In the life sciences arena, according to the OEPM patent application registry, Esteve was the most active company in 2011, with four patent applications, followed by Grífols (3) and GP-Pharm (3). In 2012, Dr. Healthcare (4 applications processed) and Esteve (4) were the most active in patent protection in the life sciences. In terms of public bodies, the UPC, with two patent applications processed in 2011 and six in 2012, has been the most active in the life sciences arena.

At the same time, it must be noted that according to the analysis carried out by Clarke & Modet for the 2012 Asebio Report,[51] companies generated 31% of all biotechnology patent applications and patents granted in 2012 of all those processed through the OEPM, EPO, USPTO, JPTO and PCT[52] (1,064) and the 13 most active companies include eight in Catalonia: Lipotec, Almirall, Inkemia-IUCT, Grífols, Bioibèrica, BCN Peptides and Pangaea Biotech.

Overarching international trends in Catalonia

The beginning of this chapter examined interest in rare diseases, open innovation and emerging markets as three of the overarching international trends that are marking the evolution of the life sciences sector. But what weight do these trends carry in Catalonia?

As we already commented in discussing technology transfer, growing interest in public-private partnerships has been seen from both research bodies and, maybe more importantly, large companies in the sector. This is the first step towards open-innovation models in the life sciences sector, as is the creation of collaboration networks in specific scientific and therapeutic areas (cancer, bionanomedicine, respiratory diseases, etc.) as discussed previously.

We are experiencing a global paradigm shift and we have examples from right here at home that show the Catalan system is also being transformed. Thus, we have large pharmaceutical companies that have cut their R&D departments and forged strategic alliances with small biotechnology companies —like the agreement between Catalan pharmaceutical group **Ferrer** and **Vivia Biotech** (Salamanca) in early 2013 to develop new therapies for blood cancers— and large corporations like **Grífols** that are broadening their field of action in R&D by acquiring shares in biotechnology firms of varying sizes with research projects of interest (**Araclon**, **Aragdim**, **Nanotherapix**, **Progenika**, **VCN Biosciences**).

All of these initiatives are steps towards more dynamic models that will help bridge the gap between research and the needs of the population, as well as ensuring that products reach the market more quickly.

51. Asebio Report 2012, p. 40-45.

52. OEPM: Spanish Patent and Trademark Office. EPO: European Patent Office. USPTO: United States Patent and Trademark Office. JPTO: Japan Patent Office. PCT: Patent Cooperation Treaty.

RARE DISEASES: FOCUS OF GROWING INTEREST IN THE PHARMACEUTICAL INDUSTRY

Marc Martinell
Mynorix Therapeutics

In recent years, the development of treatments for rare or minority diseases (orphan drugs) has generated great interest in the industry, mainly spurred on by the success of companies specializing in this sector. A large part of this success comes from the high price of the treatments, which can cost up to $100,000-500,000 per year per patient. In addition to the regulations initially introduced in the US and later in Europe, there are several important incentives, like tax cuts for development, access to specific grants, accelerated approval and, the most attractive, market exclusivity for a period of 10 years in the EU and 7 in the US. Additionally, there are also significant advantages in terms of clinical development, as these drugs are normally geared towards diseases with a more homogenous genetic makeup and studies require fewer patients, making costs more accessible for many more companies. Moreover, recent studies show that these products have shorter development times and higher rates of regulatory success, which makes them more profitable overall than treatments for more common diseases.

Despite these tempting points, the development of orphan drugs also presents significant challenges. The first of these is that knowledge on the diseases is often very limited. Although this can also be seen as an opportunity, this makes identifying the best mechanisms to treat the disease more difficult and the lack of patient registries and information on the natural history of the disease make it more difficult to define the most fitting goals. In this sense, the activity of patents' associations and academic groups specializing in these diseases is highly important in generating the basic science to enable later development of possible treatments. The small number of patients also leads to difficulties in recruiting for clinical studies, which is particularly significant when there is already a treatment available on the market. Finally, a good part of minority diseases affect children, which adds additional challenges to developing these drugs.

One of the important challenges for the future facing the sector, however, will be the issue of price. Several voices have spoken out questioning whether healthcare systems can assume a significant increase in the number of patients treated at such a high price and the need to regulate this, like for example with progressive reimbursement based on the efficacy. The current trend shows that products for serious diseases for which no treatment is available can justify higher prices, but those for which other alternatives exist or for which significant return has already been generated may have to lower their prices.

With concepts like personalized medicine, the current trend is towards stratifying the patient population based on the genetics behind each disease, which is leading to the separation of patients with more prevalent diseases into minority subpopulations. This indicates that the development of therapies for minority diseases, with the paradigm shift from blockbuster to nichebuster, is a change in the model that is here to stay. However it is still necessary to find mechanisms to ensure the system's viability, like the universal right to treatment, regardless of the pathology or its prevalence. And all of this without losing sight of the fact that the field of minority diseases has led to the development of highly innovative treatments that have later brought about significant advances in many other diseases.

Public and private research in rare diseases is also growing in Catalonia due to the fact that, as Marc Martinell of **Mynorix Therapeutics** explains in his article, in addition to the social and scientific interest in addressing serious, untreatable diseases, companies are discovering the competitive advantages —in terms of development time and the regulatory process— these orphan drugs offer. Catalonia has an important presence in research in these fields, with 18 of the 60 CIBERER (Center for Biomedical Network Research on Rare Diseases) research groups focusing on these topics. The treatment for type-A Fanconi anemia developed by this CIBER has been designated an orphan drug by the EMA. 15 drugs have this designation in Spain, 10 of which belong to Catalan companies (Advancell [2], GP-Pharm, Grífols [3], Esteve [2], Oryzon and VCN Biosciences), four to Navarra-based company Digna Biotech and one to the CSIC. The multinational corporations present in Catalonia (Actelion, Amgen, Novartis, Sanofi, etc.) have 54 drugs with EMA orphan designation currently in force.

The movement into emerging markets is a general trend, but above all it affects large multinationals and regions with more mature sectors. As we will see in chapter V, Catalan companies in the life sciences sector are interested in this option and the strongest are already taking important steps in this direction, which should yield results over the coming years.

This alignment with overarching international trends will be positive for Catalan companies in the life sciences sector if, at the same time, we can overcome the most significant weaknesses of our system. We see, thus, that despite the significant number of spin-offs created over the past 10 years by research institutions, most of these companies are very weak from a financial point of view and are facing difficulties in accessing both resources and the market. The positive development of some of these spin-offs, like **AB-Biotics**, which has successfully completed various rounds of funding since it went public on the Alternative Stock Market (MAB) in 2011 and is seeing good international projection of its products, is a good sign, but still too isolated and unique when we take into account the sector as a whole.

The participation of Catalan biotech and techmed companies in European research and innovation programs is low. The kick-off of the Horizon 2020 program and the EIT initiatives must be seen as an opportunity and a challenge. Aligning strategies, identifying strengths and finding appropriate partners will be key at a time in which Europe is shaping up to be the only alternative to compensate for the political and economic weakening of the Spanish research and innovation system.

IV.
FUNDING

FUNDING

Between January 2012 and September 2013, companies in the Catalan life sciences sector attracted €43.68 millions in venture capital (VC), more than double that seen in 2010 and 2011 (€19.53 M). This is in addition to the €8.6 millions obtained on the stock market through capital increases carried out by **AB-Biotics** and **InKemia-IUCT Group**, the two Catalan biotechnology companies traded on the Alternative Stock Market (MAB).

This growth is particularly significant, as it has come about in a highly restrictive investment panorama. The venture capital market in Spain shrunk 22.8% in 2012 from levels seen in 2011, and Catalan participation in VC investment also fell, from 27.4% in 2011 to 20.4% in 2012.[1]

Venture capital continues to be the main means of capitalization for life sciences companies in Catalonia, where the small size and short history of most companies leaves them outside the scope of interest of private equity funds (PE)[2] and where certain cultural hurdles make access to other sources of funding, like the stock market, merely anecdotal. Nevertheless, in December 2012 InKemia IUCT Group, one of the companies in Catalonia that best represents the promotion and potential of white biotechnology (industrial), launched a successful IPO on the MAB. In June 2013, the company carried out a capital increase with the aim of attracting €2.5 millions to fund their international expansion, which they successfully completed in just one month with excess demand of 4%.

Just a few days before InKemia IUCT Group launched its IPO (December 2012), AB-Biotics, the first Catalan biotech firm to go public on the MAB, closed a €5-millions capital increase, with shares bought by pharmaceutical company **Almirall** and the **Catalan Finance Institute**, through the Capital MAB FCR fund created to support companies traded on the Alternative Stock Market. AB-Biotics carried out another round of funding in 2013, attracting €1.12 millions.

Almirall's commitment to biotechnology isn't an isolated example but part of a changing trend epitomized by Catalan multinational corporation **Grífols**. Over the period covered in this report, this hemoderivatives company acquired a majority share in a series of biotechnology firms of varying sizes, ranging from spin-offs of Catalan universities and research centers (**Nanotherapix** and **VCN Biosciences**) to international companies like **Aradign** (USA) —in which it purchased 35% of stock for €20 millions in August 2013— to biotech firms from other Spanish bioregions, like **Araclon** and **Progenika**, in which they hold 51% and 60% of shares respectively.

1. ASCRI (Spanish Venture Capital Association), 2012 Report (p. 20-21) and 2013 Report (p. 22-24).
2. Following the definitions of entities like ASCRI and EVCA (European Private Equity & Venture Capital Association) venture capital (VC) is early-stage investment (seed, start-up, early-stage and later-stage) and private equity (PE) is investment in advanced stages of growth or for any of the various types of buyouts (LBO, MBO, MBI and LBU).

The overall balance is a contradictory portrait of light and shadows, where improvements in certain key indicators combine with the huge difficulties experienced by small research-based companies, whose viability depends on accessing public funding that has disappeared or isn't at the expected level, creating unsustainable financial pressure.

INTERNATIONAL TRENDS

2012 was an exceptionally good year for the finances of biotechnology companies around the world and, in particular, those in the USA. Venture capital operations totaled $12,426 millions, up 22.8% from 2011. 76% of this investment ($9,460 M) went to companies in the USA, where the value of the top publicly traded biotech companies rose 40.5% (Burrill Select Index), compared to 7.3% growth of the Dow Jones Industrial Average and 15.9% of the Nasdaq Composite Index. As a whole, in 2012, US science companies obtained $71,000 millions in financial resources through private (VC and PE) and market investment (stock and debt), up 23.9% from 2011 ($57,400 M).[3]

IN 2012, $12,426 MILLIONS IN VENTURE CAPITAL WERE INVESTED IN THE LIFE SCIENCES SECTOR GLOBALLY

Beyond improvements in general economic indicators in the USA —which unfortunately weren't shared in Europe— analysts attribute this growth in the life sciences sector in 2012 to the notable increase in approvals for new drugs (see chapter III) as well as a series of political and legal decisions made over the course of the year, from approval of new regulations for FDA activities[4] through the sentence handed down by the US Supreme Court upholding the health reforms promoted by President Barak Obama (June 2012).

One of the most highly valued factors was approval of the JOBS Act (Jumpstart Our Business Startups Act), designed to facilitate access to the stock market for US SMEs and start-ups by cutting down on and simplifying the most costly IPO requirements for emerging growth companies.[5] The law also allows companies to test investor interest before publishing all the information required to go public. This law has the potential to make a considerable impact, as any company with turnover under $1,000 millions per year is considered an emerging growth company. In fact, as of April 2013, 11 of the 13 life sciences companies that went public in the USA after approval of the law, in April 2012, did so under the JOBS Act.[6]

The stock market, on one hand, and mergers and acquisitions (M&A), on the other, are the main ways for VC to see return on investment in the early stages. One of the phenomena seen globally is that it is becoming increasingly difficult —even in large, mature markets like the USA— to find seed and start-up funding for biotechnology companies, as venture capital focuses on more advanced phases that have shorter return-on-investment times. At the conference entitled New Paradigms to Fund Life Science Innovation, held in San Francisco in January 2013, CEO of Silicon Valley Bank Jonathan Morris highlighted that Series A funding—that for start-ups and early-stage businesses— for life sciences companies fell 20% from 2005 to 2012, accounting for only 12% of all venture capital transactions in the sector in the USA.

3. The Burrill Report, Vol, 3, Issue, 2, February 2013.
4. Parts of the FDA Safety and Administration Act were modified, going into effect in July 2012 (http://www.fda.gov).
5. http://www.sec.gov/spotlight/jobs-act.shtml
6. The Burrill Report, Vol, 3, Issue, 5, May 2013.

Analyzing the top 200 mergers and acquisitions carried out by biotechnology companies (103 acquisitions for more than $75 M) and medical devices companies (104 acquisitions for more than $50 M) between 2005 and 2012, Morris pointed out that on average companies have had 2.7 rounds of funding and investors have kept their share of the company for an average of 5.5 years before seeing return on investment (ROI) by selling off stock, The ROI obtained through these operations varies widely, on average between x2.6 and x7.1. In any case, it is a small sample of results, as the analyst himself admits that as of late 2011, $38,000 millions in venture capital was invested in 1,642 biotechnology and medical technology companies in the USA awaiting positive results.

INVESTMENT IS MAINLY IN ADVANCED PHASES OF DEVELOPMENT, NOT SEED AND START-UP

On the other hand, if we look at the evolution of venture capital investment in the health sector in the USA, we see a progressive decrease in the number of transactions and volume of investment in biopharmaceutical companies and an increase in that in medical technology companies: in 2004, VC operations in pharmaceutical and biotechnology firms made up 48% of the total and only 37% went to medical technology companies, while in 2012 the proportion was completely different, with only 33% of investment going to biotech and pharma and 46% to medical technology.[7] Economic pressures on the healthcare system and the development of personalized and preventative medicine, as mentioned in chapter III, favor technology providers and digital health companies (particularly hospital software and monitoring and diagnostic devices), and investors are quick to pick up on and support these changes. According to a study by consulting firm CB Insights, between July 2012 and June 2013, 362 VC investment operations were carried out in the USA in digital health companies for a total of $1,500 millions, a 23% increase in capital invested and 18% increase in number of operations compared to the previous year.[8]

WEIGHT OF BIOTECHNOLOGY AND PHARMACEUTICAL COMPANIES IN VC PORTFOLIOS IS DECREASING AS THAT OF MEDICAL TECHNOLOGY COMPANIES IS INCREASING

Pressure from VC funds to see return on investment has also led to increased importance of business angels, corporate funds and non-profit organizations in the early stages, each with their own particular motivations. As mentioned in chapter III in discussing open-innovation networks and the growing role of patients, large pharmaceutical companies are scaling back their R&D departments and moving towards scientific collaboration and financial support for small biotech firms as a strategy to accelerate innovation, as well as opening up new lines of research. Foundations and patients' associations are actively involved in funding research in order to draw attention to rare diseases and therapeutic areas that the industry has considered unprofitable and therefore is not interested in. The personal implication of business angels in their investment also promotes their participation in projects that VC still considers too risky.

Despite this general trend, the large number of IPO carried out by life sciences companies in the first half of 2013 in the USA and the high level of return on investment obtained through these operations brings new perspectives.

IN THE FIRST HALF OF 2013, THE NUMBER OF LIFE SCIENCES IPO IN THE USA NEARLY DOUBLED AND THE CAPITAL OBTAINED IN 2012 INCREASED FOUR-FOLD

In addition to **Zoetis** —the animal health division of **Pfizer**, with a production and R&D plant in Catalonia (Olot)—, which in January 2013 obtained $2,564 millions through their IPO (NYSE:ZTS), 28 other biotechnology and medical technology companies carried out IPO (Initial Public Offerings) in the USA between January and July 2013, for a joint total of more than $2,460 millions. Individually, the amount ranges from $525 millions, for CRO **Quintiles Trans-**

7. 2013 Venture Capital Healthcare Report, PitchBook (pitchbook.com).
8. Digital Health Venture Capital and Private Equity Funding Tops $1.5 Billion Last Year Across 362 Deals, CB Insights (www.cbinsights.com).

national, to $6.9 millions raised by diagnostic company **Cancer Genetics**. In contrast, only 16 companies from the sector went public in the USA in 2012, with a total of $1,093 millions raised.

In addition to raising $5,000 millions through IPO, the 29 companies that went public in 2013 have seen joint return on investment of +40.4% since being traded on the stock market. The most significant issue for analysts is the changing attitude of investors, who have supported companies that in many cases are still far from marketing their products: four of the companies are working on new therapies for rare diseases and eight on new cancer drugs, most of which are in phase I and phase II of clinical research.

Although the first quarter of 2013 seemed to announce a drop in global VC funds, by late July the amount invested ($7,326 M) was slightly higher (0.4%) than investment over the same period in 2012 ($7,298 M).[9]

The importance and size of acquisitions of biotechnology companies over the past two years are probably having a positive impact on market perception. A recent article by Peter Winter, editor of BioWorld Insight, estimated that investors had received approximately $100,000 millions from selling companies over this period, and that these resources are being reinvested in the sector.[10] The most noteworthy operations include three mega-deals in 2011: **Sanofi**'s acquisition of **Genzyme** ($20,100 M), **Takeda**'s purchase of **Nycomed** ($13,700 M) and **Gilead**'s of **Pharmasset** ($11,000 M); and in 2012, the acquisition of **Amylin Pharmaceuticals** by **Bristol-Mayers Squibb** ($5,300 M). **Amgen** acquired three significant companies —**Micromet** ($900 M), **Kai Pharmaceuticals** ($315 M) and Icelandic company **deCODE Genetics** ($415 M)— but more importantly carried out one of the largest operations of 2013: the acquisition of **Onyx Pharmaceuticals** for $10,400 millions, a transaction closed in late August after Onyx rejected the initial offer of $10,000 millions in June.

CANCER IS THE FOCUS OF RESEARCH DONE BY THE BIOPHARMACEUTICAL COMPANIES THAT AROUSE THE MOST INTEREST AMONG INVESTORS IN THE SECTOR

The big draw of Onyx was its drug *Kyprolis* approved by the FDA in 2012 to treat multiple myeloma, a rare hematological cancer. In fact, according to The Life Science Report Watchlist 2013, cancer is the focus of interest of all biopharmaceutical companies and investors in the sector, and the volume of phase II and III clinical trials on oncology products widely surpasses that of any other therapeutic area. According to this publication, oncology trial data pushed stocks up approximately 9% and down roughly 15% in 2012.[11]

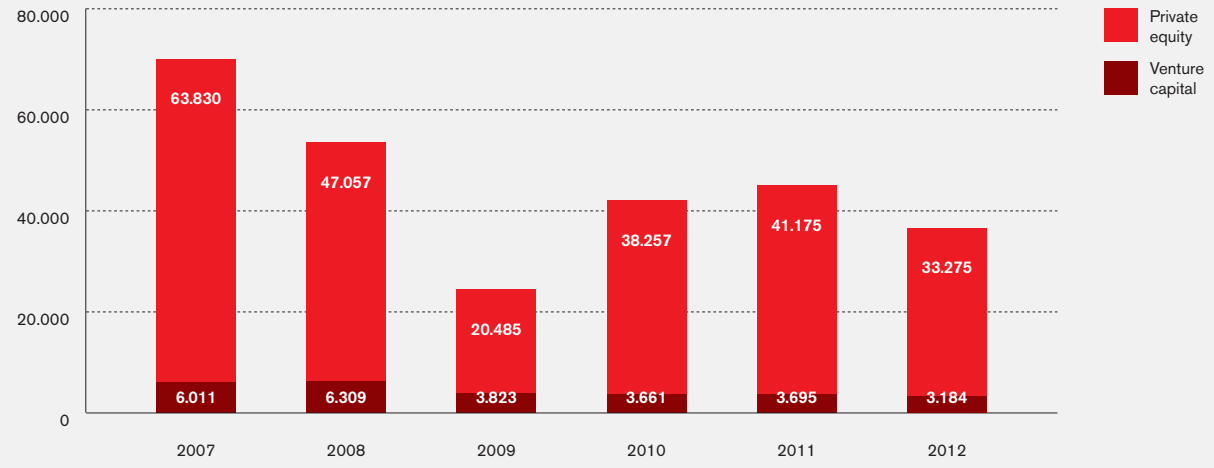
9. The Burrill Report, Vol, 3, Issue, 9, September 2013.
10. Peter Winter, "Biotech Companies Record Another Positive Quarter", BioWorld, 11-10-2013 (www.bioworld.com).
11. George S, Mack, The Life Sciences Report Watchlist 2013, 31-1-2013. http://www.thelifesciencesreport.com/pub/na/the-life-sciences-report-watchlist-2013

European perspective

Unlike what we have seen in the USA, venture capital invested in the life sciences in Europe fell in 2012. In fact, the whole venture capital and private equity market shrunk compared to 2011, a year that seemed to point towards the beginning of a recovery after the collapse of the sector in 2009 —with investment down 54%— as a result of the global financial crisis. As a whole, VC and PE funds invested in Europe in 2012 totaled €36,459 millions, 19% less than in 2011 (€44,870 M). €3,184 millions were invested in the early stages (VC), down 14% from 2011. Graph 40 shows that the global recovery of 2010 and 2011 hasn't extended to early-stage companies and VC has dropped continuously year after year since 2008, down 50% in four years.[12]

It must be noted that European VC and PE companies attracted more than €23,600 millions for new investment in 2012, €3,600 millions of which was for venture capital. In this case, the resources obtained were also below levels seen in 2009 and 2010, but also a significant drop from those in 2011, when €41,600 millions in new funds were raised, €5,193 millions in venture capital. Investor confidence in Europe seems to have deteriorated, although in relative terms the funds attracted from outside of Europe are significant: North America contributed 25% of all new VC&PE funds attracted in 2012 and 20% of that in 2011. If we focus on venture capital, however, North America only contributed 4.5% of new funds, which mainly came from France and Benelux (34.5%) and Scandinavian countries (17.5%).[13]

Graph 40 **VC and PE investment in Europe (in millions €)**



Source: European Private Equity & Venture Capital Association (EVCA)

12. www.evca.eu

13. 2012 Pan-European Private Equity and Venture Capital Activity, EVCA, 2013.

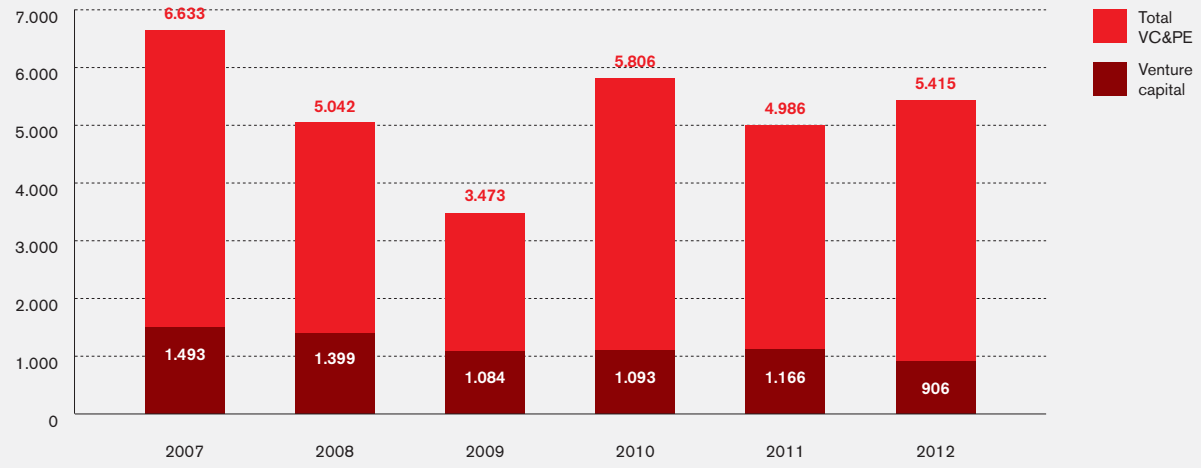
LIFE SCIENCES COMPANIES RECEIVED 28.4% OF THE Đ3,184 M IN VENTURE CAPITAL INVESTMENT IN EUROPE IN 2012

According to data from the European Private Equity and Venture Capital Association (EVCA), European life sciences companies received investment valued at €5,415 millions in 2011, 14.9% of all venture capital and private equity funds. If we focus on VC funds, the proportion increases, with the life sciences accounting for 28.4% of investment (€906 M). As shown in graph 41, global investment (VC&PE) in the biosciences has recovered and even surpassed levels seen in 2008, but not in the early stages, where VC investment dropped 35% from 2008 to 2012.

As a whole, 840 companies in the life sciences sector received VC and PE investment in 2012. The bulk of these companies, however, are in the early stages: €906 millions in venture capital went to 656 companies —with an average investment of €1.4 millions— while 184 companies saw €4,509 millions through growth or buyout operations —on average €24.5 millions per operation.

Regarding divestments, most VC divestiture (a total of €1,900 M in 999 companies in 2012) was through acquisition of a company by another (36.7% of financial volume and 15.6% of the companies), but there was also a significant number of stock-transfer operations between venture capital funds (16.8%). However in the European VC&PE market there were very few divestments through IPO: EVCA only lists seven in 2012, which obtained a total of €293 millions (five of which were from venture capital, obtaining €6.6 M).

Graph 41 **VC and PE investment in the life sciences sector in Europe (in millions €)**



Source: European Private Equity & Venture Capital Association (EVCA)

JAVIER JORBA: "WE'RE INTERESTED IN INVESTING IN BIOTECHNOLOGY PROJECTS WITH HIGH POTENTIAL THAT COMPLEMENT GRÍFOLS' RESEARCH LINES"

Javier Jorba
head of the department of biological products at Grifols

Grífols is a consolidated company that is strong in the field of hemoderivatives (third largest manufacturer in the world, with 32% of the US market and 14% of the European market), which is committed to investing in biotechnology companies in order to expand and develop their R&D line. Can you tell us why you have made this commitment to biotechnology?

The reasons behind this commitment can be summed up in two complementary aspects. First of all, Grífols' commitment, since it was founded more than 70 years ago, to helping improve the health and wellbeing of the people by advancing science and society. This pioneering spirit has led us to participate in projects and initiatives in the biotechnology sector.

In fact, Grífols has been connected with this sector, indirectly, for years now through one of the companies in the group, Grífols Engineering, which specializes in engineering services and teams for biotechnology and pharmaceutical projects. Grífols Engineering has designed and built facilities for biotech companies.

Secondly, here at Grífols we are aware of the potential of biotechnology for healthcare to promote this contribution to society, but also of the difficulties many projects being carried out in the sector experience in finding funding. For this reason, we have decided to invest in various companies with projects in biotechnology applied to medical processes, by acquiring a share in the business.

That said, I would like to clear up that, given our main sector of activity, Grífols can't be considered a biotechnology company. The biological drugs we market are extracted from plasma, and no biotechnology processes are used in manufacturing them. The plasma we obtain through our 150 donation centers in the United States is broken down into various plasma proteins, each with its own therapeutic properties.

The companies Grífols holds a stake in work in a wide variety of therapeutic areas: Araclón, in Alzheimer and Parkinson; VCN Biosciences, in oncology; Progenika, in genetic diagnostics for cardiovascular and immunohematological disorders; Nanotherapix, in inflammatory, rheumatic and autoimmune diseases; Aradigm, in pulmonary illnesses. Grífols' commitment seems highly diversified. What do you look at in selecting biotech companies to invest in?

In addition to the logical financial criteria of any operation of this type, there is a second criterion that is key: the company's portfolio of projects must complement the research lines being carried out by Grífols.

Grífols has announced that it will increase R&D expenditure, from 4.7% of revenue in 2012 (€124.4 M) to 5.5%. What are your research priorities? Will this growth be through new investment in small and medium-sized biotechnology companies in Spain or in other countries as well?

Grífols currently has 12 clinical trials underway on new products and new indications. The main lines of research and development include: the Alzheimer strategy, through which Grífols aims to take a global approach to this neurodegenerative disease, including treatment with biological drugs derived from

plasma, preclinical diagnosis of the disease, and prevention and protection using vaccines. Also, the use of albumin in hepatology, of antithrombin in cardiac surgery, and a fibrin biological glue that opens up a new specialty in biosurgery.

Grífols' strategy for growth focuses on our main area of activity: manufacturing and marketing biological drugs derived from plasma, which in 2012 accounted for more than 88% of the company's total turnover, nearly €2,621 millions that year.

That said, here at Grífols we are open to studying proposals from biotech companies to decide whether or not they may be of interest to us given their complementarity with the projects we are developing and their potential.

Is the strategic goal to diversity Grífols' pipeline or do you aim to create a large group of biotechnology-based companies specialized in various therapeutic areas?

As I mentioned before, Grífols' main goal is to help improve the health and wellbeing of the people. Without losing sight of this aim, we focus more on diversifying than on creating a group of technology-based companies, as the projects we have participated in so far complement our research lines currently underway. Ð

NATIONAL FRAMEWORK

As we pointed out in the beginning of this chapter, venture capital investment in Spain fell in 2012, as did private equity. On the whole, VC&PE investment went from €3,233 millions in 2011 to €2,472 millions in 2012 (down 23.5%), in a total of 543 operations (9% less than in 2011). 61% of these funds comes from international operators, which mainly went to large operations over €100 millions.

According to data from the Spanish Venture Capital Association (ASCRI), Catalonia received 22% of all VC&PE investment in 2012 (€714 M) in 133 operations, behind Madrid with 53.6% of the investment in 102 operations. The volume of investment in the biotechnology sector is highly limited —only 1% of all VC&PE investment in Spain (€23.7 M), made up almost entirely of venture capital funds— although it is ranked third in number of operations, with 9.2% of the total. Investment from foreign operators in the hospital arena brought €342.2 millions (13.8% of all VC&PE funds) to the medical-healthcare sector in 2012, well below the previous year (€504.1 M, 15.6% of the total in 2011).[14]

Early-stage companies obtain little more than 6% of all resources invested by venture capital funds, with a modest €158.8 millions despite the fact that, with 348 operations, these made up 64% of all those in 2012. Adding funds contributed —through participative loans— by government bodies like CDTI and ENISA and investment from accelerators and business angels, the total VC investment reaches €230.6 millions for 2012, 18% less than in 2011 (€281.4 M).

Biotechnology concentrated 14.5% of all investment from VC companies (€23 M) in 2012, while the medical-healthcare sector obtained 5.3% of all investment (€8.4 M). Catalonia received 20.4% of investment from venture capital

14. ASCRI (Spanish Venture Capital Association), 2013 Report (p. 16-17, 36 and 44).

funds (€27 M).[15] According to the list of operations from ASCRI, 12.6% of this investment (€3.4 M) was in biotechnology companies located in Catalonia; however ASCRI doesn't count operations like the €12 millions invested by British fund Asclepios Bioresearch in biotechnology firm Genmedica, increasing the global total of VC invested in Catalonia as well as the percentage that went to biotechnology (thus making up more than 39% of investment). Table 8 shows information collected by Biocat on VC investment and other private equity funds in companies in the BioRegion since 2004.

Public funding

Beyond venture capital and the stock market, the development of the life sciences sector over the past 10 years has been made possible by public grants for research-intensive companies, above all in the earliest stages. In Spain, various lines of funding from the Center for Industrial Technological Development (CDTI) have been key to R&D and internationalization programs in SMEs (68% of companies have received grants). Catalonia received support for more activities than any other autonomous community between 2000 and 2011, as well as receiving the most money over this period, except for 2009 and 2010, when slightly more went to Madrid. Specifically, **Catalan companies received a total of €280.76 millions from the CDTI in 2011 to partially fund 511 activities and projects**, which had a global budget of €386.29 millions. With 23.34% of the funds distributed and 23.8% of the projects, Catalonia was first in the nation, followed by Madrid, which received 18% of the funds (€230.38 M) for a total of 305 projects (19.15% of the total).[16]

Graph 42 shows the evolution of these grants, which include subsidies for R&D projects (individual and cooperative), the Línia Banca-CDTI and the Neotec and Cenit programs, for a total of €1,202.98 millions in 2011. **A total of 36 companies in the BioRegion benefited from these grants for 41 projects**. These lines are in addition to the €173 millions devoted to the Innvierte program and the Neotec Venture Capital fund. In both cases, CDTI funds go to leverage and complement private investment: the Innvierte program aims for large companies "with the ability to assess the technological challenge posed and the business model" to join the equity holders in technology SMEs; Neotec Venture Capital is a fund to complement operations led by VC companies, which has a line devoted specifically to biotechnology.

In total, the CDTI committed €1,380 millions to a total of 2,224 operations (1,744 projects) in 2011, down 50% in 2012 with investment cut to €635 millions for 1,086 operations. Previsions for 2013 show that CDTI investment will increase again, to €1,000 millions. This reduction in funds led some lines of support for companies that had been in place through 2011 to be cut (programs like Innpronta, FEDER-Interconecta and Banca CDTI). The CDTI doesn't provide investment statistics broken down by sector, so it isn't possible to estimate the extent to which the drastic reduction in resources seen in 2012 has impacted companies and projects in the life sciences.

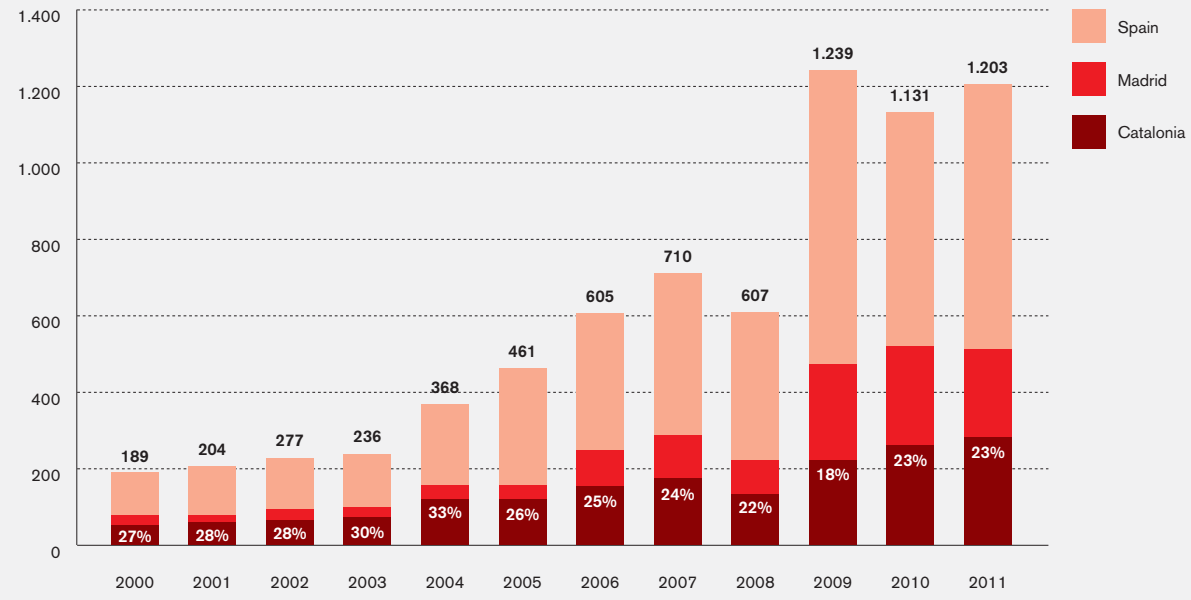
15. We must remember that ASCRI statistics don't assign 16% of VC funds to any autonomous community. Additionally, the tables included at the end of each report are based on the figures from the previous report. Thus, the 2012 Report attributes 27.4% of all VC investment to Catalonia, and on the table of statistics in the 2013 Report (p. 45) this percentage is 41.9%.

16. CDTI, 2011 Annual Report, p. 28.

THE CDTI COMMITTED Đ1,380 MILLIONS TO A TOTAL OF 2,224 OPERATIONS IN 2011, DOWN 50% IN 2012 WITH INVESTMENT CUT TO Đ635 MILLIONS

One fact that is relevant in analyzing the evolution of CDTI grants for companies is the growing weight of public contributions to the overall budget of projects. In 2000, public money, on average, made up 44% of the budget for these projects, while in 2011 it was nearly 72% of the budget for all projects receiving funds. This shows a high level of dependence on CDTI subsidies to carry out projects and maximizes the impact of budget cuts in 2012.

Graph 42 **Catalonia participation in CDTI funds for R+D programs (in milions €)**



Source: Observatori de la Recerca (IEC)

JOSEP CASTELLS: "IT'S DIFFICULT TO RAISE CAPITAL FROM NOTHING FOR A COMPANY THAT THE MARKET DOESN'T KNOW"

Josep Castells
executive president of InKemia IUCT Group

InKemia IUCT Group is the second Catalan biotechnology firm to go public on the Spanish Alternative Stock Market (MAB) with the aim of growing internationally. When did you decide to take the step to go public on the MAB?

We've been watching the MAB since it began in 2006. It's a project that has matured slowly over time to see which model best fit our situation. Initially, the initial public offerings on the MAB raised significant resources, but the evolution of these companies afterwards was irregular and entailed certain risks in tackling the following phases. After that, we fell into a deep recession.

Our strategy was based on putting all the available stock up for trading, but without raising funds when going public on the MAB. In recent months, there has only been one IPO, which was ours, however there are four capital increases underway. It's difficult to raise capital from nothing for a company that the market doesn't know, but when it is already publicly traded and has stabilized, it is easier to value the stock and attract resources.

Would you recommend that other companies in the sector opt for this method of funding?

Yes, but you have to have a very clear idea of things. In order to avoid what had happened in previous cases, when stock plummeted, we tried to go public with a moderate price to allow for a significant upward trend. The initial price was calculated based on an increase of €1.3 millions before going public on the MAB, in which relevant, qualified shareholders entered the company —49% from Escola Sant Gervasi and 35% from the company's researchers and professionals— and based on real numbers. Meaning that the value is based on the history of the company and not on future expectations, which doesn't mean they don't exist but just that we will allow the market to assess them. Unlike many technology companies, we haven't valued a single patent.

Created 15 years ago in Mollet del Vallès, this group of high-technology SMEs employs a unique business model focused on creating and exploiting your know-how, which is later transferred to the chemical, pharmaceutical and biotechnology industries. This activity, which involves a team of 44 workers and 200 collaborators, is structured into three units: IUCT SA (knowledge division), IUCT Emprèn SL (entrepreneurship and venture capital division) and IUCT Espais SL (facilities division). Through IUCT Emprèn, you have created a seed capital fund.

For some of our discoveries, it makes sense to exploit the patent ourselves; it's not necessary to license it to a large pharmaceutical company. In this case, we decided we could start up a new business line creating spin-offs, but outside the company as otherwise it would distort our activity. As we aren't specialists, what we must do is join forces with companies and people who know how to exploit our know-how. We have also created the Capital Knowledge Fund to invest in companies created by external entrepreneurs, which have synergies with our know-how and participation in which reinforces and accelerates business growth. So far we have closed agreements with Plasmia Biotech, in which we hold 19.6%; Phyture Biotech, with 21%; and Enemce Pharma, with 1%.

How important is industrial biotechnology in Catalonia?

It's just like us: a great unknown! I mean in terms of the media, but on the other hand, on an industrial level it is a reality. We have part of the industry that is innovating and improving productive capacity thanks

to white biotechnology. We call them user companies, there are many and could be more because we have a very significant fine chemicals, detergents and agrifood sector. There is also a group of companies that are devoted purely to developing white biotechnology processes like the production of antibiotics and enzymes.

Industry was blasphemed until the crisis and has now once again become important. White biotechnology makes no sense without industry, because white biotechnology is industry! Plus, time to market is much shorter than for red or healthcare biotechnology. But with this technology there is never zero risk, so the bank won't give you funding. We aren't talking about large multinational corporations, but small local companies that have a certain capacity for investment when thinking about implementing biotechnology production. We need more venture capital options and support from the government.

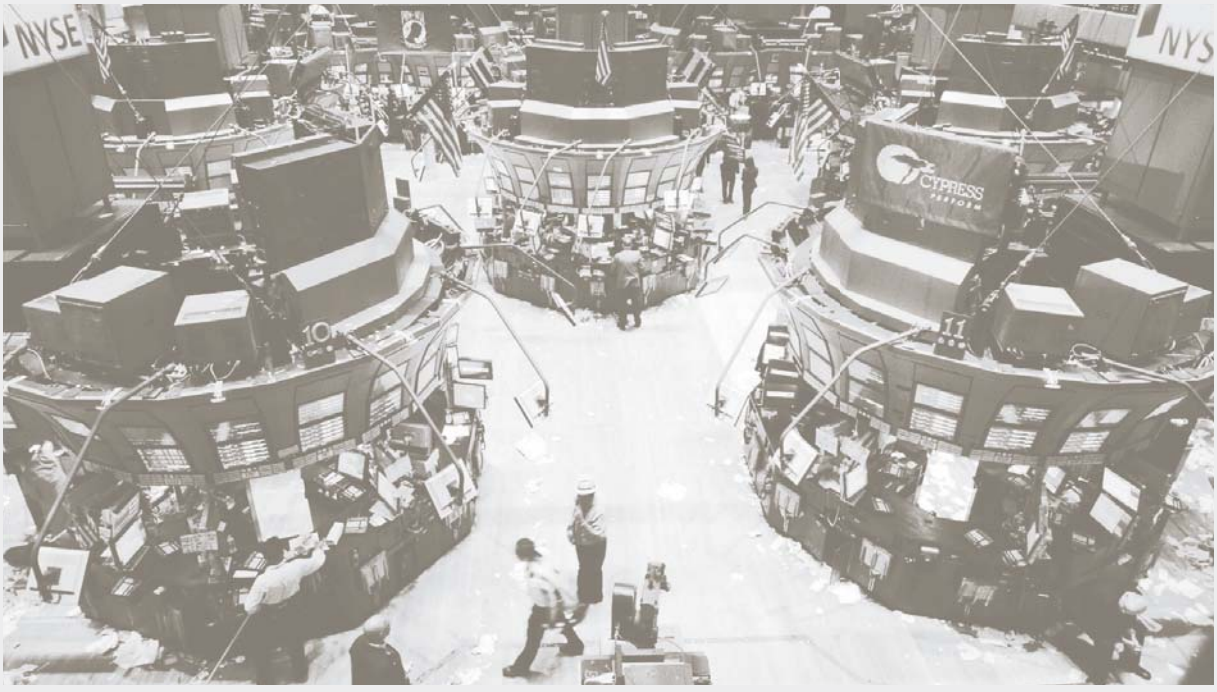
On 12 June 2013, you held an Investor Day at the Barcelona Stock Exchange to present the company's evolution to current and potential investors and to launch a €2.5-millions capital increase. What are the group's plans for the future?

In late July 2013 we closed our first capital increase on the MAB, which raised funds for the next step in our expansion process, which is based on 3 main focal points: internationalization; increasing investment in our own pipeline; and reinforcing the Capital Knowledge Fund in order to invest in other technology companies.

In terms of international expansion, our strategy is based on priority countries, like Brazil and Colombia in the BRIC countries, where we want to be present through direct technological activity. In the EU, we want to reinforce our presence in Poland and France. And also begin analyzing the possibilities in the USA.

Investment in our pipeline is key to accelerating development of the products, processes and technology we have in areas that are priorities for InKemia, like green chemistry, second-generation biofuel, and drug-discovery projects. We want to take the results of R&D as close to market as possible, and improve processes of technology transfer and the licensing of patents and know-how.

A significant part of the capital investment raised in this capital increase will go to the Capital Knowledge Fund, through which we hope to invest in technology-based companies at the rate of at least two per year. In short, we are taking a balanced approach to expansion, thanks to the capital raised through the increase.



FINANCIAL RESOURCES IN THE BIOREGION

The situation in Catalonia regarding funding for companies in the BioRegion is ambivalent. Although there has been an increase in private funding for companies in the BioRegion, as we mentioned at the beginning of this chapter and is shown in the information in table 8, there has been a significant drop in public grants, even more notable than that seen on a national level.

The funds available through the call for proposals for innovation grants run by ACCIÓ, the Catalan agency for business promotion of the Ministry of Enterprise and Employment, has fallen substantially, available resources down between 70% and 75%, and the delays that affect all payments from the government lead to serious financial pressure on small and medium-sized companies, which have to execute and justify the expenditure in order to receive the grant. Other lines of support (technological, management, financial and project-management advisory services) that were highly useful for small start-ups with few employees and a more scientific than business profile have also disappeared.

The life sciences sector has been affected by cuts to programs like InnoEmpresa, geared towards product development in small and medium-sized companies to allow them to fund laboratory trials and user testing through to prototyping or industrial phases. This program, which gave out grants for a total of €7.5 millions in 2010, has been cut to €2 millions per year in the 2012 and 2013 calls. The Nuclis d'Innovació Tecnològica program, which gave out €12 millions in grants for 32 projects in 2010 —and a total of €54 millions for 119 projects between 2007 and 2010— was cut to a maximum of €4 millions in 2012, €2.8 millions of which were for transnational projects partially funded by the EU.[17] In 2013, the call has been restricted to transnational hubs, with a total of €2.1 millions.

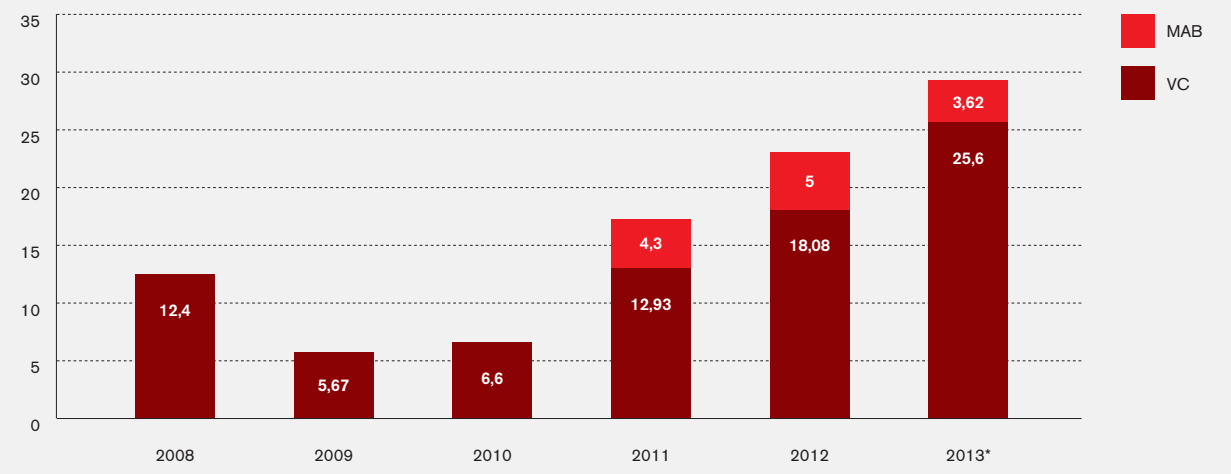
In contrast, private capitalization of biotechnology companies, either through venture capital or the stock market, has grown significantly since 2011, boosted in 2013 by the operation carried out by STAT-Diagnostica, headed by Ysios Capital, with an investment of €17 millions in this company specializing in diagnostic technology. Operations of this size in a company in the BioRegion led by local investors hadn't been seen in Catalonia previously, highlighting the positive evolution of the maturity of projects, as Raúl Martin-Ruiz explains in his article.

PRIVATE CAPITAL IN THE LIFE SCIENCES SECTOR HAS GROWN SIGNIFICANTLY SINCE 2011, ALONGSIDE A DRASTIC REDUCTION IN PUBLIC GRANTS

In the first half of 2013, companies in the BioRegion received investment of €25.6 millions in VC, with additional participation from corporate equity funds, business angels, and venture capital from public entities (National Innovation Enterprise, ENISA). From July through September, two publicly traded Catalan companies closed rounds of funding: InKemia IUCT Group —attracting €2.5 millions— and AB-Biotics, which closed a €1.12-millions round of funding in September just months after that of 2012 through which the company obtained €5 millions.

17. The transnational Nuclis d'Innovació Tecnològica correspond to give programs under the ERANET initiative that ACCIÓ has progressively joined in recent years: Manunet (manufacturing), since 2007; Eurotransbio (biotechnology), since 2009; OLAE+ (printed electronics), since 2012; Biophotonics (biophotonics), since 2012; and Transport III (electronic vehicles and passengers of the future), since 2013. The transnational hubs call also includes Israel-Catalonia collaboration agreements to incentivize business collaboration between the two countries in experimental research and development projects, with €757,000 in 2012 and €200,000 in 2013, according to data published in the DOGC.

Graph 43 **Evolution of private capital in companies in the BioRegion (2008-2013)**



* 2013 data, through 30/9/2013

Source: BiotechGate / Biocat Directory

FROM 2009 TO 2013, VENTURE CAPITAL INVESTMENT IN THE BIOREGION HAS INCREASED FIVE-FOLD

Graph 43 shows the evolution of private capital in companies in the BioRegion, which in 2011 attracted €17.23 millions and in 2012, more than €23 millions, showing very positive growth taking into account the trend over previous years and the restrictive economic context. From 2009 to 2013, private capital in the life sciences sector has grown five-fold. Over the coming years we must work to accompany entrepreneurial business projects in the sector towards a level of maturity that will bring about sustained growth in private investment. It will also be key for the growth of these projects to allow for venture capital funds and private investors from the early stages to see good return on investment from the projects in which they have participated. The option of going public on the MAB as a capitalization strategy allowing for profitable divestment of VC is an option that proper development of the companies could make quite attractive.

Furthermore, it is very important for Catalonia to have VC funds specializing in the biosciences and private investors that ensure the continuity of our companies and their growth in the area. Otherwise, many funding operations could result in our companies moving to other locations, as happened in the operation led by Sodena (Sociedad de Desarrollo de Navarra) on biotechnology company Palobiofarma, closed in June 2013. The company, which is researching various adenosine antagonist compounds as drug candidates for various diseases (diabetes, asthma, glaucoma and schizophrenia), obtained €4.5 millions, which allowed them to begin clinical trials, but left the Barcelona Science Park, where the company was previously located, to move to the Navarran European Business Innovation Center.

Table 8 **Investment attracted by companies in the BioRegion (2004-2013)**

Year	Compsny	Phase	Investment	Main investor/s	Remarks
2004	AB Biotics	Seed	€50,000	Not published	
2006	ERA Biotech	Participatory loan	€1.4 M	Uninvest	With Invertec, Reus Capital Riesgo and Talde Capital II
2007	Genmedica Therapeutics	Start-up	€3.5 M	BCN Emprèn, Uninvest and Innova 31	
2007	InKemia IUCT Group	2nd round	€6 M	Not published	
2008	Agrasys	1st round	€360,000	Uninvest	
2008	Anaxomics Biotech	1st round	€1 M	Founders and partners	
2008	ERA Biotech	Start-up	€2.8 M	Axis	With Highgrowth and Uninvest
2008	Oryzon Genomics	2nd round	€8.6 M	Najeti VC	With Corsabe and Investments Costex
2009	Ability Pharmaceuticals	Seed	€360,000	Founders and partners	
2009	ERA Biotech	1st round	€3.75 M	Crédit Agricole Private Equity	With Highgrowth Barcelona, Axis, Uninvest and other Spanish entities
2009	SOM Biotech	Start-up	€110,000	CEO and founder	With three private investors
2009	Thrombotargets Europe	1st round	€1.3 M	Not published	
2009	Thrombotargets Europe	1st round	€150,000	Not published	
2010	Ability Pharmaceuticals	Seed	€1.1 M	Founders	Includes public subsidy of €850,000
2010	Ability Pharmaceuticals	Seed	€400,000	Not published	
2011	Sabirmedical (closed 2013)	1st round	€5 M	Ysios Capital with Caixa Capital Risc	
2010	SOM Biotech	1st round	€100,000	Not published	
2011	AB-Biotics	MAB-capital increase	€4.3 M		
2011	Genmedica Therapeutics	1st round	€3 M	Caixa Capital Risc	With participation from BCN Emprèn and Catalan Finance Institute
2011	ImicroQ	Participatory loan	€50,000	Caixa Capital Risc	
2011	Mynorix Therapetutics	Participatory loan	€50,000	Caixa Capital Risc	
2011	Neurotec Pharma	Start-up	€500,000	Inveready and Caixa Capital Risc	
2011	Omnia Molecular	2nd round	€2.1 M	Caixa Capital Risc	With participation of ENISA
2011	Plasmia Biotech	Participatory loan	€1.18 M	IUCT Emprèn	
2011	Sabirmedical (closed 2013)	1st round (increase)	€1 M	Axis-ICO	
2011	SOM Biotech	2nd round	€750,000	Innova 31	With six private investors and public contributions from ACC1Ó, Ministry of Health and Ministry of Science and Technology

Year	Company	Phase	Investment	Main investors/s	Remarks
2011	STAT-Diagnostica	1st round	€2 M	Ysios Capital , Axis	
2011	Transbiomed	1st round	€1.2 M	Inveready (0,25)	With business angels and public soft loans
2011	VCN_Biosciences	1st round	€1.1 M	Fundación Genoma España, CDTI and ACC10	
2012	AB-Biotics	MAB-cspital increase	€5 M		
2012	Ability Pharmaceuticals	1st round	€1 M	Inveready Seed Capital SCRSA	With founders and business angels, along with grants and soft loans from government institutions
2012	BCN-Innova	Participatory loan	€150,000	Catalan Finance Institute	With family office
2012	Enemce Pharma (Life Science Entrepreneurs)	1st round	€5,500	IUCT Emprèn - Fons de Capital Coneixement	
2012	Genmedica Therapeutics	2nd round	€12 M	Asclepios Bioresearch	
2012	Inbiomotion	Start-up	€2 M	Ysios Capital	With Vila Casas Fundation and JVRisk Technologies
2012	Iproteos	1st round	€110,000	Private investors (3Fs)	
2012	Palobiofarma	2nd round	€1 M	Inveready Seed Capital	
2012	Phyture Biotech	2nd round	€270,000	IUCT Emprèn - Fons de Capital Coneixement	
2012	Plasmia Biotech	Participatory loan	€1.18 M	IUCT Emprèn	Complement operation of same value in 2011
2012	SOM Biotech	Other early-stage rounds	€410,000	Not published	VC fund with pharmaceutical company and business angels
2012	VCN_Biosciences	Acquisition of shares	40%	Gri-Cel (Grífols)	Amount of investment from Grífols not published
2013	AB Biotics	MAB-capital increase	€1.12 M		
2013	Bionure	Other early-stage rounds	€1.5 M	Fundadors	With Technomark and a loan from ENISA (€0.5 M)
2013	ImicroQ	Other early-stage rounds	€1.1 M	Caixa Capital Risc	With business angels
2013	InKemia IUCT Group	MAB-capital increase	€2.5 M		
2013	Minoryx Therapeutics	Start-up	€1.5 M	Caixa Capital Risc and Inveready Biotech II	
2013	Palobiofarma	Other early-stage rounds	€4.5 M	Sodena (Sociedad de Desarrollo de Navarra)	With Inveready and Fitalent
2013	STAT-Diagnostica	2a ronda	17 M€	Kurma Life Sciences Partners	Amb Idinvest, Boehringer Ingelheim Venture Fund, Caixa Capital Risc, Ysios Capital i Axis

Font: BiotechGate / Directori Biocat

STAT DIAGNOSTICA AND INVESTMENT PERSPECTIVES IN CATALONIA

Raúl Martín-Ruiz
Ysios Capital

On 6 May, STAT Diagnostica announced the closing of a €17-millions financing round. It was the largest operation by a company in the Catalan biocluster to date, and from our point of view this round of funding is relevant for reasons that go beyond the amount raised.

Firstly, this operation was carried out through a syndicate of specialized investors, including three international ones. Being a company that is considered early stage, this fact breaks with the axiom that young companies can't find sufficient specialized funding to bring continuity to their projects. The syndicate of investors saw the great potential of STAT's technology, team and approach, and this facts were key to overcome the early stage of the company.

Secondly, it validates the quality of the Catalan biocluster, which is currently carrying out highly significant market-oriented projects geared towards unmet medical needs. Projects designed from the very beginning to be carried out according to international standards and that are destined to compete in a market that is, and can only be, global.

Finally, it shows that it is possible to get quality funding in significant amounts even in the current economic climate. This in itself is encouraging for our sector, as it boosts its international visibility and puts it in the spotlight of? specialized investors.

As investors in STAT since June 2011, we have monitored their evolution closely. At that point, their project was little more than an attractive, well-formulated idea, and in less than two years they have been able to move from that original idea to a prototype, from two employees to thirteen, and to closing a €17-millions financing round. These funds will allow them to hire more top-notch professionals and take significant steps in the development of their diagnostic platform.

Is this a one-off or an inflexion point? Only time will tell, but from our position on the biotechnology scene and after five years of interacting with entrepreneurs and companies, we can say that we've seen a substantial increase in the quality of the business plans put forth by the Catalan companies we've been monitoring over these years. This, along with the ever-increasing exposure to international investors and awareness of their investment criteria, leads us to believe that operations like that carried out by STAT will not be an exception.

The various public and private stakeholders in the development of the biotechnology sector will continue striving day after day to show that we are at an inflexion point. Meanwhile, this can serve as a message of optimism for a strategic sector that aspires to be key to the future of our economy

Interests of Catalan investors

Of the 23 investment entities listed in the Biocat Directory, 11 companies carried out operations in the life sciences arena in 2011 and 2012, a significant amount of which involved companies outside of the BioRegion. Furthermore, seven of the entities listed are networks of business angels, which invested €2.5 millions in the health/life sciences arena over this period. According to data from ACCIÓ and that from the Private Investor Network (XIP) program, these operations benefited a total of 17 companies and were carried out by four networks in 2011 and four networks in 2012 (table 9). The bulk of this investment was in the form of capital investment with a smaller part in participative loans (€0.1 M in 2011 and €0.15 M in 2012).

Table 9 **Investment by Catalan networks of business angels 2011-2012**

	2011	2012
Total number of investment operations by networks	66	52
Total volume of investment	€10.7 M	€13.3 M
Operations in health/life sciences	10	7
Value of investments in health/life sciences	€1.2 M	€1.3 M

Source: ACCIÓ, Private Investor Network program

Tables 10 and 11 provide a summary of investment and shares managed in the health/life sciences sector by Catalan venture capital companies that belong to ASCRI. To this amount we must also add the operations carried out by Innova 31 —which led a second round of funding for SOM Biotech in 2011 for €750,000— and, above all, by IUCT Emprèn, the InKemia IUCT Group Knowledge Capital Fund. Since it was launched in 2011, this fund has given participative loans and capital investment to Catalan companies Plasmia Biotech (19.26% share), Phyture Biotech (in which it holds 21.26% of equity) and Enemce Pharma (0.67% share), as shown in table 8.

BETWEEN 35% AND 50% OF OPERATIONS IN THE LIFE SCIENCES BY CATALAN VC FUNDS GO TO COMPANIES OUTSIDE THE BIOREGION

Coinciding with publication of this report, InKemia announced IUCT Emprén had invested €240,000 in Biodan Science (Madrid) in exchange for 19% of the equity of this company devoted to developing and manufacturing organic active ingredients for the cosmetic and pharapharmacy sector.

One of the points that must be noted is the weight of operations carried out by the BioRegion's VC funds outside of Catalonia: 10 of the 24 investment operations in 2011 (35%) and 13 of the 23 in 2012 (50%) benefited international companies or those from other autonomous communities, noteworthy among which is Navarra. The lack of financial data for some of these operators, like Caixa Capital Risc, makes it impossible to determine what percentage of the funds go to operations outside of Catalonia, but it is worth noting that the weight of international operations is significant.

INVESTMENT OPPORTUNITIES IN SPANISH BIOTECHNOLOGY. THE CASE FOR CATALONIA

Sara Secall
Director of Inveready Biotech II. Inveready Technology Group

In recent years, Spanish science has reached world-class levels. Spain ranks number 4 in Europe in Scientific production, only behind Germany, the UK and France, all countries with higher investment in R&D and bigger economies. Spain, with a 1% share of the world's GDP, contributes to 3% of the world's scientific production. Biotechnology new patent applications in Spain more than doubled in the last decade with round 2000 new patent applications. Furthermore, the Spanish healthcare system allows for world-class clinical trials and its local-go-global pharmaceutical industry contributes with market access and the talent pool necessary for the development and growth of biotechnology startups. Within Spain, Catalonia is among the top contributing regions in scientific production and has the most developed local pharma industry.

However, Spanish biotech companies have yet to realize sizeable exits for their investors. At the time of writing this article (in June 2013), fourteen biotechnology companies had had an IPO globally since the beginning of the year. Of those, 12 were based in the US, one in Europe and one in Japan. In Spain, the Alternative Market for technology companies has been able to raise modest amounts of capital for only 6 biotechnology companies since it started a few years ago. As for M&A activity, globally, according to a recent report by PWC, 2013 has so far seen a rise on pharmaceutical and biotech M&A, driven by a rise of deals over USD 1 billion. 14 pharma deals were valued at more than USD 71Bn and 5 biotech deals valued at about USD 1Bn worldwide. None of those happened in Spain. However, 2013 saw an important milestone in M&A activity within Spanish companies that we hope will set up a trend. The multinational biopharmaceutical company Grifols, headquartered in Barcelona, reported a step-approach acquisition of Basc molecular diagnostics company Progenika Biopharma beginning with 60% of the company for 37Million Euros.

The bottom line for an investor looking into biotechnology companies in Spain in general and Catalonia in particular is clear: there are plenty of good opportunities to invest and excellent science but exits are still to be realized at world-class values.

Since Inveready begun in 2008 with our first vehicle, Inveready Seed Capital, our group has invested more than 20 Million Euros of equity in IT and Biotech start-ups. We have leveraged these investments with public grants and soft loans to total investments of well over 50 Million Euros. Along with leveraging our deals, Inveready actively seeks co-investors that add value to our portfolio companies and reduce exposure and risk. Such is the case of our framework agreement with Indian pre-clinical CRO ADVINUS --which will co-invest with us in the majority of our deals—or the ability to attract generalist investors in deals such as diagnostics and personalized medicine company Althia, to give some examples. Our strategy makes equity investments profitable even at modest exit values, thus driving up our investor's IRR. At the same time, structuring deals with relatively less equity financing has meant that our entrepreneurs have been able to retain control and value in the companies they have started.

The ability to drive up returns for our LPs has allowed us to raise, in 2012, our fourth fund, Inveready Biotech II, which targets biotechnology startups that are 12 months or less from nominating a candidate in drug discovery, drug repurposing, developing molecular and genetic diagnostics, nutraceuticals and --to a lesser extent-- medical devices.

As a Venture Capital firm based in Barcelona, we look at investments everywhere within a 3-hour radius. Our view of the biotech industry in Catalonia is clearly positive: excellent scientists, an increasingly innovative tractor pharma industry, great hospitals and CROs for clinical trials and professionals with the relevant experience. Two aspects are key, in our opinion, to keep Catalan Biotechnology companies ahead of the game: a steady and consistent public financing system for public R&D and biotechnology companies and support for the local pharma industry to engage in open innovation with the nascent biotechnology sector.

The international market has brought about the first large-scale divestment operations. Ysios Capital carried out its first successful divestiture in 2011, selling BioVex, a Boston-based cancer-treatment company, to Amgen for $1,000 millions (€728.5 M). This Catalan VC management fund held a share in BioVex valued at €2.7 millions, from investment made in 2010 under the framework of a $70-millions round of funding alongside other international investors. In 2013, Ysios obtained €15 millions (from an investment of €5 millions) selling Endosense, a Swiss medical technology company in which it had held a share since 2009.

In line with the global trend, a good part of investment from Catalan venture capital funds focused on medical technology. Specifically, 17 of the 47 investment operations (36%) carried out by Catalan VC funds in the 2011-2012 period went to med-tech companies. In late October, Ysios announced a €6-millions investment —its largest to date since the creation of the Ysios BioFund I— in a US medical technology company, CVRx, specializing in devices for cardiovascular illnesses.

With this operation, Ysios Capital has nearly closed **Ysios BioFund I**, which was created in 2008 with €69.2 millions in capital, and is preparing to launch a new one. Caixa Capital Risc restructured its funds in late 2011 to specialize them by sector. The **Caixa Capital Biomed** fund, with €22 millions, is the tool for investment in the biomedicine and life sciences sector. The **Catalan Finance Institute** (ICF) has managed the **Barcelona Emprèn** fund since 2010, which has €15 millions and includes public partners like the ICF, Barcelona City Council, Zona Franca Consortium, ENISA and the University of Barcelona, among others, and private companies like Agbar, Banc de Sabadell, BBVA, Banco de Santander, Gas Natural and Telefónica. Four of the eight companies in which this fund has invested are biotechnology firms. Finally, we must mention Inveready, which invests in the life sciences sector through two instruments: the **Inveready Seed Capital** fund, created in 2008 with €15.5 millions in capital, which has channeled investment to 12 biotechnology companies and two medical technology firms; and the **Inveready Biotech II** fund, created in 2012 with available capital of €15 millions, which has so far invested in three life sciences companies (Althia, Minoryx Therapeutics and Palobiofarma). The article by the head of this specialized fund, Sara Secall, analyzes the opportunities available for investors in the biotech sector in Catalonia.

Table 10 **Operations by Catalan venture capital funds in the life sciences sector (2011)**

Investor	Company	Activity	Investment	Amount	Phase
Active Venture Partners	European Telemedicine Clinic	Telematic radiology diagnostics	Investment		Expansion
ACCIÓ	Ysios	Contribution to biotechnology investment fund		€2,000,000	Start-up/Expansion
	Inveready	Contribution to biotechnology investment fund		€3,000,000	Seed
Caixa Capital Risc	Ingeniatrics (Seville)	Technology for biotechnology and pharmaceutical sector	Investment		Seed
	Sagetis	Drug-delivery system for the brain	Investment		Seed
	Medlumics (Madrid)	High-resolution imaging diagnostics	Investment		Expansion
	Gemmedica Therapeutics	Development of drugs to treat type-2 diabetes	Investment		Expansion
	Sagetis	Drug-delivery system for the brain	Participatory loan	€50,000	Start-up
	nLife (Granada)	Proprietary technology to redirect drugs to specific neurons	Participatory loan	€50,000	Start-up
	iMicroQ	Kits to detect pathogens and toxins	Participatory loan	€50,000	Start-up
	Wirs	Rehabilitation solution for medical centers and individual use	Participatory loan	€50,000	Start-up
	Sphera Global Health	Healthcare	Participatory loan	€50,000	Start-up
	Gladiolus	Genetic treatments for better bulb varieties	Participatory loan	€50,000	Start-up
	Minoryx Therapeutics	Treatments for minority diseases	Participatory loan	€50,000	Start-up
	Omnia Molecular	Discovery of new antibiotics	Share		
	Sanifit (Mallorca)	Compounds for pathologies related to human calcification	Share		
	Sabirmedical	Non-invasive monitoring technology	Share		
Catalana d'Iniciatives	e-Diagnosis	Remote clinical specialties	Share	€4,000,000	Expansion
Highgrowth Partners	Baolab Microsystems	Technology to manufacture MEMS	Share	€2,800,000	Start-up
	Era Biotech	Production of proteins and peptides	Share	€1,400,000	Early-stage
Catalan Finance Institute	Gem-Med	Medical devices	Investment	€200,000	Increase
	Gemmedica Therapeutics	Biotechnology	Investment	€500,000	Increase
	Era Biotech	Production of proteins and peptides	Share	€1,130,000	Early-stage
	Gem-Med	Medical devices	Share	€460,000	Start-up
	Gemmedica Therapeutics	Biotechnology	Share	€1,800,000	Start-up
	Oryzon Genomics	Biotechnology	Share	€300,000	Start-up
	Teknokroma	Medical devices	Share	€400,000	Expansion
Inveready	Transbiomed	Pharmaceuticals	Investment	€250,000	Seed
	Amadix (Valladolid)	Pharmaceuticals	Investment	€250,000	Seed
	ProRetina Therapeutics (Noain, Navarra)	Pharmaceuticals	Share		Start-up
	Palobiofarma	Pharmaceuticals	Share		Seed
	Neurotec Pharma	Pharmaceuticals	Share		Seed
Riva y Garcia Gestión	Indelor Lens (Thailand)	Manufacturing organic lenses	Investment	€100,000	Expansion
Ysios Capital Partners	STAT-Diagnostica	Development of rapid-diagnostic solutions	Investment	€700,000	
	Cellerix-Tigenix (Madrid)	Innovative drugs based on cell therapy	Investment	€2,000,000	
	Cardoz (Sweden)	Therapeutics for cardiovascular diseases with inflammation	Investment	€1,700,000	
	Sabirmedical	Diagnostic medical technology	Investment	€1,000,000	
	AM Pharma (Netherlands)	Treatment of kidney diseases	Investment	€1,700,000	
	Endosense (Switzerland)	Medical devices for ablation in cardiac surgery	Investment	€800,000	
	Medlumics (Madrid)	Optical coherence tomography	Investment	€700,000	
	Endosense (Switzerland)	Medical devices for ablation in cardiac surgery	Share	€3,400,000	
	Cellerix-Tigenix (Madrid)	Innovative drugs based on cell therapy	Share	€6,900,000	
	Cardoz (Sweden)	Therapeutics for cardiovascular diseases with inflammation	Share	€3,300,000	
	Sabirmedical	Diagnostic medical technology	Share	€1,600,000	
	AM Pharma (Netherlands)	Treatment of kidney diseases	Share	€1,700,000	

Source: ASCRI, 2012 Yearbook

Table 11 **Operations by Catalan venture capital funds in the life sciences sector (2012)**

Investor	Company	Activity	Investment	Amount	Type
Active Venture Partners	European Telemedicine Clinic	Telematic radiology diagnostics	Investment		Expansion
Caixa Capital Risc	Idifarma (Noain, Navarra)	Drug formulation and analysis, quality control and batch release	Investment		Expansion
	Neurotec Pharma	Development of new therapeutic targets for neurodegenerative diseases	Investment		Expansion
	ProRetina Therapeutics (Noain, Navarra)	Drugs to treat ophthalmological and neurodegenerative diseases	Investment		Expansion
	Pharmamodelling (Noain, Navarra)	Clinical trials using pharmacokinetic and pharmacodynamic modeling	Investment	€ 50,000	Start-up
	Genocosmetics	Personalized cosmetics based on genetic profile	Investment	€ 50,000	Start-up
	ResBioAgro (Sevilla)	Biotechnology solutions for sustainable agriculture	Investment	€ 50,000	Start-up
	Applied Foods (Tudela, Navarra)	New sustainable materials	Investment	€ 50,000	Start-up
	GemBioSoft (Valencia)	Biomedical IT systems	Investment	€ 50,000	Start-up
	DBS Screening	Preventative diagnosis with filter paper	Investment	€ 50,000	Start-up
Highgrowth Partners	Baolab Microsystems	Technology to manufacture MEMS	Share		Start-up
	Era Biotech	Production of proteins and peptides	Share		Early-stage
Catalan Finance Institute	AB-Biotics	Biotechnology	Investment	€800,000	Expansion
	Era Biotech	Production of proteins and peptides	Share	€1,130,000	Early-stage
	Gem-Med	Medical devices	Share	€460,000	Start-up
	Genmedica Therapeutics	Biotechnology	Share	€1,800,000	Start-up
	Oryzon Genomics	Biotechnology	Share	€300,000	Start-up
	AB-Biotics	Biotechnology	Share	€800,000	Expansion
Inveready	Ability Pharmaceuticals	Pharmaceuticals	Investment	€300,000	Start-up
	Amadix (Valladolid)	Pharmaceuticals	Investment	€150,000	Start-up
	Bionanoplus (Noain, Navarra)	Pharmaceuticals	Investment	€70,000	Start-up
	Europath Biosciencies (Granada)	Pharmaceuticals	Investment	€1,350,000	Growth
	Formune (Noain, Navarra)	Biotechnology	Investment	€250,000	Start-up
	Nanoscale Biomagnetics (Saragossa)	Pharmaceuticals	Investment	€ 60,000	Start-up
	Palobiofarma	Pharmaceuticals	Investment	€210,000	Start-up
	Amadix (Valladolid)	Pharmaceuticals	Share		Growth
	Europath Biosciencies (Granada)	Pharmaceuticals	Share		Growth
	Neurotec Pharma	Pharmaceuticals	Share		Start-up
	Palobiofarma	Pharmaceuticals	Share		Start-up
Riva y Garcia Gestión	Biopharm	Pharmaceutical laboratory	Investment	€7,600,000	Expansion
Ysios Capital Partners	Endosense (Switzerland)	Medical devices for ablation in cardiac surgery	Investment	€1,800,000	
	Inbiomotion	Diagnostics for bone metastasis	Investment	€1,500,000	
	STAT-Diagnostica	Development of full NPT diagnostic systems	Investment	€325,000	
	Cardoz (Sweden)	Cardiovascular and metabolic diseases with inflammation	Investment	€700,000	
	Endosense (Switzerland)	Pharmaceutical laboratory	Share	€4,500,000	
	Tigenix (Madrid)	Innovative drugs based on cell therapy	Share	€6,900,000	
	Sabirmedical	Medical technology for diagnostics	Share	€1,600,000	
	STAT-Diagnostica	Solutions for fast diagnostics	Share	€1,000,000	
	AM Pharma (Netherlands)	Treatment of rare diseases	Share	€1,700,000	
	Medlumics (Madrid)	Optical coherence tomography	Share	€700,000	
	Inbiomotion	Diagnostics for bone metastasis	Share	€1,500,000	

Source: ASCRI, 2013 Yearbook

Large companies and foreign investment

The growth of private investment in the biosciences sector in Catalonia has come about at the same time as a notable shift in the role of large companies in the sector, which as mentioned at the beginning of this chapter are investing in the capital of Catalan biotech companies. To date this has been seen in Almirall (AB-Biotics) and Grífols (Nanotherapix and VCN Biosciences), but new operations are on the horizon involving some of the large pharma corporations in the BioRegion. As Javier Jorba, head of the department of biological products at Grifols, explained in the interview included in this chapter, the aim is to complement the company's own lines of research. However, as we have seen in analyzing overarching global trends (chapter III), pharma-biotech collaboration also accelerates innovation and reduces risk, as it is shared.

In 2013, Grífols announced that it will increase R&D investment to 5.5% of turnover —in 2012 the company invested €124.4 millions in research, 4.7% of its turnover of more than €2,600 millions— and the company heads haven't discarded the possibility that this investment may be made through new collaborations with biotechnology companies. In order to coordinate all of these investments and external research projects in which it invests, Grífols created a subsidiary called Gri-Cel in 2011.

To conclude this view of the main trends and changes seen in funding for companies in the BioRegion over the past two years, we must also mention three large foreign investment operations that took place during this period.

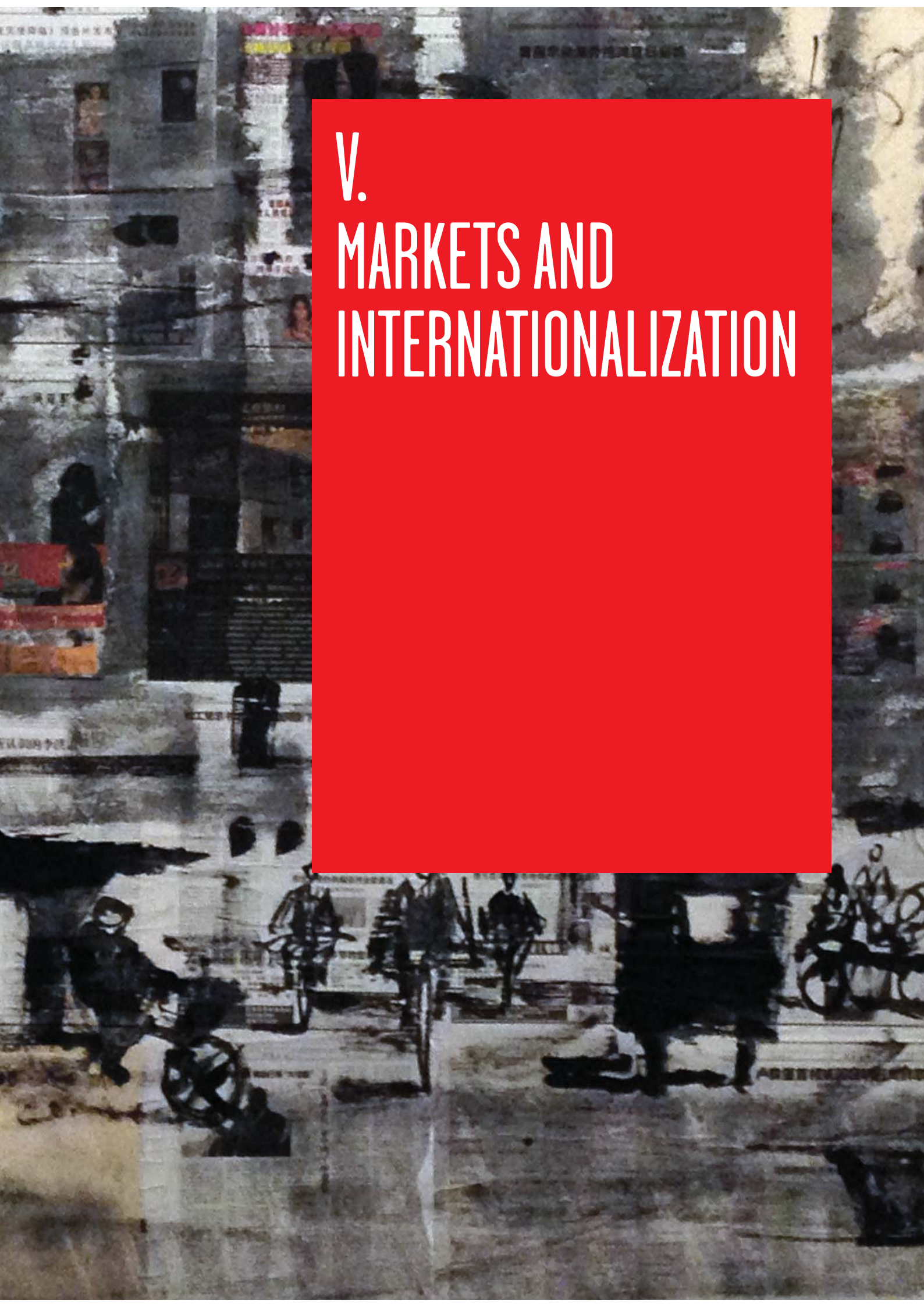
In January 2012, the European Commission authorized the operation through which German Saria Group and Dutch Teeuwissen (50% held by Saria) acquired Bioibèrica, a Catalan biopharmaceutical company specialized in manufacturing heparin —the second-largest manufacturer in the world— that has extended its activity to the areas of animal feed, nutritional supplements and human health, in the field of osteoarthritis. The Saria Group didn't make public the amount invested to acquire Bioibèrica, which in 2012 saw turnover in excess of €237 millions and had 334 employees. Although the German group controls 100% of the company, no changes have been made to the executive team since acquisition of the company —which has plants in Palafolls, Olèrdola and Toledo, and production centers in Poland, Brazil and the United States— and it has continued to carry out the firm's research and sales strategy without notable changes.

In June 2012, Warren Buffet's Lubrizol group acquired Catalan company Lipotec (active ingredients for cosmetics), which gave name to the group of bio companies promoted by businessman Antonio Parente, which also included GP Pharm (drug-delivery systems, especially for oncology), BCN Peptides (production of peptides and proteins), Prima-Derm (cosmetics), Diverdrugs (cosmetics and dermatology) and Lipofoods (food ingredients). The last two were also transferred to Lubrizol in the same operation, the financial terms of which were not made public.

The third significant operation was the Japanese group Azbil Corporation's (previously Yamatake Corporation) acquisition of a majority share (80%) of Telstar in

November 2012. Azbil was founded in 1906 and specializes in automation and control technology, especially for industry and large buildings. The company, which has subsidiaries in 27 countries in Asia, Europe, America and Oceania, employs more than 5,500 workers around the world. The Catalan subsidiary, which is now called Azbil Telstar, is one-of-a-kind in the group given its specialization in the biomedical arena. No financial data was made public regarding the acquisition of this Catalan company, which posted turnover of €108 millions in 2012 and has a team of 950 workers in 16 countries.

The investment of international capital in these Catalan companies shows that their projects are highly competitive. Obviously, there are positive aspects — capital investment and synergies within the group that can help boost growth of these companies and have a positive impact on employment and the business and economic arenas— but it also entails risks, as profits flow towards the origin of the capital and decision-making centers move away from the region. For the future of the BioRegion, it is key to ensure that good industrial projects that develop here at home can be tools to dynamize the ecosystem, holding on to R&D investment and interactions with the research arena, and can contribute to the country's economic development.



V.
MARKETS AND INTERNATIONALIZATION

MARKETS AND INTERNATIONALIZATION

As mentioned throughout the *2013 Biocat Report*, the wide-reaching concept of life sciences does not correspond to a single market, but several, many of which are interconnected and overlapping: products and technology for human and animal health; the food sector (from components for the food-processing industry through new functional foods and nutraceutics); agricultural production (for consumption or production of biomass); biofuels (from plants or waste materials); transformation of industrial processes in the pharmaceutical, chemical (detergents, cosmetics, etc.) and textile sectors, among others.

This chapter reviews the economic and geographic size of these markets and the opportunities available for companies in the BioRegion. Additionally, it also analyzes the degree of internationalization of companies in the BioRegion, with data from a survey carried out in June and July 2013.

BIOSCIENCES MARKETS: HEALTH, AGRICULTURE, FOOD, INDUSTRY, ENERGY

The life sciences sector in Catalonia has focused mainly on the health market, particularly in producing new drugs. The potential of this market is enormous, despite the restrictions to which the pharmaceutical sector has been subjected over the past three years as a result of government budget cuts at the national and autonomic levels. In 2012, sales in the pharmaceutical sector in the national market totaled €13,180 millions,[1] still a significant figure despite the 5.5% drop from 2011 and 11% from 2010. Additionally, Spanish pharmaceutical companies exported products valued at €9,843 millions in 2011, somewhat less than the €11,670 millions in pharmaceutical products imported (table 12).

According to data from the EFPIA (European Federation of Pharmaceutical Industries and Associations), production in the European pharmaceutical industry totaled more than €210,000 millions in 2012, up 2.5% from 2011. Europe makes up 26.7% of the global pharmaceutical market, estimated at €667,653 millions ($857,800 M).[2] The USA makes up 41% of this market and Japan, 11.7%.

However, given the long value chain from basic research through drugs fitting specific patient needs, the final volume of the pharmaceutical market is just a small part of the story of business opportunities and challenges facing companies in the BioRegion. As we have seen in chapter II, the activity of biotechnology companies working in therapeutics and diagnostics (48 companies) currently focuses on the early stages of product development (discovery, pre-

THE BIOTECH SECTOR CAN BENEFIT FROM THE NEARLY Đ370 MILLIONS THE PHARMACEUTICAL INDUSTRY INVESTS IN R&D IN CATALONIA

1. 2012 Annual Report, Farmaindustria, p.97.
2. EFPIA citing calculations from IMS MIDAS.

Table12 **Evolution of the Spanish pharmaceutical market 2003-2011**

Year	R&D investment (millions €)	Pharmaceutical production (millions €)	Employment (people)	Domestic sales (milions €)	Exports (millions €)	Imports (millions €)	Balance of trade (millions €)
2011	981	14,022	37,971	13.941	9,843	11,670	-1,827
2010	966	14,387	39,932	14.858	8,920	11,492	-2,572
2009	967	14,152	39,155	14.744	7,902	12,208	-4,306
2008	914	14,108	40,385	13.949	7,734	10,371	-2,637
2007	885	14,004	40,117	13.209	7,194	8,904	-1,710
2006	850	12,459	39,117	12.154	6,076	7,667	-1,591
2005	764	11,114	39,285	11.332	5,430	7,230	-1,800
2004	684	9,656	39,000	10.671	3,999	6,716	-2,717
2003	610	9,374	39,000	9.890	3,876	6,534	-2,658

Source: EFPIA (European Federation of Pharmaceutical Industries and Associations)

clinical and phase I and II clinical trials) and, above all, these companies offer their knowledge and research capacities to other companies that can spearhead later stages of development. Additionally, we have some seventy biotechnology firms whose main activity is to provide R&D services.

The Spanish pharmaceutical industry invested €972 millions in R&D in 2012, 45% externally, meaning for clinical trials in hospitals and collaborations with universities and research centers. Of the €434 millions devoted to funding external research, €87.5 millions were invested in Catalonia (€96.6 M in Madrid and €125.2 M in projects in other countries), but 52% of the €538 millions pharmaceutical companies spent on internal research was also invested in Catalonia. Thus, if we are able to align the interests of the pharmaceutical industry, market opportunities and research capacities of our biotechnology firms and public centers, these nearly €370 millions that pharma spends on R&D in Catalonia can play a significant role in the sector's growth.

Opportunities in biosimilars

In terms of the production of biotechnology drugs, experts highlight the market potential of biosimilars. These are drugs created by *copying* the characteristics —and thus therapeutic properties— of biotechnology drugs whose patent exclusivity has expired. The complex process of creating biotechnology molecules —using recombinant DNA techniques— makes it difficult to make biosimilars, which is beyond the scope of many companies (unlike generics, which are copies of chemically synthesized drugs).

The impact of the production process on the final properties of a biotechnology, or biosimilar, drug have led regulatory agencies —specifically the EMA, which has the most advanced, stringent regulations in the world— to require complementary clinical trials, after bioequivalence has been demonstrated, to show that the biosimilar drug offers the same level of safety and efficacy as the reference drug. This puts the cost of developing a biosimilar drug between €10 millions and €100 millions, compared to between €1 million and €1.5 millions on aver-

age for a generic drug. Nevertheless, the final price of biosimilars can be 30% lower that the original biotechnology drug, which in many cases is approximately $100,000 per year of treatment.

Despite the elevated cost and long development time —between 5 and 7 years on average— the long biosimilar value chain opens up more opportunities than hurdles: biotech companies working in research into innovative biotechnology drugs can find a market niche by developing biosimilar molecules, carrying out bioequivalence tests and licensing the product to large biotechnology firms with manufacturing capabilities or to pharmaceutical companies that want to break into the biotechnology sector, taking advantage of their resources and expertise to get through the clinical and regulatory phases. Catalonia also has CMO (contract manufacturing organizations) that can help pharmaceutical companies start manufacturing biosimilars.

Some emerging economies that are highly interested in the biomedical arena, like India and China, are making a decided commitment to manufacturing biosimilars, but for now their regulatory frameworks are too lax and none of the products approved in those countries have been authorized in Europe, which has much more stringent standards. However this is a window of opportunity that must be taken advantage of now, because it is to be expected that in the not-so-distant future these Asian giants will also be competing on the EU and US markets.

Medical technology

One of the areas that have seen the most growth in the health market is undoubtedly that of medical technology. As mentioned previously, the ageing population, increase in chronic diseases, and pressure on healthcare expenditure are leading to a shift from hospital care towards home care, which entails the development of technology to collect and handle data, on one hand, and for telecare and self-medication, on the other. However, while this leads to a wider range of opportunities for ICT companies, there is a growing trend to lengthen the lifespan of the most costly technology and a clear commitment to products that reduce the staff needed to care for patients or cut costs by shortening hospital stays and reducing readmissions.

The market is being transformed, and while healthcare budgets in Europe and North American are stagnating or, at least, growing at a slower pace, emerging economies are clearly expanding. According to data from LEK Consulting,[3] the medical device market in China was $11,000 millions in 2009, just 10% of that of the USA, which was more than $100,000 millions. Per capita expenditure in China was just $9, compared to $329 in the USA. This gap, along with the strong growth of the Chinese economy —with a year-on-year growth in GDP of 7.7% in of October 2013— and national plans to extend medical coverage put forecasts for growth of the Chinese medical technology market for 2012-2017 at 20% per year, with the huge potential this entails for companies in this arena.

The same consultancy firm, in June 2013, estimated the value of the Chinese medical device industry at $17,000 millions. Despite the difficulties in accessing this market —given the complexities of purchasing decision-making processes and regulatory hurdles— three fourths of the Chinese medical device market is controlled by western countries, many of which manufacture devices in China.

3. Study cited in Focus on China: Medical Device Market, BiotechGate Resource Center, 14-6-2013.

In this regard, it is worth noting that class I and II, non-invasive, medical devices regulated by provincial standards benefit from local manufacturing to gain quick access to the market; however class III devices (implantable) require national authorization from the SFDA (Sino Food and Drug Administration) and the approval process is quicker if they arrive in China having passed clinical safety and efficacy tests in one or more western countries, even when they will be manufactured locally.[4]

According to data from Ernst & Young (Pulse of the Industry 2013), the global medical technology market totaled $339,000 millions in 2012, $210,000 millions of which correspond to the US market and the rest ($129,000 M) to the European market. The real numbers are probably higher, as E&Y only took into account 368 publicly traded companies in their study (227 in the USA and 141 in Europe). According to Eucomed (European Medical Technology Association), there are 25,000 companies working in the medical technology market in Europe, 95% of which are SMEs, employing 575,000 workers (300,000 of these jobs are in publicly traded companies).[5]

Fenin indicates that there are 720 companies working in the medical equipment and hospital technology market in Spain —520 of which are manufacturers— that employ 32,000 workers and posted joint turnover of €8,300 million in 2012. 42% of this production is in Catalonia. As seen in the pharmaceutical industry, the Spanish balance of trade in the medical technology sector is negative: according to calculations from ICEX, exports in 2010 totaled €958 millions (up 5% from 2009), just one third of the €3,137 millions in imports.[6] The bulk of Spanish medtech exports go to other EU countries; in fact, 10 countries make up 75% of all exports, all in Europe except for the USA and China.[7]

The commitment to innovation and internationalization in medtech companies must allow us to equilibrate the balance of trade and access markets with greater opportunities for growth. The most dynamic companies in this arena, like **Telstar** (technology for hospitals, laboratories and the pharmaceutical industry) with offices in 15 countries and production plants in China, the USA, the United Kingdom, Germany and the Netherlands, and **Biokit** (in vitro diagnostics), which exports 90% of its production, are leading the way.

The most significant venture capital transaction in the sector —the €17-millions investment in STAT-Diagnostica led by Ysios Capital (see chapter IV)— was in an innovative medical technology company, which highlights the potential of this subsector in the BioRegion.

4. H. Chen, J. Wang, J. Stevens, Expanding in China's MedTech Market: Where to Go From Here, IN VIVO, Vol. 31, Issue. 6 June 2013.
5. http://www.eucomed.org/medical-technology
6. España: sector de equipamiento médico y tecnología sanitaria, ICEX, 2011
7. Idem, p. 5.

MEDICAL TECHNOLOGY: OPPORTUNITIES FOR SMES FACING THE CHALLENGE OF INNOVATION

Mark Bruzzi
National University of Ireland (Galway), director of BioInnovate Ireland program

There is a general consensus that the healthcare scene is changing quickly and that significant innovation in healthcare products and services is needed to sustainably address the ageing population in the western world. The cost of the European and North-American healthcare systems, which is quickly mounting, is leading to drastic changes in the treatment patients receive and, as a result, governments and healthcare professionals are clearly geared towards making healthcare more efficient.

In order to cut healthcare costs, the main goals are to shorten hospital stays, relocate tertiary care services in primary care centers and, in general, cut the technological and pharmaceutical costs of care. These actions pose significant challenges for the biotechnology, pharmaceutical and medical device industries, which are under pressure to provide better therapeutic and diagnostic technology at a lower price.

Nevertheless, this challenge opens up new opportunities in the medical device sector, like designing and developing new products and services that provide the same or better service while cutting overall costs of the healthcare system[1].

As Anderson[2] explained, devices can be broken into three categories:

1 – High-volume and low-cost commodities

2 – Low-to-mid volume with mid-to-high cost (including those with comparative improvements over existing products)

3 - First-in-category products

The first category (high-volume and low-cost commodities) often struggles to break into markets controlled by large group-purchasing organizations (GPO), distributors and hospital systems, even if it may result in significant cost savings[2]. The low-to-mid volume with mid-to-high cost category, with comparable products, is most easily subject to pricing pressure. This category includes most implants, ablation catheters, pacemakers and stents. Innovation regarding these products runs into huge hurdles when it is geared towards maintaining prices and can only be justified when it brings down the cost of healthcare services. This situation is becoming increasingly common as decisions regarding the purchase of medical technology are left up to hospital managers and purchasing departments[2].

Finally, first-in-category products are in the best position for innovation, as long as they can demonstrate greater medical advantages (measured with clinical studies) and cut costs for healthcare providers. Thus, products that stand out in new categories are more sensitive to pricing pressure from purchasing departments[2]. However, new reimbursement opportunities are increasingly attractive for early-stage investors in medical technology, as a result of the growing length of time needed for approval and coverage (profitability) of new products.

1. Bruzzi, M.; Linehan, J. H. “BioInnovate Ireland - Fostering Entrepreneurial Activity Through Medical Device Innovation Training”. Annals of Biomedical Engineering DOI: 10.1007/s10439-013-0787-5 Springer.
2. Anderson, E., http://biodesignalumni.com/2012/10/29/death-of-a-medtech-salesman/, consultat el 17 de juny de 2013

Animal health

BIOTECHNOLOGY PRODUCTS MAKE UP 26% OF THE GLOBAL ANIMAL HEALTH MARKET, WHICH IN 2012 TOTALED $22,500 MILLIONS

Beyond human health, the animal health market has grown steadily over the past 10 years. According to the International Federation for Animal Health (IFAH), the global animal health market in 2012 was $22,500 millions, double that in 2002, with year-on-year growth over 9.5% in 2011. Possibly the most significant issue is the weight of this segment among all biotechnology products, making up 26% of all revenue, while 12% corresponds to medicinal food additives. 59% of this market is geared towards animals for human consumption, with the remaining 41% focusing on pets.[8] The joint turnover of the top 10 companies in the sector —Pfizer (Zoetis), Merck, Merial (Sanofi), Elanco (Ely Lilly), Bayer, Boehringer Ingelheim, Novartis, Virbac, CEVA and Vétoquinol— makes up 81% of the whole market.

There are 35 biotechnology companies in the BioRegion of Catalonia working in the veterinary sector, with activity in health, food and production (artificial insemination, animal models for research, etc.). As a whole, these companies posted turnover of more than €400 millions in 2012 and employ more than 1,300 workers. By volume, the top company is **Hipra**, which markets pharmacological and biological products and diagnostic kits for farm animals in more than 20 countries, followed by **Zoetis** —the veterinary division of **Pfizer**— which employs more than 200 workers at their plant in Olot, a significant part of which are devoted to research —mainly in the field of vaccines— which has generated fifteen patents and more than 80 specialized scientific publications. Other multinational corporations with headquarters in Catalonia include **Merial** — the veterinary division of **Sanofi**—, **Virbac** and **CEVA**. Regarding local veterinary companies, in addition to Hipra, other noteworthy companies include **Invesa**, **Laboratoris Jaer**, **Divasa-Farmavic**, **Mevet** and **Cemavisa**, all of which have significant R&D activity and are export oriented. It must be noted, also, that the large pharmaceutical companies in the BioRegion, like **Esteve**, **Boehringer Ingelheim** and **Novartis**, have important animal health divisions.

Experts estimate that growth in this sector will be between 5% and 6% per year on average and, despite the dominance of large companies, there is a margin for growth in small and medium-sized companies that produce biotechnology products for this sector, as many countries in which livestock is an important part of the economy —in Asia, America and Africa— don't have the technology to produce vaccines or biotechnology diagnostic kits.

Green biotechnology

Agriculture and livestock production is one of the fields that directly benefit from breakthroughs in biotechnology, above all —as the article by Dr. Pere Arús explains— from knowledge regarding the genetic basis of specific traits —that are more interesting from a productive standpoint— of certain species: resistance to adverse climate conditions and disease, productivity, adaptability, etc.

Agriculture is an essential activity to humanity, first and foremost to produce food but also for industrial raw materials —and increasingly for materials to produce energy (biofuel). Although its contribution to the global GDP has decreased, due to the tertiarization of the economy —making up 5.9% in 2011 ($4.2 billions) according to data from the International Monetary Fund (IMF)—, agriculture accounts for between 20% and 60% of the GDP in 30 countries —mainly

8. IFAH citing data from Vetnosis.

in Africa and Asia— and between 10% and 20% of the GDP in at least 32 countries in Latin America, Eastern Europe, Africa and Asia. In less developed countries, moreover, agriculture is less mechanized and more labor-intensive, thus employing most of the population.

These figures explain the growing interest of developing countries in green biotechnology, which as mentioned in chapter III already produce 52% of all genetically modified crops (GMO). These were planted on more than 170 million hectares around the world in 2012. Beyond GMO and the controversy surrounding their use, the FAO is committed to biotechnology as a tool for agricultural development that can improve food safety in the least developed countries. According to this United Nations body, there are many low-level biotechnology processes —like the use of biofertilizers, biopesticides and growing textiles in fields and trees; artificial insemination; and fermentation and the use of bioreactors in food production— and mid- or high-level processes —diagnostic tools for polymerase chain reaction (PCR), biomarker-assisted selection and in vitro fertilization in livestock— that can effectively contribute to increasing agricultural production and, unlike GMO (which are developed and patented by the industry, expensive and strongly regulated), are processes and products "that don't normally require regulatory approval, which means they can be adopted quickly by farmers at a low cost."[9]

In any case, FAO analysts also highlight that biotechnology programs are effective when they are implemented as part of well-structured agricultural-development programs and under the framework of appropriate policies that include active participation of local stakeholders (farmers, institutions, researchers and companies). Therefore, this seems to be a field that is ripe for scientific collaboration and technological advisory services and, from a business standpoint, has a lot of potential for internationalization, as long as the products and services are adapted to the specific needs of each local market.

The BioRegion has a small number of companies —widely varied in size and origin— that work in agrobiotechnology (10), mainly focusing on improving seeds and developing plant species of commercial interest. In this regard, it is worth highlighting the launch to market in early 2013 of the first foods made with *Tritordeum*, the first newly created cereal marketed around the world and developed by Agrasys. Agrasys is a spin-off of the CSIC, which was created in 2005 to develop and commercially exploit the qualities of the new cereal resulting from the hybridization of hard wheat and a variety of wild barley. Professor Antonio Martín, of the Institute for Sustainable Agriculture of Cordoba (IAS), began research into this cereal in 1977. The specific traits of this cereal make it suitable for functional foods, with beneficial effects on cardiovascular health, diabetes, obesity and even colon cancer and eye conditions.

IN APRIL 2013, MARKETING BEGAN OF FOOD PRODUCTS MADE WITH TRITORDEUM, THE FIRST NEWLY CREATED CEREAL TO BE USED FOR HUMAN CONSUMPTION, DEVELOPED IN CATALONIA

9. Andrea Sonnino and John Ruane, Innovation in agriculture as a tool in food security policies: The case of agricultural biotechnologies, FAO, 2013 (http://www.fao.org/docrep/018/ar635s/ar635s.pdf)

GREEN BIOTECHNOLOGY

Dr. Pere Arús
scientific director of the Center for Research in Agricultural Genomics (CRAG)

A key factor in the booming growth of green biotechnology in recent years has been the falling price of DNA sequencing technology, which has allowed us to decode the complete genome not only of model species but also of most domesticated plants and animals. These sequences are the foundation for efficiently identifying the genes involved in valuable hereditary traits and understanding the molecular mechanisms behind characteristics like adaptation, productivity, resistance to biotic and abiotic stress, and the quality of products from these plants and animals. They also open up a path to understanding overall genetic variability in genomes, and the influence this variability has on the phenotype, both in terms of genetic and epigenetic variability.

Researchers at various institutions located in Catalonia (IRTA, UAB, CSIC, CNAG, CRAG and CRG) have participated in the "de novo" sequencing of species like the melon, peach tree, strawberry, pig, beetroot and beans, among others. The sequencing of the melon genome was led by researchers from the IRTA and the CSIC that work at the CRAG, with participation from a Catalan company, Semillas Fitó, that contributed funding for the project alongside other public and private bodies. The creation of the CRAG, which brings together the majority of researchers in agrigenomics from the CSIC of Catalonia, IRTA, UAB and UB, and the CNAG, as a large-scale facility for mass sequencing, has helped solidify this field in our country.

Growing knowledge about genes and genomes and how they affect the phenotype boosts and accelerates the development and application of biotechnology. The most important element is the production of genetically modified organisms (GMO) through genetic transformation technology in soy, corn, cotton, canola and rice, which were planed on approximately 170 million hectares in 2012. Despite the limits on its application, particularly in Europe due to negative social perception, the potential of this technology is enormous, and is being explored in Catalonia in various areas, in particular regarding the introduction of drought-resistant and salt-tolerant cereals (UdL) and the study of how genetically modified and conventional crops coexist (IRTA and UdG).

There are also non-transgenic ways to induce gene modification in order to obtain plants with inheritable genetic modifications. One of these is the search for natural mutations or those induced with chemical mutagens in genes of particular interest, with technology called TILLING that is being used by the IRTA in collaboration with several companies. Another latest-generation technology uses transgenesis as an intermediate step to obtain non-GMO plants with modifications in specific genes from SNDs (site-directed nucleases). This technology is being studied at the CRAG and has a bright future as an alternative or complement to transgenic crops.

Molecular markers, an area that has been boosted by latest-generation sequencing technology, are a tool in constant evolution that have been used for years in genetic improvement companies. They are used for selection based on the genotype of traits, both simple inheritance and quantitative, to predict which individuals may pass on desirable alleles for these traits or to control the quality of propagation products (seeds). The challenge we are currently facing is to develop strategies based on selection of the complete genome in order to incorporate more complex and less inheritable traits into crops and do so more quickly that conventional methods allow. There are teams at the IRTA and UAB that are working on these issues and often in long-term collaborations with Catalan and foreign companies on various agricultural and livestock species.

Biofuels and industrial biotechnology

One of Agrasys' activities is producing improved agricultural varietals for energy production, or the production of biofuel. Falling between agricultural biotechnology (improved production and treatment of biomass, including the development of species exclusively for energy production) and white biotechnology (industrial), focusing on the production of bioethanol and biodiesel, the field of biofuels is one of the areas with the most potential for growth around the world, as mentioned in chapter III, with a global market of $227,000 millions.

BIOFUELS HAVE A GLOBAL MARKET OF $227,000 MILLIONS

Spain is the third largest producer of biodiesel (fuel derived from vegetable oil and animal fat) in the EU, with 604,000 tons in 2012 (925,000 million tons in 2011), and the fifth largest producer of bioethanol (fuel from vegetable sugars), with 381 million liters in 2012 (463 million in 2011). It is also the third largest consumer of biofuels in Europe, with demand of 1.7 million tons of oil equivalent (toe)[10] in 2011 and 1.9 toe in 2012.

Although Catalonia led the introduction of biofuel production in Spain —with the company Stocks del Vallès, in Montmeló, founded in the seventies, which created the brand BDP-Biodiésel Peninsular in 2002— its current participation in this market is merely anecdotal. In fact, Stocks Vallès BDP, producing 31,000 millions tons of 3rd generation biodiesel exclusively with recycled oils, is the only Catalan company active in the sector after various business projects were terminated or discarded before being officially set up (Bionet Europa, Bioseda, Biocarburants Tarragona, Green Fuel Catalunya, etc.).

The Spanish biofuel sector is concentrated in four large companies: Abengoa Bioenergía, Acciona Biocombustibles, Infinita Renovables and Bio-Oils. Abengoa, which originated in Andalusia but is now a multinational corporation with headquarters and production plants in Spain, France, the Netherlands, the United States and Brazil, is the leading European producer of bioethanol (with 1.3 million liters in 2012). The company, with turnover of €2,138 millions in 2012, devoted €207.2 millions mainly to the production of bioethanol from recycled urban waste (organic waste).[11]

Today biofuels make up 4.7% of all energy consumed in the European transport sector and the aim is to reach 10% by 2020. However, despite growing demand, European production of biofuels fell 10% in 2012 —after increasing more than 5% in 2011[12]— in part due to intense pressure in this market resulting form the new ILUC regulations (Indirect Land Use Change), which indirectly penalizes crops used for energy production. The aim is to avoid pressure from the energy market from leading to higher prices of agricultural products for food or these being substituted by energy crops. The EU's aim is to boost 3rd generation biofuels (produced with waste, fats and algae).

THE EU GOAL IS FOR BIOFUELS TO MAKE UP 10% OF ALL TRANSPORT ENERGY IN EUROPE BY 2020

Beyond the controversy regarding the calculation of greenhouse-gas emissions, the impact of the ILUC and the distribution of subsidies among producers of fossil fuels and renewable energies, it is true that the pressure to move the production of biofuels towards 3rd generation methods means that white bio-

10. One toe (ton of oil equivalent) measures the energy released by burning one ton of crude oil and allows for comparison of the energy value of various fuels. One ton of biodiesel equals 0.86 toe and one ton of ethanol equals 0.64 toe.

11. Biofuels Barometer, EurObserv'ER, July 2013, p. 60.

12. European Biodiesel Board, www.ebb-eu.org

technology companies can contribute innovations in this field. Companies like **InKemia IUCT Group** and the **Leitat** technological center, and research bodies like the **Institute of Chemical Research of Catalonia** (ICIQ) and the **UAB Unit of Biochemical Engineering**, are working actively in this field, which offers numerous opportunities for organizations in the BioRegion.

As shown in table 13, research and production of biofuels is just one of the many areas in which industrial biotechnology can be applied, offering tools to make industrial production more sustainable, especially in the chemical arena (producing detergents, cosmetics, pharmaceuticals, etc.) and the treatment and manufacturing of various materials. This analysis is the result of work begun by a group of companies and organizations active in white biotechnology with support from Biocat. The aim is to identify and promote the BioRegion's strengths in this arena.

White biotechnology uses processes like biocatalysis or employs living organisms (bacteria or other microorganisms) to provoke chemical reactions that generate the desired transformation but significantly reduce the contamination footprint of the industry. From an environmental standpoint, white biotechnology helps save energy and water, reduces emissions of CO_2 and other contaminants, and allows for more efficient use of raw materials. All of this can contribute economic benefits to the industry, in some cases reducing the cost of processes (above all due to energy savings) and, in others, making them more eco-sustainable, thus boosting the industry's competitive advantage.

Table 13 **Areas of application of white biotechnology and economic potential in Catalonia**

Àmbits		Biocatalysis	Microbal biotransformation	BBiotransformation with higher organisms
Energy	Biofuels	+	++	++
Cleaning	Bioremediation and waste management	×	++	×
	Revalorization of waste	++	++	×
Production	Bulk bioproducts and commodities	+	++	++
	High value added bioproducts	++	+	+
	Food bioproducts	++	++	++
	Production bulk enzymes	×	++	×
	Production high value added enzymes	×	++	++

Biocatalysis: use of enzymes to speed up chemical reactions (or industrial processes) or make them more efficient in producing new products

Microbial biotransformation: use of microorganisms to produce new products or improve processes

Biotransformation with higher organisms: use of higher organisms to produce new products and/or improve processes

Applicability of technique:

++ **High**

\+ Mid

× None

Economic potential of the BioRegion:

Very high

High

Mid

Low

Source. Work group on industrial biotechnology. Biocat

BIOTECHNOLOGY AND GREEN CHEMISTRY

Dr. Antoni Planas
director of the Bioengineering Department, IQS - Institut Químic de Sarrià, Ramon Llull University

Industrial biotechnology, also known as white biotechnology, is the use and application of biotechnology for sustainable production and processing of chemical products, materials and fuel. In a productive context, white biotechnology aims to contribute solutions to industrial processes, with an emphasis on sustainability, a concept commonly broken down into three areas: environmental, economic and social sustainability. These concepts make industrial biotechnology and the methods associated with it one of the core elements of the knowledge-based bioeconomy (KBBE).

Unlike red biotechnology, geared towards health and biomedicine, whose operational framework has been consolidated in recent years with Biocat as one of the main forces behind promoting and coordinating the sector, industrial biotechnology isn't as organized in Catalonia despite being a sector that feeds directly into the activities of the Catalan chemical industry. Nevertheless, the chemical, pharmaceutical, food, cosmetics and energy sectors are showing growing interest and there are opportunities to develop new approaches with white biotechnology in these important Catalan industrial sectors.

Although companies and research groups are actively working on white biotechnology projects, the sector is still fragmented. Various stakeholders have noted that Catalonia has the potential to integrate more actively as a network in order to carry out activities in research, innovation and the search for market opportunities. Biocat recently promoted an initiative with a group of companies and research groups to identify these opportunities, with the aim of establishing an *Industrial Biotechnology Platform* that can bring together all of the Catalan stakeholders potentially involved in production activities using biotechnology tools. The most significant areas in which there is activity or potential for development in Catalonia include:

Manufacturing products and developing industrial processes using living organisms or their constituent parts, with the aim of generating productive processes that make better use of resources, are more energy efficient and less harmful to the environment. In this regard, biotechnology tools complement, and in some cases replace, conventional chemical processes in producing basic and value added chemical products. Under the concept of Green Chemistry, which encompasses new methods to bring traditional chemistry towards clean chemistry, biotechnology is undoubtedly one of the most efficient and noteworthy approaches for the production of chemical products and materials. This technology includes biocatalysis and biotransformation, which use enzymes, cell extracts or whole organisms to synthesize chemical compounds like pharmaceutical intermediates, food ingredients and additives, cosmetics ingredients, biodegradable polymers and plastics, food complements, materials and biomaterials, etc.

Waste management, bioremediation and waste revalorization, in which the use of microorganisms and plant species helps isolate and eliminate contaminating substances. The revalorization of waste from various industries using biotechnology tools is of particular interest in the Catalan context in order to create new sectors of activity and integrate them into the value chain.

Renewable energies, with the sustainable exploitation of biomass and use of other renewable raw materials to produce biofuel. Although some years ago investment was made in biodiesel plants, this sector has stagnated due to the high price of first-generation biofuels and competition on the global market. Second-generation biofuels, based on the use of lignocellulose biomass and other non-edible

raw materials, is a sector seeing significant international investment, with the need for new technology, and can be an opportunity for Catalonia.

The interaction of research groups and companies working as a network to establish an industrial biotechnology platform is an opportunity to develop the sector in Catalonia and make it competitive. This is a project for the future through which Biocat can help bring together and promote the industrial biotechnology sector in Catalonia.

The focus on recycling waste materials and bioremediation (treatment of soil and water) can lead to new models to valorize industry. And beyond productive sectors, the application of white biotechnology can bring general advantages to society as a whole, from reducing our energy dependency and increasing environmental sustainability to creating jobs in new business models.

Industrial biotechnology, in its various forms, has a greater economic impact than other areas of biotechnology, mainly because it can be applied much more broadly and in high-consumption industries (food, cosmetics, paints, textiles, etc.). In this regard, there is a lower risk in terms of return on investment and, in Catalonia, there is a varied group of companies that use and generate products and services with good international positioning. The potential for growth, however, is enormous, as only 8% of the 530 companies in Catalonia that say they use biotechnology[13] say they apply it in the industrial arena (see chapter II).

To conclude this section, it is worth noting some of the data that can put the potential of the white biotechnology market into perspective. According to calculations by the OECD, companies in Europe devoted to managing contamination; collecting, controlling and treating waste and garbage; renewable energies; and recycling have a joint turnover of more than €300,000 millions and employ more than 3.5 million people (between 30% and 40% of the global market). The sector posts annual growth above 8% and is expected to generate value added jobs from the perspective of a "greener" economy. The use of biotechnology for waste management and revalorization and to treat contaminated soil and water is one of the priorities for growth of the bioeconomy.

WASTE MANAGEMENT AND REVALORIZATION AND THE COSMETIC SECTOR OFFER GREAT OPPORTUNITIES FOR GROWTH IN INDUSTRIAL BIOTECHNOLOGY

To give just one example of the high value added industries that can boost application of bioprocesses, we can look to the cosmetics industry, which in 2012 posted turnover of €72,000 millions in Europe —the largest market in the world, ahead of the USA (€59,000 M) and Japan (€30,000 M)— and employs 1.7 million workers in the EU, including 17,000 researchers, in a total of 4,000 companies (2/3 of which are SMEs). It must be noted that the average life cycle of a cosmetic product is 5 years and that the sector renews 25% of its catalog of products each year, with all of the opportunities this affords biotechnology companies working to discover and create new components (peptides and proteins, new molecules, etc.) as well as those that work to design and implement new biotechnology-based production processes.

13. Survey on the use of biotechnology. INE, 2011.

INTERNATIONALIZATION OF COMPANIES IN THE BIOREGION

We want to devote this final section of the last chapter of the *2013 Biocat Report* to the degree of internationalization of companies in the BioRegion of Catalonia, focusing, for operational reasons as well as interest, on those at the heart of the sector: biotechnology, pharmaceutical and innovative medical technology companies.

Given the intrinsic characteristics of the markets in which these companies participate, which we covered in the first part of this chapter as well as chapters III and IV, they are immersed in an international setting from the day they are created. As it has been said, for a molecule discovered in a Catalan research center to become a drug commonly used by diabetics, for example, requires such a significant investment that it necessitates participation of large pharmaceutical companies with the potential to make it profitable on the global market, and our biotech firms must seek out development partners wherever they can, be it in the USA or India. But moreover, in price-controlled markets, like healthcare, an innovative product with competitive advantages must seek out profitability by competing on the global market.

In order to obtain updated information on the international activities of companies in the BioRegion, we carried out a telephone survey in June and July 2013 with 288 of the 292 biotechnology (194), pharmaceutical (40) and innovative medical technology (54) companies listed in the Biocat Directory. A total of 98 companies (34%) completed the survey and this analysis is based on those answers.

65% OF CATALAN BIOTECHNOLOGY, PHARMACEUTICAL AND MEDICAL TECHNOLOGY COMPANIES MARKET THEIR PRODUCTS INTERNATIONALLY

The respondents to this survey were 65 biotechnology, 15 pharmaceutical and 18 medical technology companies, with a similar proportion in each segment to the general percentage of responses. Most of the companies surveyed (67%) already have products on the market and nearly all of those who do, market them internationally. Of the companies that do not yet have products on the market (33% of those surveyed), most have scientific and technological development agreements with international partners (companies and research centers). International collaboration —through development agreements or purchasing or licensing products— is also a priority for companies that already have products on the market and most of these (57%) have signed some sort of agreement with other companies, hospitals or research institutes.

The sector's international orientation is wide reaching and only 3% of the companies surveyed said they have no commercial or scientific activity abroad and that it isn't in their immediate plans to initiate any sort of collaboration on this level.

By subsectors, biotechnology companies devoted to researching and producing new therapeutics and diagnostics have the least international commercial activity. Only one third of the companies in this segment —to which 22% of those surveyed belong— have products on the market, although most of them have international scientific or technological collaboration agreements. Biotechnology companies devoted to animal health and nutrition (10% of those surveyed), however, show intense international activity and, along with some medical technology companies, have the most products on the market.

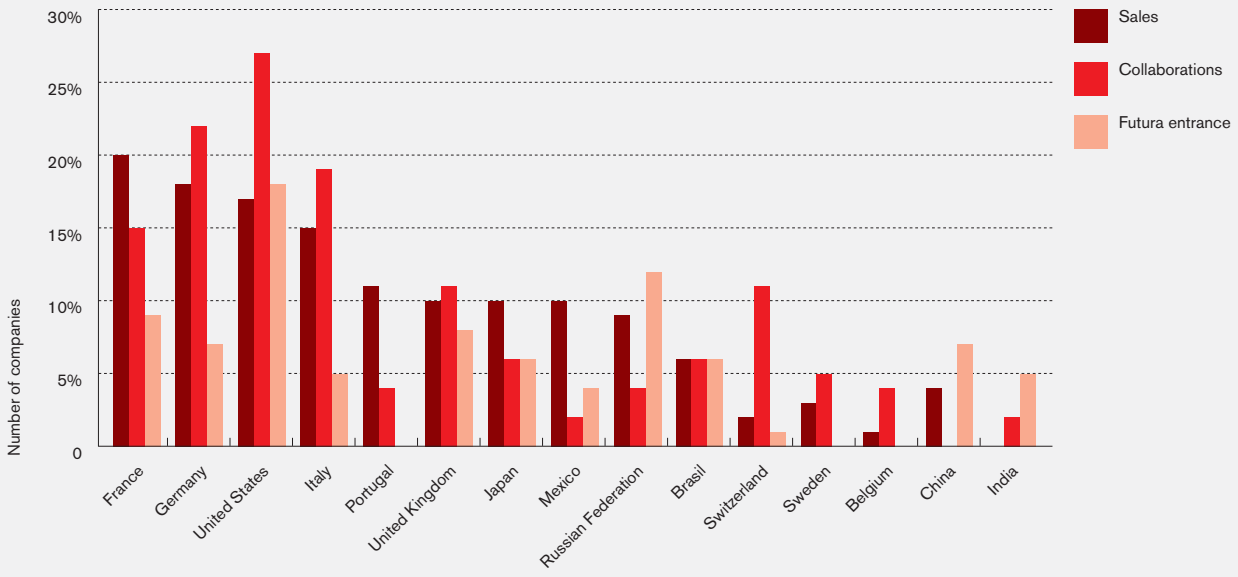
FRANCE, GERMANY, UNITED STATES AND ITALY ARE THE COUNTRIES WHERE COMPANIES FROM THE BIOREGION HAVE THE MOST COMMERCIAL ACTIVITY AND SCIENTIFIC COLLABORATIONS

Commercialization of these products is done, in most cases, through local distributors, although 20% of companies with international commercial activities have stable subsidiaries in various countries.

The survey shows a highly scattered geographic focus of internationalization among companies in the sector. Graph 44 shows the countries with the highest concentration of sales and scientific and technological collaborations currently, and which are priorities when considering opening up new markets or beginning new collaborations. France, Germany, the United States and Italy are the main markets and the countries with which there is the greatest scientific and technological collaboration, however in most cases the percentage of companies surveyed present in these markets is at or below 20%, and only collaborations with organizations in the USA involve more than 25% of companies.

The USA is also the target market for most companies not currently working there, aiming to move into this country in the near future despite the difficulties and challenges that this poses, as Karin Hollerbach explains in her article.

Graph 44 **Priority markets for companies in the BioRegion**



Source: 2013 Biocat internationalization survey

CHALLENGES AND OPPORTUNITIES FOR EUROPEAN COMPANIES IN THE US HEALTHCARE MARKET

Karin Hollerbach
(Taku Group)

The US often seems to Europeans like an "easy" market to enter, because "they are so much like us." Is this true? Not really. Many of our legal and cultural norms are rooted in Europe. Nonetheless, there are key differences. Sometimes the similarities hide the nuances of critical differences, leaving Europeans bewildered when those same nuances cause their market entry plans to go awry.

Regulatory & reimbursement

Most medical SMEs realize they need to comply with FDA requirements, which are different from requirements in Europe. Requirements are being streamlined, but they remain different. Companies must have someone in the US with expertise in working with the FDA. Currently, both the regulatory and the reimbursement systems are in flux, and timely and local expertise is critical. E.g., an acceptable submission a few years ago may today require additional clinical data; what wasn't reimbursable a few years ago, may be now – but how and at level?

Culture

In terms of cultural differences, it is worth focusing on one problem that we see frequently: the "do it yourself" mentality that causes European SMEs to not hire sufficient resources in the US. Companies either think they can do it all themselves (risking not knowing what they don't know but should, thus losing time, money and opportunities) or think they can hire resources purely on the promise of future income. Unfortunately, in the US you largely get what you pay for – not much of anything if you're not willing to pay for services you receive.

Differentiation

Think you're the only one with a great product in the US? Think again. The US is highly competitive. One of the biggest problems is appreciating how much more differentiated companies need to be than they expected. It is simply not enough to have great technology. Specifically, how does it perform relative to your competition? In the US, you must be able to talk about your uniqueness. Culturally and in terms of expertise, this is often a problem for SMEs that are more focused on technical aspects of their offering.

IP

Major issues uncovered during due diligence that may either terminate discussions with investors or pharma or device companies or that adversely affect valuation may be due to some of the following mistakes that are especially problematic in the US: Lack of understanding of local legislation, litigation, and procedure rules. It is critical that SMEs work with an experienced patent attorney with a practical understanding of the local legal landscape. In the US, diagnostic as well as product (formulations, devices) patents are in a constant state of transformation due to rule changes and the impact of litigation. To commercialize a product or process, the company needs an innovation that can be put into practice and protected, that has a market; and that someone will pay for. The timing of filing, along with sufficiency of disclosure (often significantly affected by the experience of the attorney), will have a great impact on these issues.

Funding

Many SMEs look to the US first for funding rather than for revenue. This may be realistic – but is not easy. Many US investors still prefer companies to have a base in the US before investing. This presents a problem for those that can't yet afford to get set up in the US. We suggest "soft landing" approaches that can provide the benefits of having a US base without the costs of establishing a full, operating subsidiary. Unless this hurdle is overcome, accessing US capital markets is difficult.

Resources

Depending on where you are in Europe and where you are looking in the US, the distances may not seem that great. Still, expect to fly to the US frequently and to hire resources in the US. This is not inexpensive. If an SME is unable to commit the time, money and focus to do this well, it may be better to look first to other markets. For those who are successful here, the US can be highly lucrative – but it is neither cheap nor easy to build that success.

The BRIC countries (Brazil, Russia, India and China), which with their emerging economies are seen as places of great opportunities for the life sciences sector, are irregularly represented in the current panorama of internationalization of companies in the Catalan biocluster. All four countries are among the top 10 markets companies are interested in entering in coming years, however they have very different baselines: the Russian Federation is already the focus of commercial activity by our companies, but not of any scientific or technological collaboration. 4% of the companies surveyed have commercial activity in China, but there are no scientific collaborations. It is just the opposite in India, where there are collaborations but not sales. The situation is more balanced in Brazil, where there is activity in sales, technological collaborations, and growing interest from Catalan companies in moving into this market.

China and Brazil, which as seen in the box below are areas of great opportunities that are easier to access with a local partner, have been the focus of several international networking activities promoted by Biocat over the past two years to facilitate access to these strategic markets for companies in the BioRegion.

To conclude this summary of the internationalization activities of companies in the BioRegion of Catalonia —as well as this chapter and the whole *2013 Biocat Report*— it must be noted that for 38% of the companies surveyed, more than 50% of sales come from international markets. The survey only confirms the trend we have seen in recent years, pressure and competition in interior markets have led even the most traditional companies to open up to foreign trade. Internationalization is a key part of the Catalan biocluster's commitment to growth and value that we must continue to promote in the future.

CHINA AND BRAZIL: OPEN TO INTERNATIONAL COLLABORATIONS

China will soon be the second largest pharmaceutical market in the world and Brazil is one of the most important in Latin America, where previsions for growth in the sales of pharmaceuticals between 2009 and 2014 are 12%-15% per year. Additionally, Brazil is the second largest producer of biotechnology crops in the world, after the United States.

These two new economic superpowers both have a growing middle class, and increased demand for medical care and quality of life. This is an opportunity for the biomedical arena in Catalonia, both for companies and for research centers.

"There is a growing number of Chinese companies interested in doing business with European companies. China and Europe are complimentary. You have good projects, good technology and top-notch talent," explains Gao Ronghui, a consultant specializing in the life sciences and president of G-Med Consulting.

In China, "over the past 10 years, we have begun to develop a true R&D&i system and now have some well-established research companies. However there aren't many in the medical device sector," says Ronghui. Many regional hospitals have been built and the government aims to have more than 20,000 to care for the whole population. This means that the healthcare system will require diagnostic tools and technology to cover basic medical needs. In terms of diseases, there are a very large number of people with diabetes, high blood pressure and childhood obesity, and the most common cancer is lung cancer.

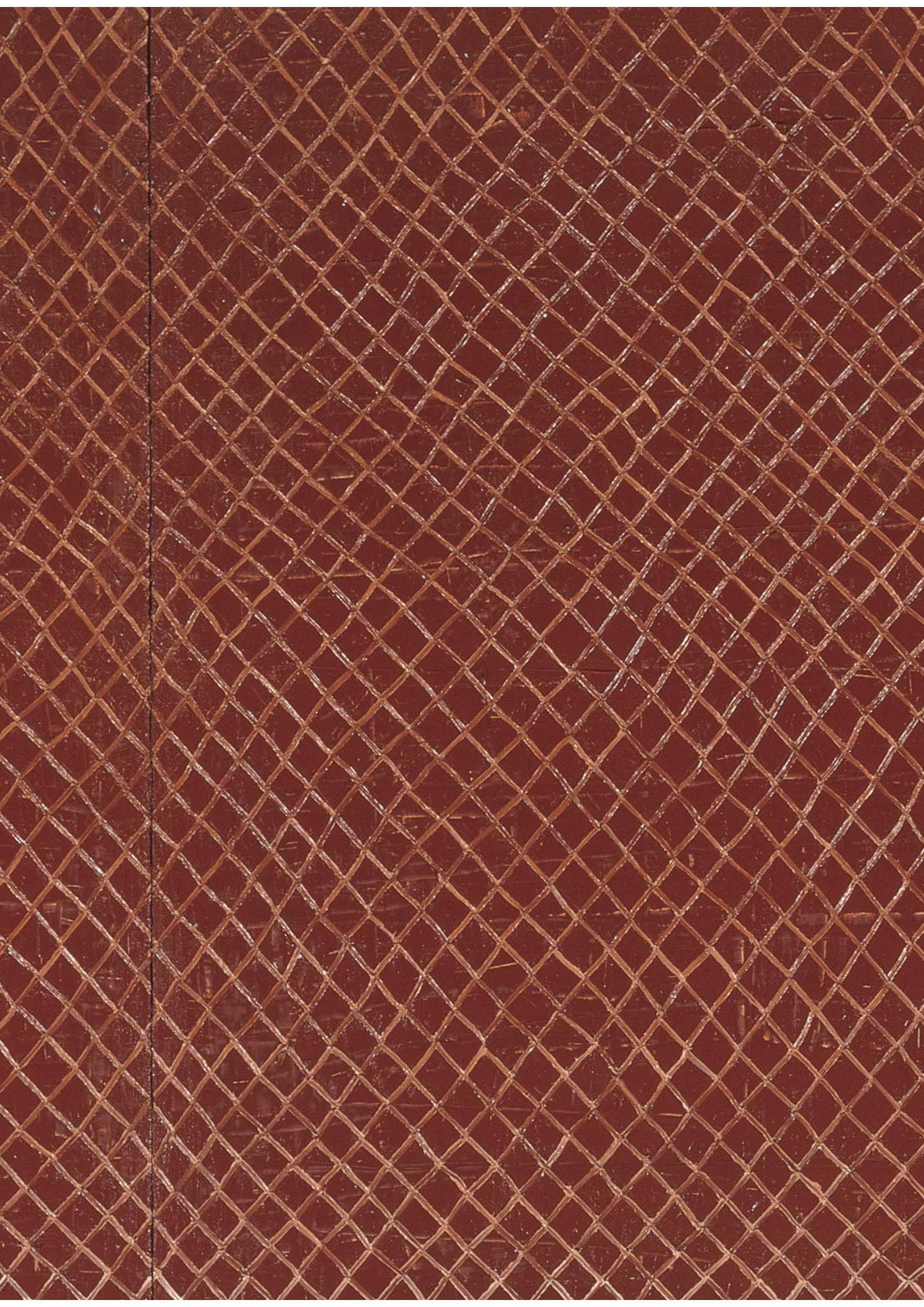
Regarding Brazil, Eduardo Emrich Soares, president of Biominas in Minas Gerais, explains that "we are opening ourselves up more and more, especially to bringing in new technologies. International companies that want to come to Brazil and open a subsidiary should establish a cooperation agreement with a Brazilian firm, which then gives them access to all of the mechanisms and programs available on a state and federal level."

The wealthiest region of Brazil is the southeast, with 66% of the country's GDP. Life sciences and biotechnology companies are found mainly in the states of São Paulo (38%) and Minas Gerais (30%). By area, the most important are human health (33%), agroindustry (31%) and the production of reactives (18%). The bioindustry in Brazil is still very young; nearly 70% of companies are less than five years old.

"Regarding causes of mortality, we are moving from a high number of deaths from infectious disease towards a higher rate of cancer, respiratory disease and circulatory diseases. The number of cases of diabetes is also increasing," says Soares.

2,700 clinical trials are carried out each year in Brazil, nearly double those conducted in Mexico, their main competitor. Some of the most significant areas of R&D include regenerative medicine; genomics, with important investment to create a network of sequencing laboratories (the sugar cane genome is currently being sequenced); bioinformatics; and nanotechnology, with a program to invest more than $28 millions in centers.

To conclude this summary of the internationalization activities of companies in the BioRegion of Catalonia —as well as this chapter and the whole 2013 Biocat Report— it must be noted that for 38% of the companies surveyed, more than 50% of sales come from international markets. The survey only confirms the trend we have seen in recent years, pressure and competition in interior markets have led even the most traditional companies to open up to foreign trade. Internationalization is a key part of the Catalan biocluster's commitment to growth and value that we must continue to promote in the future.



REFERENCES

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BIBLIOGRAPHY

The sources used (books, periodicals, websites, databases and press releases, mainly) are cited in the bibliographical notes in each chapter. This bibliography only includes the main reports and publications used to compile the 2013 Biocat Report, not the reports from organizations in the BioRegion, which are cited specifically within the report where applicable.

- *2012 Pan-European Private Equity and Venture Capital Activity, European Private*, Equity and Venture Capital Association (EVCA), April 2013
- *2013 Venture Capital Healthcare Report*, PitchBook Data, 2013
- *Análisis del mercado hospitalario 2008-2012*, IMS Health, 2013
- *Articulación de las RIS3 con la Estrategia Española de Ciencia y Tecnología y de Innovación 2013-2020*, III Pleno de la red de políticas públicas de I+D+I, State Secretariat for Research, Development and Innovation. Ministry of Economy and Competitiveness. Government of Spain. March 2013
- *ASCRI. Informe 2012. Retos para el cambio*, Asociación Española de Entidades de Capital-Riesgo (ASCRI), 2012
- *ASCRI. Informe de actividad Capital Riesgo en España 2013*, Asociación Española de Entidades de Capital-Riesgo (ASCRI), 2013
- *Beyond borders. Global Biotechnology Report 2012*, Ernst & Young, 2012
- *Beyond Borders. Matters of evidence. Biotechnology Industry Report 2013*, Ernst & Young, 2013
- Bueno, David (Ed). *Ciència i universitat a Catalunya*, Universitat de Barcelona, 2012
- *Burrill Report 2012: Innovating in the New Austerity*, Burrill & Co., 2012
- *Burrill Report 2013: Capturing Value*, Burrill & Co., 2013
- "Catalunya i l'estratègia Europa 2020", *Nota d'economia*, Núm. 100, General Management of Economic Affairs, Ministry of Economy and Knowledge, Government of Catalonia, 2012
- Chinchilla-Rodríguez, Zaida. *Informe sobre la calidad de la Producción Científica (2003-2009) en Biotecnología*, FECYT, 2012
- *Closing the gap? Big pharma's growth challenge and implications for deals*, Ernst & Young, January 2013
- *Datos y cifras del sistema universitario espanyol. Curso 2012-2013*, Ministry of Education, Culture and Sport, Government of Spain, Madrid, 2013
- *Document de treball de l'estratègia per a l'especialització intel·ligent de Catalunya (RIS3CAT),* Government of Catalonia, July 2013
- *El mercado del medicamento en España*, Farmaindustria, Boletín de Coyuntura, 94 (February 2013), 95 (March 2013) and 96 (April 2013).
- *El Venture Capital en España en 2011*, Webcapitalriesgo, May 2012
- *El Venture Capital en España en 2012*, Webcapitalriesgo, April 2013
- *Ensayos en oncología en Cataluña, Análisis a partir de la 11ª publicación de BDMetrics*, Plataforma de Medicamentos Innovadores, Farmaindustria, June 2012
- *Estadística sobre el uso de Biotecnología 2011*, National Statistics Institute (INE), December 2012
- *Estrategía Española de Ciencia y Tecnologia y de Innovación 2013-2020*, Ministry of Economy and Competitiveness. Government of Spain

- *From vision to decision. Pharma 2020*, PwC, 2012
- *Hospital Readmissions in Europe*, The Burrill Report, May 2013
- *Implementation of Medical Research in Clinical Practice*, European Science Foundation, September 2012,
- *Indicadors de recerca i innovació de les universitats públiques catalanes. Informe 2012*, ACUP, Barcelona, December 2012
- *Informe Asebio 2012*, Asociación Española de Bioempresas, Madrid, July 2013
- *Informe COTEC 2012. Tecnología e Innovación en España*, Fundación COTEC, Madrid 2012
- *Informe COTEC 2013. Tecnología e Innovación en España*, Fundación COTEC, Madrid 2013
- *Innovating for Sustainable Growth: A Bioeconomy for Europe*, COM(2012) 60 final, European Comission, Brussels, February 2012
- *Innovation Union Scoreboard 2011,* Maastricht Economic and Social Research Institute on Innovation and Technology (UNU-MERIT), February 2012
- Jenkins, John K. *New Drug Review: An Update and a Look Ahead*, FDA, June 2012
- *La Economía de Cataluña: diagnóstico estratégico*, "la Caixa" Economic Research Department, 2012
- Mack, George S., *The Life Sciences Report Watchlist 2013*, Streetwise Reports, 2013
- Morelli, Gabriel; Almarza, Concha. *El Mercado Farmacéutico Español*, IMS Health, February 2013
- Norris, Jonathan, *Private Funding & Exit Trends, New Paradigms Presentation*, Silicon Valley Bank, January 2013,
- *Optimism tempered by reality in a "new normal". 2013 Global Life Sciences Outlook*, Deloitte, 2012
- *Pharma Survey*, KPMG Spain, February 2013
- *Pla de Salut de Catalunya 2011-2015*, Ministry of Health, Government of Catalonia, 2012
- *Pla estratègic de recerca i innovació en salut 2012-2015*, Ministry of Health, Government of Catalonia, September 2012
- *Plan de estímulo económico y apoyo al emprendedor*, Government of Spain, February 2013
- *Plan estatal de Investigación Científica, Técnica y de Innovación 2013-2016*, Ministry of Economy and Competitiveness. Government of Spain, 2013
- *Potencial de la biotecnologia en el tractament de residus*, ACC1Ó, December 2011
- *Pricing & Market Access Outlook*, IMS Consulting Group, 2012
- *Report of the MIT Taskforce on Innovation and Production,* Massachusetts Institute of Technology, February 2013
- *Reports de la recerca a Catalunya 2003-2009. Biotecnologia*, Institut d'Estudis Catalans, 2012
- Robles, Elisa, *Apoyo y financiación para emprendedores, Ciclo FINAVES: Apoyo público a emprendedores*, Centro para el Desarrollo Tecnologico Industrial (CDTI), February 2013
- Samitier, Josep, *Nanomedicine in Spain: 2006-2012. Spanish Nanomedicine Platform*, Barcelona, February 2012
- *Scientific American Worldview*, 2013
- *Serveis terciaris o d'alta especialització a Catalunya*, CatSalut, Ministry of Health, Government of Catalonia, 2011
- Sparrow, Norbert, *Western Europe's Medical Device Market under Increasing Pressure*, European Medical Device Technology (EMDT), July 2013
- *Spotlight on Personalized Medicine, A pharma matters report*, Thomson Reuters, August 2012
- *The Brazilian Life Science Industry. Pathways for growth,* PwC-Biominas, 2011
- *Una aproximación al impacto económico de la innovación en el desarrollo del sector empresarial de la salud en España*, Club Innovación y Futuro - Fundación OPTI, 2012
- *Visión de futuro para el sector de la salud 2025*, Club Innovación y Futuro - Fundación OPTI, 2012
- *XVIII Fòrum d'Inversió. Catàleg de proveïdors de fons,* Agència de Suport a l'Empresa Catalana, ACCIÓ, Government of Catalonia, January 2013

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Finally, we want to thank the artists and entities —MACBA. Museu d'Art Contemporani de Barcelona and Museu d'Art Jaume Morera, in Lleida— that have allowed us to reproduce their work to illustrate and bring character to the 2013 Biocat Report. Again this year we wanted to associate the image of this publication and the life sciences sector with the creativity and international projection of Catalan art, because we believe that artistic creativity and entrepreneurship in the scientific arena have shared values we can promote: seeking out new paths to address social challenges, commitment to risk, passion and personal dedication.

These are the pieces and artists that bring light to this report and that, in some way, express the sprit of the Catalan biocluster.

Miquel Barceló, *La taula blanca* (1989)
Miquel Barceló, La taula blanca (1989)
Pigment and latex on canvas
225 x 287.5 x 5 cm
MACBA Collection. Government of Catalonia Art Fund. Former Salvador Riera Collection
Photograph: Gasull Fotografia
© Miquel Barceló, VEGAP, Barcelona, 2013

Miquel Barceló (Felanitx, 1957) is one of the most international Catalan artists. Africa, and specifically Mali where he has spent long periods of time since 1988, has had an important influence on his work. La taula blanca shows the suggestive plasticity of the hot African sun; perhaps without knowing, it speaks of the value of knowing how to look.

Leandre Cristòfol, *Harmonia estel·lar (Ralentí)* (1957)
Metal bars, wood, pins and glass on cork
72 cm
Donated by Leandre Cristòfol, 1990
© Museu d'Art Jaume Morera, Lleida, 2013

Leandre Cristòfol (Os de Balaguer, 1908 – Lleida, 1998) was a pioneer in surrealist sculpture in Catalonia. His work, both poetic and experimental, uses everyday materials to create extraordinary, evocative images, like this star that, here, reminds us of a strange cell or unknown microbe.

Antoni Llena, *Blanc, negre, verd i vermell* (1986)
Mixed media on paper
129 x 110 cm
MACBA Collection. Barcelona City Council Fund
Photograph: Rocco Ricci
© Antoni Llena, 2013

Antoni Llena (Barcelona 1943) is an artist that has always sought out the ephemeral, both in his sculptures and paper pieces. Nearly 30 years ago, he created a piece with the colors of biotechnology: white, green and red, and despite its apparent fragility it is standing the test of time, just like the stakeholders in the BioRegion of Catalonia.

Albert Ràfols Casamada, *Pintura núm. 2 (Homenatge a Miró)* (1971)
Mixed media on canvas
114 x 146 cm
MACBA Collection. MACBA Foundation. Donated by Catalana Occidente Foundation
Photograph: Jordi Nieva
© Albert Ràfols-Casamada, VEGAP, Barcelona, 2013

Albert Ràfols Casamada, *Barcelona Triangle* (1987)
Acrylic on canvas
200 x 270.5 x 3 cm
MACBA Collection. Barcelona City Council Fund
Photograph: Gasull Fotografia
© Albert Ràfols-Casamada, VEGAP, Barcelona, 2013

Albert Ràfols Casamada (Barcelona, 1923-2009), a versatile artist, knew how to create his own world, somewhere between expressionism and abstraction, with soft colors and Mediterranean light. In this painting the artist celebrates his city and reminds us that Barcelona is the epicenter of the Catalan life sciences sector.

Carles Bros, *Hutong VI* (2012)
Mixed media on canvas (India ink, newspapers and rice paper)
150x200 cm
© Carles Bros, 2013

Carles Bros (Terrassa, 1956) created the series Impressions de la Xina (Impressions of China) after a trip to Beijing, when he was surprised by the changes that had come about in the city as a result of the 2008 Olympic Games. In his work, Bros wanted to capture the spirit of the traditional neighborhoods (hutongs) at odds with the breakneck transformation and growth of this Asian giant.

Joan Hernández Pijuan, *Tríptic de Granada* (1994)
Oil on canvas
146 x 309.5 cm
MACBA Collection. MACBA Foundation
Photograph: Julio Cunill
© Joan Hernández Pijuan, VEGAP, Barcelona, 2013

Joan Hernández Pijuan (Barcelona 1931-2005) created an organized world with his geometric figures, ruled by beauty and poetry. He sought order in landscapes humankind had altered through farming and found poetry in the isolation of a flower or tree. The best gateway to a section that brings order to the references in this study.

REPORT biocat

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