ASEBIO Report 2015

News and trends from the Spanish Biotech Sector and company guide

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ASEBIO Report

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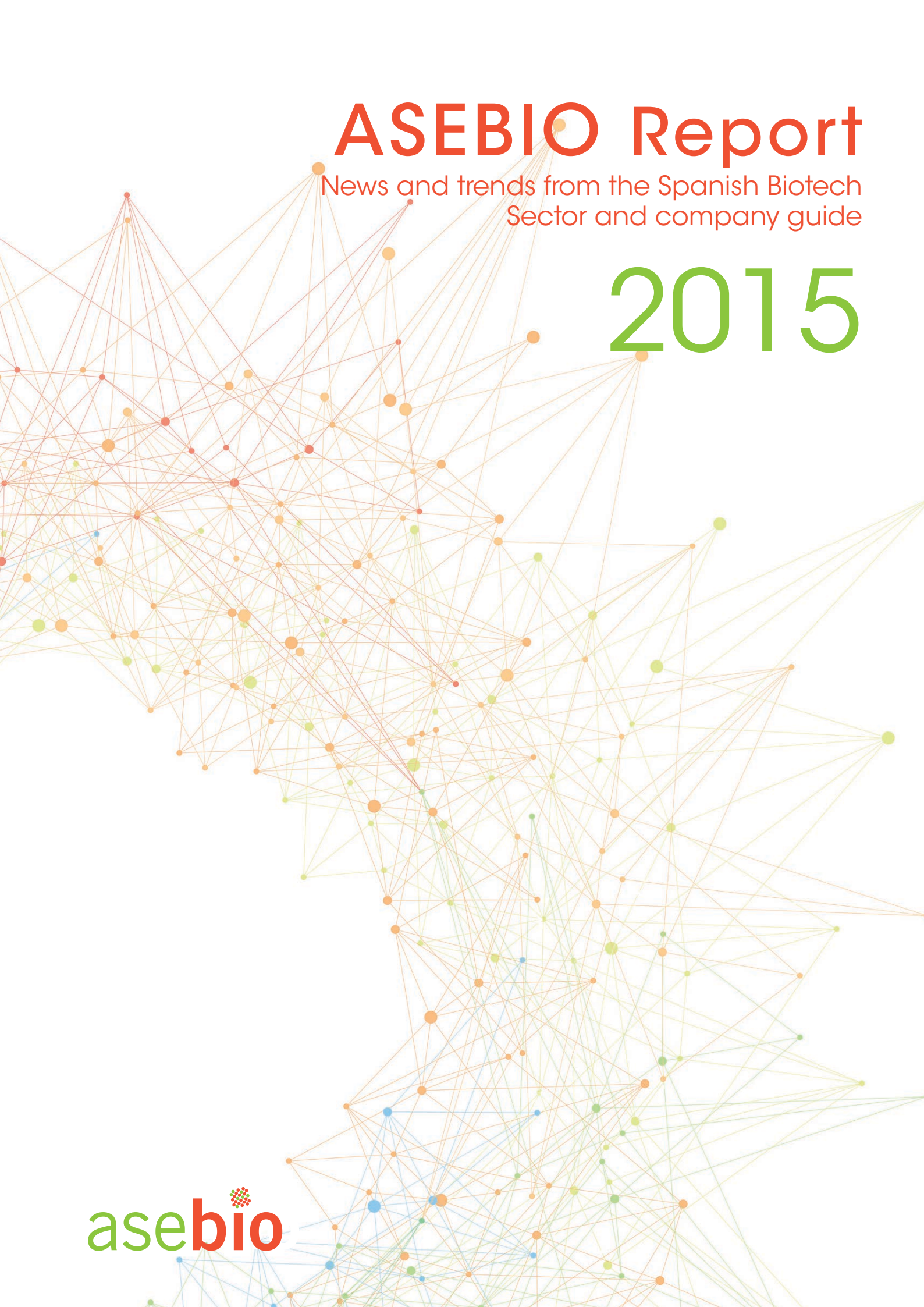
2015



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1.

THE SPANISH BIOTECHNOLOGY SECTOR IN 2015

1. The Spanish biotechnology sector in 2015

The figures reveal mixed results in the main key indicators. When we look at companies declaring that they are engaged in biotechnology related activities the indicators show a clear improvement, but when we focus on the biotechs, some of the data is less positive:

- The number of companies declaring in the survey that they are engaged in biotechnology related activities has fallen by 3.14% over the year (meaning a reduction of 89 companies compared to the previous year).
- 628 companies confirmed biotechnology to be their main and/or exclusive activity (companies known as biotechs), up by 13.36% compared to 2013 (an increase of 74 companies compared to the previous year), making up for the fall of the previous year and getting back to 2012 levels
- In net terms, 5,034 new jobs have been created during 2014, an increase of around 3%, marking a return to the upward trend after the previous year's fall.
- For the first time in recent years, internal expenditure on biotechnology R&D rose, with a year-on-year increase of 3.75%.
- It should be noted that Biotechs increased their turnover by 6.75% compared to the previous year, although a total of 2,043 jobs were lost (-6.9%) in net terms.
- Global industry turnover continued to grow, rising to 107,788 in 2014 (13.28% more than the previous year). This growth was in large part down to the performance of companies with over 250 employees, whose turnover grew by 17.82%.
- Lastly, the contribution towards the Spanish GDP of companies active in biotechnology (another key indicator for the sector) rose to 10.35% compared to 9.07% in 2013 (in 2008 this indicator stood at 3%).

Table 1 shows the evolution of the key indicators for the biotechnology sector. Figure 1 and Figure 2 focus on the year-on-year evolution of two key indicators: employment and turnover. Table 2 breaks down the results of the same indicators according to whether biotechnology is the main or exclusive activity (biotechs), a secondary activity, or a necessary tool for production.

Tabla 1. Main results from the biotechnology section of the 2014 survey on innovation in companies

Main variables	Under 250 employees	Over 250 employees	Total 2014	Total 2013	Variation	Growth rate
Companies active in biotechnology	**2,644**	**98**	**2,742**	**2.831**	**-89**	**-3,14%**
Dedicated biotechnology using biotechnology as main or sole activity	610	18	628	554	74	13.36%
Biotechnology companies using biotechnology as a second line of business	224	26	250	271	-21	-7.75%
Biotechnology companies using biotechnology as a tool for production	1,810	54	1.864	2.006	-142	-7.08%
Companies active in biotechnology R&D	**1,006**	**73**	**1.079**	**983**	**96**	**9.77%**
Total employment	**69,665.8**	**108,307.2**	**177.973,0**	**172.939**	**5.034**	**2.91%**
Turnover (in millions of euros)	**12,287**	**95,501**	**107.788**	**95.152**	**12.636**	**13.28%**
Number of biotechnology R&D staff	**7,556**	**2,239**	**9.795**	**9.135**	**660**	**7.23%**
A) Total by role						
Researchers	4,379	1,194	5.573	5.148	425	8.25%
Technicians and assistants	3,177	1,045	4.222	3.987	235	5.90%
B) Number of women	4,032	1,267	5.298	5.095	204	4.00%
Researchers	2,279	646	2.925	2.730	195	7.14%
Technicians and assistants	1,752	621	2.373	2.364	9	0.38%
Internal expenditure on R&D (in thousands of euros)	**402,391**	**131,434**	**533.826**	**514.529**	**19.296**	**3.75%**
A) Type of expenditure						
Operating expenses	365,997	126,959	492.955	468.698	24.258	5.17%
- Salaries for researchers	153,274	50,166	203.439	184.319	19.120	10.37%
- Salaries for technicians and assitants	67,291	29,559	96.850	93.506	3.345	3.58%
- Other operating expenses	145,432	47,234	192.666	190.873	1.793	0.94%
Capital expenditure	36,395	4,476	40.870	45.832	-4.961	-10.82%
- Land and buildings	6,634	888	7.521	9.058	-1.536	-16.96%
- Equipment and devices	28,691	3,388	32.078	35.185	-3.107	-8.83%
- Specialised R&D software	1,071	200	1.271	1.589	-319	-20.07%
B) Sources of funding						
Funding from Spain	329,975	102,895	432.869	431.113	1.756	0.41%
- Own funds	239,006	80,039	319.046	314.177	4.869	1.55%
- Companies	30,715	8,538	39.254	43.200	-3.946	-9.13%
- Public funding	57,667	12,396	70.063	67.770	2.293	3.38%
- Universities	156	0	156	248	-92	-37.10%
- Private non-profit institutions	2,431	1,921	4.351	5.719	-1.367	-23.90%
Funding from overseas	72,417	28,540	100.956	83.416	17.540	21.03%
- EU programmes	18,073	1,998	20.070	14.892	5.179	34.77%
- Other overseas funding	54,344	26.542	80.886	68.524	12.362	18.04%

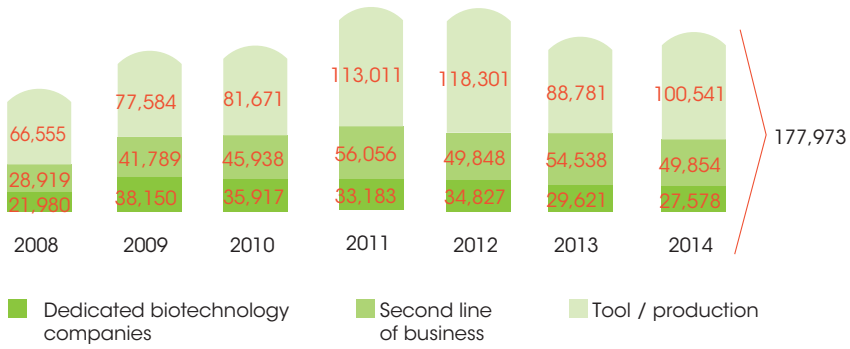
Table 2. Main indicators for the biotechnology sector in 2014 by type of activity

Main variables	Principal			Secondary			Tool			Total in 2014	Total in 2013
	Value in 2013	Value in 2014	% over total in 2014	Value in 2013	Value in 2014	% over total in 2014	Value in 2013	Value in 2014	% over total in 2014		
Units active in biotechnology	554	**628**	22,90%	271	**250**	9,12%	2.006	**1.864**	67,98%	**2.742**	2.831
Units active in biotechnology R&D	495	**519**	48,10%	200	**179**	16,59%	288	**381**	35,31%	**1.079**	983
Number of jobs in biotechnology	6.619	**6.911**	37,20%	2.049	**2.142**	11,53%	8.882	**9.522**	51,26%	**18.575**	17.550
Expenditure on biotechnology (thousand of euros)	522.320	**549.621**	62,10%	92.290	**114.103**	12,89%	231.227	**221.354**	25,01%	**885.078**	845.837
Internal R&D expenditure in biotechnology (thousands of euros)	371.259	**364.396**	68,26%	68.719	**71.517**	13,40%	74.552	**97.913**	18,34%	**533.826**	514.529
Turnover (thousands of euros)	7.111.375	**7.591.397**	7,04%	62.493.746	**55.566.647**	51,55%	25.547.334	**44.629.922**	41,40%	**107.787.966**	95.152.455
Total employment	29.621	**27.578**	15,50%	54.538	**49.854**	28,01%	88.781	**100.541**	56,49%	**177.973**	172.939

Table 1 shows that despite some negative results for certain key indicators, it appears as though the previous year's poor results have not continued and we may be witnessing the start of an upswing. Employment growth, a second yearly increase in the industry turnover and the growth in the number of dedicated biotechnology companies (biotechs) are the key indicators that suggest this is the case.

The number of companies which stated that they were active in biotechnology over the year fell by 3.14%, while the number of dedicated biotechnology companies rose by 13.36% (meaning there are 74 more biotechs than the previous year), reversing a two year downward trend in one of the most important indicators when measuring the wellbeing of the sector. However, a closer look at the data (see Table 2) reveals that the biotechs suffered the most over the year; although their turnover rose by 6.75% compared to the previous year, a total of

Figure 1. Employment (number of jobs)



2,043 jobs were lost in net terms (a decrease of 6.9%) and there was also a small -1.85% decrease for internal expenditure on biotechnology R&D.

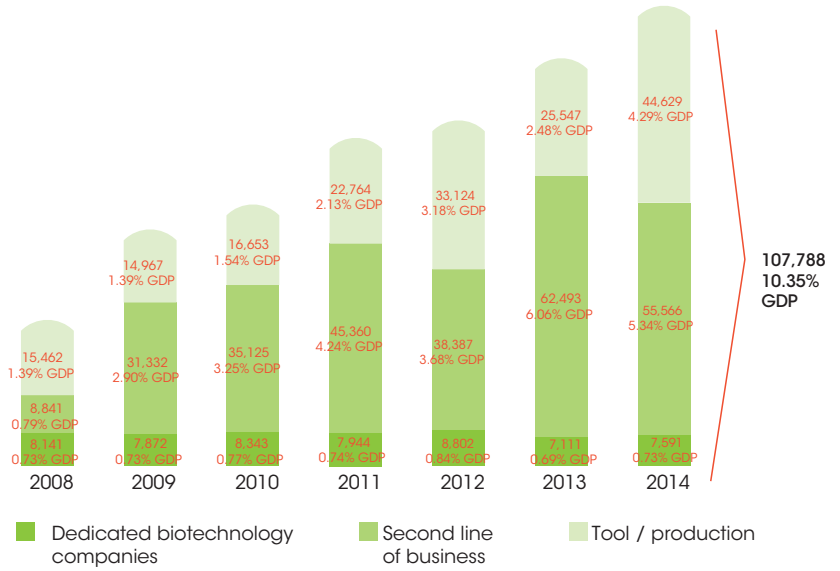
Total turnover for the sector, i.e. those companies stating that they were active in biotechnology, rose sharply up to €107,788 million (+13.28%). This increase in the total turnover is largely due to the performance of companies with over 250 employees, which account for 88.6% of total industry turnover (compared to 85.2% last year). As we have said in previous annual

reports, though the turnover figures are very positive, ASEBIO urges caution when interpreting these numbers as the companies active in biotechnology category includes all user sectors (food, pharma, chemicals, energy etc.) and many of the corporations in them. That is precisely why we focused above on the evolution of key indicators associated with the biotechs as the most accurate barometer for the health of the sector.

As a complement to the previous conclusions on company size, the latest survey revealed that distribution of turnover in the sector is as follows: 51.55% by companies using biotechnology as a second line of business, 41.4% by companies using biotechnology as a necessary tool of production and only 7.04% by dedicated biotechnology companies or biotechs. The distribution changes significantly, however, when considering employment: tool for production accounted for 56.49%, second line of business contributed 28.01% and dedicated biotechnology companies provided 15.5% of jobs. As mentioned earlier, the total contribution of the sector as a proportion of Spanish GDP at constant prices rose to 10.35% (a percentage point more than the previous year and three times that of 2008, when it was just under 3%) .

We must point out the change in the falling trend seen in recent years for an indicator that can help predict the future competitiveness of the sector: inward R&D investment in biotechnology. As Figure 3 illustrates, the indicator has experienced growth of 3.75% (just over 19 million in absolute terms). Looking into the source of these funds, this increase can be explained by an increase in overseas funds, worth a total of 17.5 million euros (+21% more than the previous year), probably returns from the H2020 programme. Spain based funding accounted for 81% of all internal expenditure on R&D, with the sources of funding remaining similar to the previous year: own funds (73.7%), Public Administration (16.18%), other companies

Figure 2. Turonover (millions of euros) and sector to GDP ratio[1]



[1] It is again worth noting that, as we will see later, GDP is revised every September but a definitive number is not released until after four years. We should also remember that new statistical rules were introduced in 2014, leading to a revisión of all total back to 1995. These factors mean that the sector to GDP ratio for the last few years differ from those published in earlier reports.

Figure 3. R&D expenditure (millions of euros)

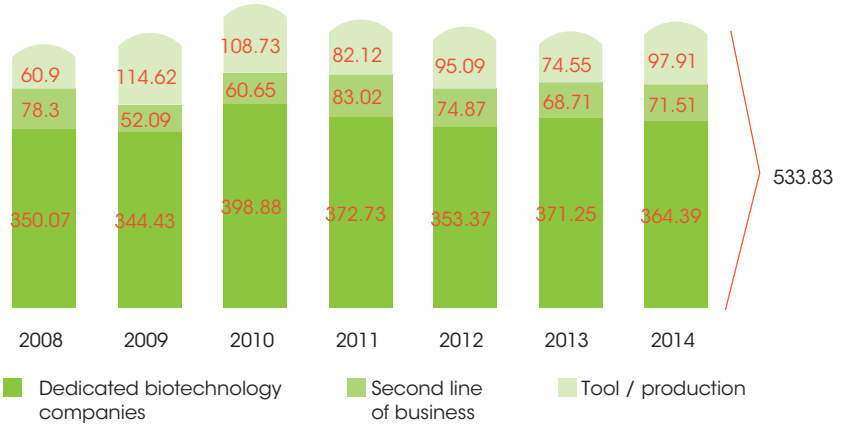
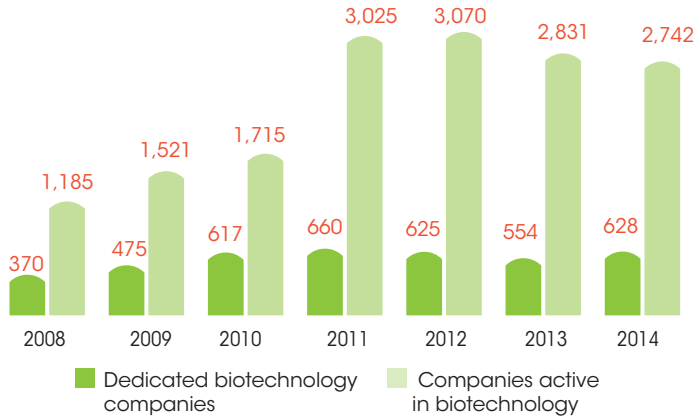


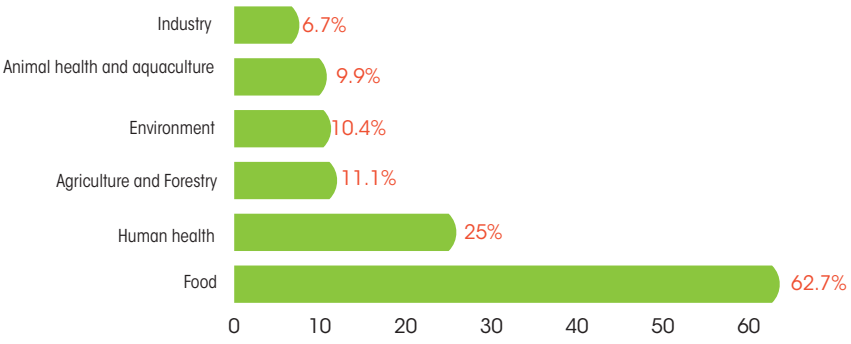
Figure 4. Number of companies active in biotechnology



(9.07%), private non-profit institutions and universities (1.04%).

In regards to gender, the percentage of women working in biotechnology R&D is 54.1%, a percentage which closely mirrors that of previous years. In terms of sectorial distribution of companies involved in biotechnology R&D and biotechs operating Spain, Figures 5 and 6 shows that food (62.7%) and human health (25%) predominate when analysing data for companies active in biotechnology. While in the case of *biotechs* the order is reversed: human health (61.9%) and food (28.8%).

Figure 5. Percentage of user companies by application of biotechnology



Source: Spanish Statistical Office, Innovation Survey in Companies 2014.

A geographical analysis of the indicators

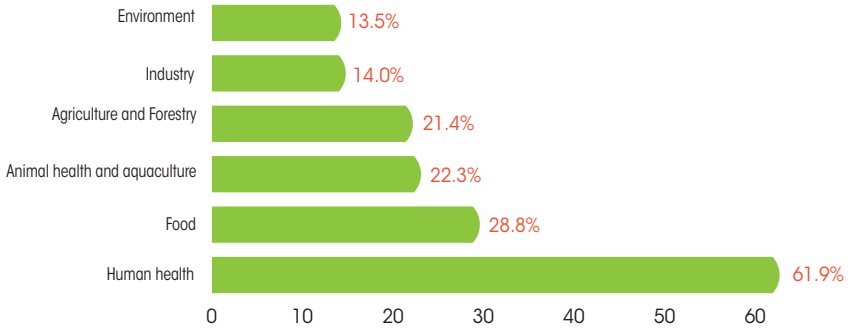
Figure 7 shows Catalonia extending its lead (21.21%) in the ranking of companies active in biotechnology, followed by Andalusia (11.83%) and Madrid (11.52%).

The chasing group includes: The Basque Country (9.53%), Castile-Leon (8.56%), Galicia (7.34%) and Valencia (6.79%).

We should again bear in mind that due to the random sampling method used for the survey, regions with a less developed sector may show significant variations compared to previous reports.

In terms of the geographical distribution, Figure 8 shows that the leading group is the same as the previous year: Catalonia accounted for 22.45%, followed by Madrid (16.69%), Andalusia (11.75%) and Valencia (10.35%). The chasing group is made up of the Basque Country (7.17%),

Figure 6. Percentage of dedicated biotechnology companies by final application of biotechnology



Source: Spanish Statistical Office, Innovation Survey in Companies 2014.

Castile-Leon (6.78%) and (unexpectedly) the Canary Islands (5.4%), a region which has probably been overrepresented by the sampling method, given that we are not aware of the existence of a biotechnology sector of such size in the islands.

2 From a methodological perspective we should also consider that this indicator is revised and updated every September, with the definitive number being released four years after the time (i.e. the de nifinitive GDP for 2014 will be determined in 2018), although revisions are not usually significant. We should also note that in September 2014 new statistical rules were introduced, leading to a revision of all totals back to 1995. This has meant a slight change in the size of the sector to GDP ratio for the last few years when compared to the numbers published in previous reports.

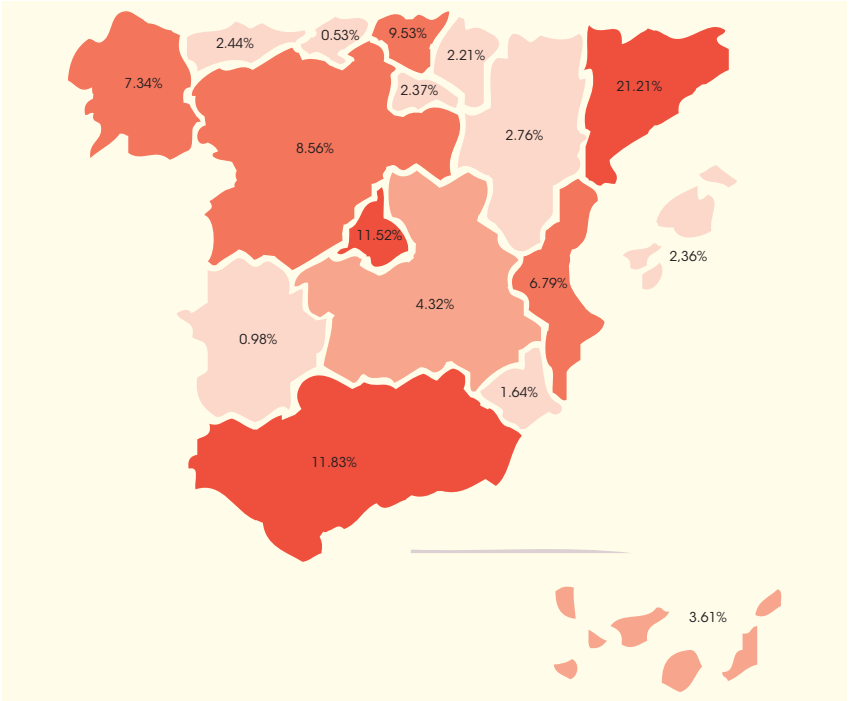
Competitive cooperation in the Spanish biotechnology sector

This last section focuses on the *innovative biotechnology companies;* user companies which responded that during the two years leading up to the survey they carried out technological innovations, either in terms of products or processes.

Of the 628 *biotechs*, those for whom biotechnology is the main or sole activity, 46.02% stated they had carried out technological innovations over the 2013-2015 period. 192 of these have collaborated with another entity in some way. Figure 9 breaks down the numbers to show which agents have participated the most in such collaborations with innovative biotechnology companies.

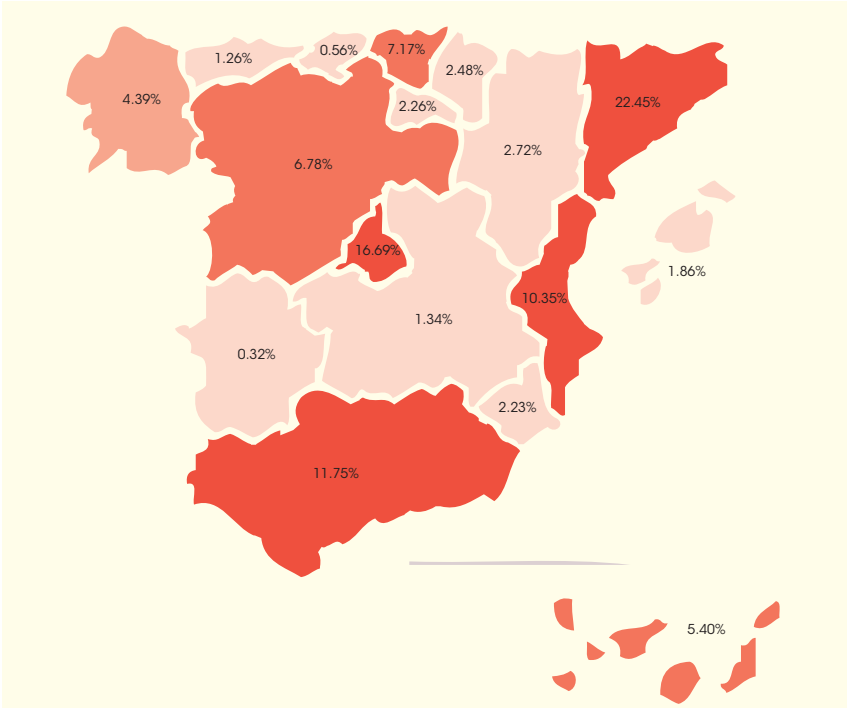
This year collaborations with public or private research centres top the ranking (with 72.39% or respondents claiming to have participated in collaborations with such organisations), followed by collaborations with universities and other higher education institutions (67.2%), which in turn are followed by collaborations with clients, competitors, providers, consultants or laboratories, other companies from the same group and public sector clients.

Figure 7. Geographical distribution of biotechnology user companies



Source: Spanish Statistical Office, Innovation Survey in Companies 2014.

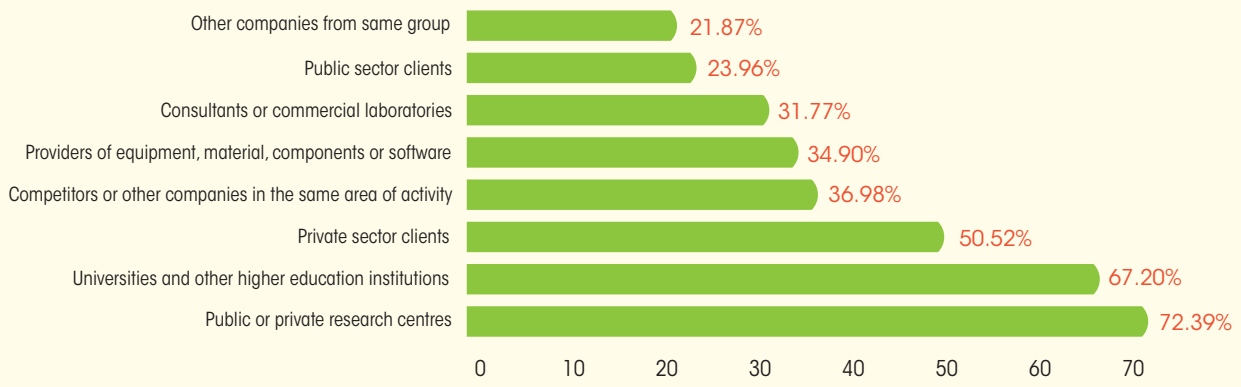
Figure 8. Geographical distribution of dedicated biotechnology companies



Source: Spanish Statistical Office, Innovation Survey in Companies 2014.

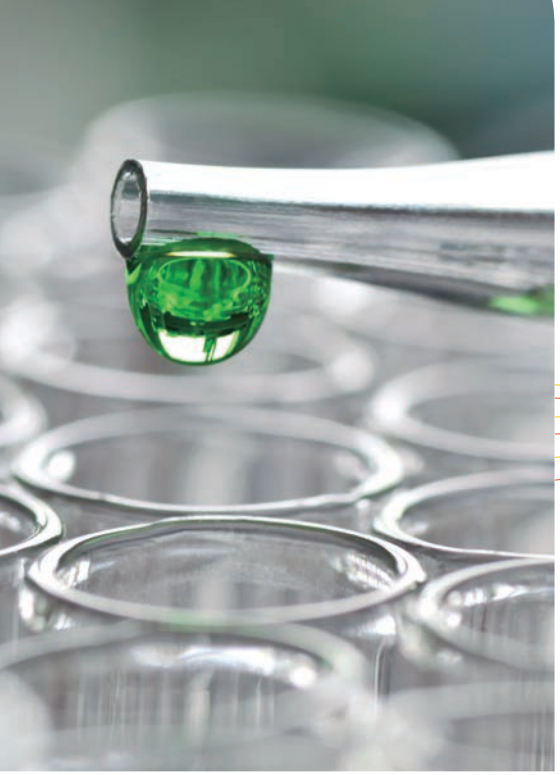
3 In 2010 The Spanish Statistical Office introduced a change in the methodology whereby the companies included in the data would no longer be taken from census data, instead some of the companies under study are selected by random sampling.

Figure 9. Innovative biotechnology companies that cooperated for innovation during the 2010-2014 period, by collaboration partner



2.

COMPANIES LAUNCHED IN 2015



2. Companies Launched in 2015

52 new biotechnology sector companies were launched in 2015. Table 3 shows the complete list as well as area of activity.

The following entities collaborated in the study: Bioga, Cluster Tecnolóxico Empresarial das Ciencias da Vida, el Centro Europeo de Empresas e Innovación del Principado de Asturias (CEEI), SODERCAN, el Parque Científico de Madrid, Biocat, SODENA, el Área de Planificación Sectorial de la Junta de Castilla y León, SPRI, BIOIB, BIOVAL, la Dirección General para la Innovación de la Consejería de Industria, Innovación y Empleo del Gobierno de La Rioja, el Instituto de Fomento Región de Murcia, CEEIM- Centro Europeo de Empresas e Innovación de Murcia, la Zona Especial Canaria (ZEC), la Oficina de Transparencia y Buen Gobierno de la Junta de Castilla la Mancha, la Fundación Parque Científico y Tecnológico de Castilla-La Mancha, la Dirección del Servicio de Innovación y Transferencia del Conocimiento de la Dirección General de Industria, Energía e Innovación del Gobierno de Navarra, CEIN - Centro Europeo de Empresas e Innovación de Navarra, Madrid+d and the Agencia IDEA.

Among the autonomous communities, Catalonia had the largest number of new companies (19), followed by the Basque Country (11), four new companies were launched in Andalusia and Galicia. Madrid witnessed the creation and launch of three companies.

Table 3. Biotechnology companies launched in 2015

Company name	Autonomous community	Activity
Abac Therapeutics	Catalonia	Therapeutic solutions for infected patients with highly antibiotic-resistant bacterial pathogens
Aelix Therapeutics	Catalonia	HIV research
Anaconda BioMed	Catalonia	The company is developing the next generation of catheters to perform mechanical thrombectomies safely and efficiently
Animalstemcare	Balearic Islands	Stem cell therapy for animals
Artax Biopharma	Catalonia	Designing and developing new drugs for the treatment of autoimmune diseases.
ASTURIAN BIOTECHNOLOGY	Asturias	Research, development and application of new reproductive technologies and molecular genetics aimed at livestock species
Atlas	Basque Country	Company based on a technological platform for drug discovery focused on rare diseases. They design Pharmacological chaperones (PCT) to correct misfolded mutant proteins
Betanzos HB	Galicia	Company dedicated to the assessment of by-products generated in wastewater evaporation plants. They obtain a 100% natural product made of concentrated wood fibre. This is used as raw material for the agrifood, pharmaceutical, cosmetic and chemical industries
BIOCHROM ESPAÑA	Andalusia	Cell culture sera and media manufacturer
BioCloud	Catalonia	Biological data analysis
Biofina Diagnostics	Madrid	Dedicated to the development of more efficient non-invasive diagnostics methods to improve the quality of life of patients, and to save time and money for doctors and health systems UROBEST® is a non-invasive method for the effective diagnosis and monitoring of bladder cancer based on Reverse Transcription Polymerase Chain Reaction (RT-qPCR) technology

Table 3. Biotechnology companies launched in 2015 (cont.)

Company name	Autonomous community	Activity
Biohope	Madrid	Development of diagnostic and therapeutic solutions for the immunological clinical management of kidney transplanted patients, with potential application to other immune-based diseases
BIOMEDICAL HEALTH SYSTEM	Basque Country	Development of a health system using wearables to detect and process medical parameters and develop diagnosed conclusions and scheduled health alarms
BIOQUOCHEM	Asturias	Development of kits for the measurement of antioxidant capacity in biological fluids
BMG LABORATORIOS SPAIN	Community of Valencia	Biomedical company specialised in providing early detection cancer services
Celtalga Extract	Galicia	Acquirement and commercialisation of natural extracts from Galician seaweed for the natural cosmetics, food and nutritional supplements industries
Charles River Laboratorios España	Castile-La Mancha	The company offers products and services to pharmaceutical and biotechnology companies, government agencies, and academic institutions around the world
CLOVER BIOANALYTICAL SOFTWARE	Andalusia	Bioinformatics company specialised in Bioanalytical Chemistry data analysis, Microbial ID and other clinical diagnostics applications using Mass Spectrometry (MS)
ENEO AGROALIMENTARIA	Castile-Leon	Perform analysis related to Food Security
Fastbase	Basque Country	Technological service in the field of microscopy imaging aimed at cancer diagnosis and a platform for the development of new biomarkers in early detection
Funds4Science	Catalonia	*Crowdfunding* platform specialised in life sciences
GEROA Diagnostics	Basque Country	Develops innovative products for the treatment and diagnosis of CNS diseases
Hearttrack	Catalonia	Electromechanical medical devices
Horus Pharma Ibérica	Basque Country	Development of new drugs and medical devices for ocular surface diseases based on new natural peptide compounds. The company will distribute the HORUS PHARMA pipeline product
IDP Discovery Pharma	Catalonia	IDP Pharma is a drug discovery company that develops first-in-class drugs, aiming at a new class of therapeutic targets, Intrinsically Unstructured Proteins (IUPs) / Intrinsically Disordered Proteins (IDPs) / Natively Unfolded Protein
Ikan Biotech	Navarre	Preclinical studies of new compounds using zebra fish model
IMMPULSO MEDICAL SCIENCES	Madrid	R&D Consulting in the field of Biomedicine and Biotechnology
INNOPLANT	Andalusia	Specialised services to overcome scientific and technological problems in the agricultural area
KARUNA Good Cells Technologies	Basque Country	Develop, manufacture and commercialise new molecular tools in the fields of Regenerative Medicine and Advanced Therapies
Larvamed	Catalonia	Development of sanitary bandages from Lucillia Sericata larvae for pressure ulcers chronic type and hard-to-head wounds, this product provides an effective, natural treatment which is less painful and sustainable
Lentimed Medical Devices	Galicia	Development, manufacture and commercialisation of new materials and specialised pharmaceutical products for the care of vision, human ocular health and applications in optometry. R&D on the development of new materials and drug delivery systems
Loop Therapeutics	Catalonia	Focused on developing products for the treatment of cornea diseases
mAbxience	Castile-Leon	Research, development and production of biosimilar medicines

Table 3. Biotechnology companies launched in 2015 (cont.)

Company name	Autonomous community	Activity
Made of Genes	Catalonia	Genome sequencing for personalised medical services
Molomics Biotech	Catalonia	Discovery of safer and better small molecule therapeutics with better efficacy by optimising ADME/Tox from the beginning of the discovery process
Nasasbiotech	Galicia	Development, manufacture and commercialisation of therapeutical solutions applied to oncological diseases and medical devices
Neural Therapies	Castile-Leon	Contract Research Organization (CRO) that performs assays addressed to test the neuroprotective effect of molecules against stroke. Services include in vivo and ex vivo assays in rat, gerbil and mouse
NUTEXA INGREDIENTS	Community of Valencia	Development, manufacture and commercialisation of ingredients. They are rich in bioactive compounds including, among others: carotenoids, phenolic compounds, flavonoids, fibres, prebiotics, proteins, vitamins
Peptomyc	Catalonia	Development of a new generation of Cell Penetrating Peptides (CPPs) targeting the Myc oncoprotein for cancer treatment
PHARMAMEL	Andalusia	Applications of *antiaging* melatonin
Procare Health	Catalonia	Clinical research and development of health products and medicines that provide innovative and effective solutions and are made from natural high-tech ingredients
PROSPERO BIOSCIENCES	Basque Country	Development of molecule detector based on a nanomembrane for use in mass spectrometer (MS) in order to identify particular molecules and disease biomarkers, even before the patient shows disease symptoms
QbD Pharmaceutical Services	Catalonia	The company delivers high added-value services and specialised outsourcing solutions to pharmaceutical and biopharmaceutical companies
REGENESIS	Basque Country	Regenerative medicine and tissue engineering. Production plant for collagen and growth factors
Scientific Projects	Madrid	Works in the fields of Neurobiology, Developmental Biology, Molecular and Cellular Biology and Biotechnology
STEMVITAL	Cantabria	The collection, cryopreservation and storage of cord blood stem cells, to allow for eventual future therapeutic application. It is focused on the treatment of established diseases when an autologous or allogeneic transplants are recommended
The Art of Discovery	Basque Country	Research and development of new drugs for cancer treatment and damage caused by ageing in human tissues. The company offers capture services and experimental data analysis of therapeutic efficacy based on pharmacokinetic - pharmacodynamic studies in humanised models for optimal design of clinical trials in humans
Tractivus	Catalonia	Bioactive surface technology with antibacterial properties to stop bacterial colonisation
Vegytech	Murcia	Plant improvement and biotechnology applications
VIVEbioTECH	Basque Country	Gene transfer technologies related to the production of viral vectors in GMP conditions and its application for gene therapy
Whole Genix	Catalonia	By using next-generation sequencing platforms (NGS) and real-time PCR genotyping, they generate and analyse genetic data (panels, transcriptome, exomes, genomes) with the most advanced bioinformatic techniques
ZIP Solutions	Catalonia	Zera® is a family of self-assembly peptides that can be fused to protein-recombinant peptide

LIFE13 ENV/ES/000445

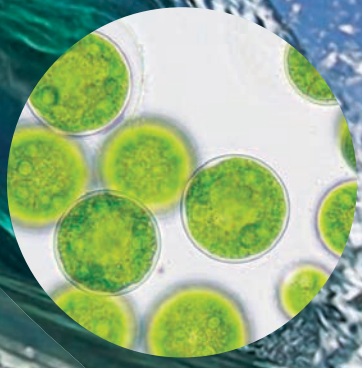
Sea Colors

Demonstration of new natural dyes from algae as substitution of synthetic dyes actually used by textile industries.

SEACOLORS main aim is the demonstration and validation of obtaining natural dyes from algae, a sustainable and renewable natural resource. The goal is to replace the synthetic dyes currently applied in the textile industry which are pollutant and harmful for the environment. Due to the higher biodegradability of natural dyes, a reduction in the water purification industrial process is expected.

SEACOLORS will require a validation on the types of micro and macro-algae with higher dyeing capacity and on the optimization of extraction processes. The investigation of the variables involved in the dyeing process in order to obtain dyed fabrics with acceptable quality parameters will also be carried out. This process is expected to be complex due to: 1) A huge variety of fibers in the market and the range of colors demanded by the fashion, and 2) the specific requirements colour fastness.

A semi-industrial scale test will validate the growth conditions of algae and the dyes' extraction in sufficient quantities before proceeding for a demonstration on the validity of dyes in a textile company industrial dyeing operation.
The project wants to produce dyes extracted from algae without generating waste so a study of the possible applications of the waste biomass generated after dye-extraction will also be carried out.



For further information:
AITEX Plaza Emilio Sala, 1
03801, Alcoy Alicante
Telf: 34 965 54 22 00
FAX: 34 965 54 34 94
emira@aitex.es - lmperez@aitex.es

www.seacolors.eu

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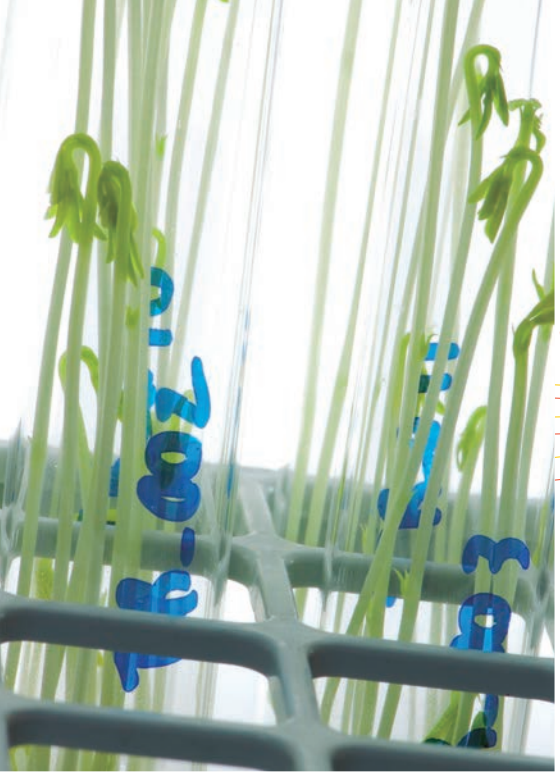
3.

BUSINESS ACTIVITIES



3. Business activities

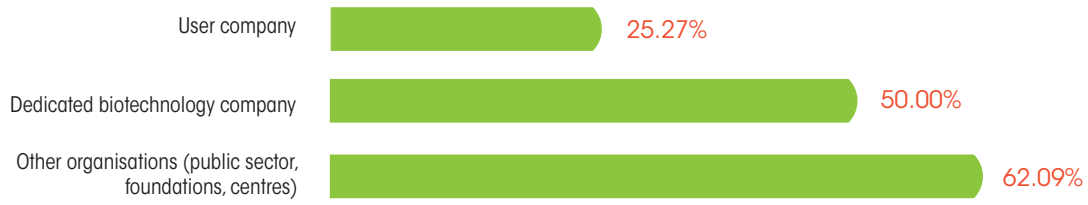
Alliances and business development

This section covers business development by members of ASEBIO. Specifically, it details alliances and/or collaborations such as co-marketing, co-development and product or market exchanges agreed during 2015 for biotechnology ends.

2014 saw a total of 182 new agreements. 50% of those (Figure 10) involved another biotechnology entity, 25.27% involved a user company and 62.09% involved a public sector body, foundation, or technology centre. Over 62% of these business agreements were between Spanish entities (Figure 11), 17.58% with European entities, 7.69% with US entities and 4.4% with Asian entities.

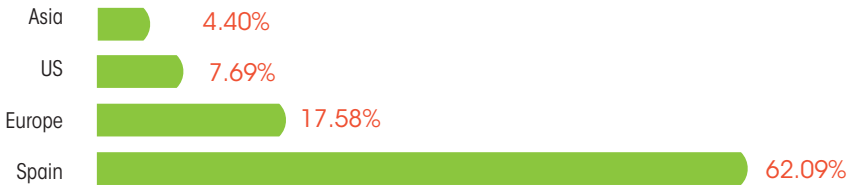
Figure 12 shows the main objectives of these collaborations. A total of 55% had objectives to do with clinical development or field trials, 33.52% had R&D objectives, 22.33% were marketing or distribution agreements, nearly 14% involved production and 8.24% were related to regulation or industrial protection.

Figure 10. Alliances in the Spanish biotechnology sector 2015 by profile of partner



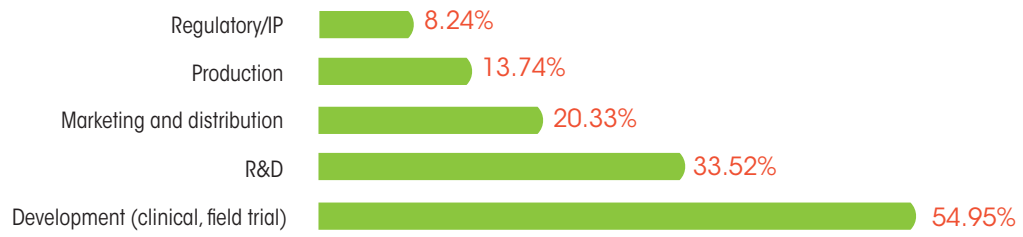
Source: ASEBIO.

Figure 11. Alliances in the Spanish biotechnology sector 2015 by global location of partner



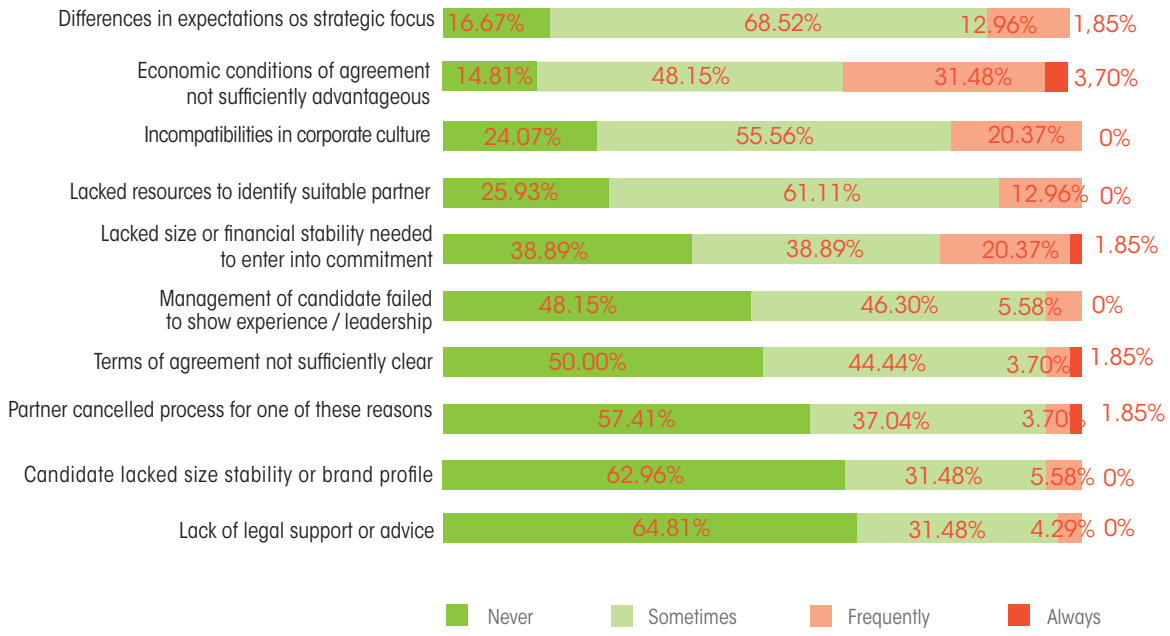
Source: ASEBIO.

Figure 12. Alliances in the Spanish biotechnology sector 2015 by objective of alliance



Fuente: ASEBIO.

Figure 13. Barriers to to forming alliances encountered by those taking part in survey



Source: ASEBIO.

Figure 13 shows the results of the survey on the barriers ASEBIO members have faced when forming alliances. It is the third year in a row that this survey has taken place. As in the two previous years, a lack of legal support or advice is not a determining factor in reaching alliances, as shown by the fact that 64% of respondents claim never to have faced such obstacle.

Insufficiently advantageous economic conditions was cited by companies as the main obstacle to agreements. 4% of respondents claim to always came up against this impediment, while a further 32% said that they had faced this problem frequently.

Another barrier which, according to the results, warrants further study is lack of size or financial stability. Nearly 40% of respondents claim to have come up against this obstacle sometimes, while 20% did so frequently.

Product launches

In 2015 a total of 98 products or services were launched to market by ASEBIO members.

Table 4 shows the complete list of products and services by name of the entity, product name and purpose, while Figure 14 shows how they are distributed.

Figure 14. Products and services launched to market by ASEBIO member in 2015

Source: ASEBIO.

Table 4. Products and services launched to market in 2015 by ASEBIO members

Entity	Product name and purpose
3P BIOPHARMACEUTICALS	Process based on cell free technology, which allows intracellular enzyme production through a continuous fermentation process with no cellular mechanism control
AbbVie	Humira: treatment for moderate and severe Hidradenitis Suppurativa (HS)
AbbVie	EXVIERA for hepatitis C virus (HCV)
AbbVie	VIEKIRAX for hepatitis C virus (HCV)
ALTERNATIVE GENE EXPRESSION	Technology to improve Baculovirus expression systems for recombinant protein production
Artinvet Innovative Therapies	Serviskin: is an artificial skin produced by tissue engineering techniques for epithelial regeneration of large lesions caused by traumas, burns or surgical wounds
Bayer Cropscience	Hispano F1, Salzillo F: two new varieties of toad skin melon
BIOGENETICS	GENOMID METABARCODING: Metabarcoding system for the identification of species and geographical origin (migratory species included (for example tuna) through microbiota footprint
Bioibérica	Goodogs® Light: tasty low-calorie snack for dogs made with high-quality natural ingredients
Bioibérica	ArthroSTEM®: Autologous cell therapy recommended in dogs, cats and horses with advanced osteoarthritis and as an adjuvant in the treatment of partial fractures or tearing of tendons and ligaments. The stem cells selected have enormous immunoregulating and regenerative capacity, they are able to go to the site of the injury, reduce inflammation and regenerative damage tissue
Bioibérica	Plantstress Management App: a mobile app for the management of plant stress. It provides personalised treatment recommendations for optimal stress management for each type of crop, season and location
Bioibérica	Calcium Heparin: Anticoagulant and antithrombotic drug
Bioibérica	Separan salfate: Interacts and regulates the activity of many essential proteins for pathological or physiological processes such as: growth and cell communication, inflammation, embryonic development, pathogens adherence/attachment and neurodegeneration

Table 4. Products and services launched to market in 2015 by ASEBIO members (cont.)

Entity	Product name and purpose
Bioibérica	AminoQuelant®-Cu: product designed to increase the assimilation of copper during the critical moments of greatest necessity, allowing faster and more efficient transport to new leaves and growth areas of the plant. Protects from oxidative stress. Rapid nutritional correction in cereal crops. Effective in the prevention of peacock-eye disease of the olive tree
Bioibérica	AminoQuelant®-Ca/Mg: formulated from amino acids derived from the process of enzymatic hydrolysis combined with calcium and magnesium, allows the plant to rapidly absorb these elements as well as their transport to the growth areas of the plant where they are needed
Bioibérica	Aquasorb®: product line for psoriasis and atopic dermatitis. It incorporates chondroitin sulphate, an innovative ingredient in dermatology, which is combined with sphingolipids, omega-3, hyaluronic acid, vitamins B7, B3 and B2. They have been scientifically proven to reduce inflammation and irritation, control itchiness and improve the hydration of the skin
Biomedal	iVYDAL in-vitro Diagnostics®: for diagnosis and monitoring of celiac disease
Bionos Biotech	New assay to determine protective capacity of a cosmetic product against oxidative stress under physiological conditions
Biosearch	Go-Functional®: Biosearch Life new unit offers a complete service for the development of functional foods
Canvax	Retroviral Packaging Vectors: ASSEMBLE 10A1 Retroviral Packaging Vector, ASSEMBLE Ecotropic Retroviral Packaging Vector and ASSEMBLE Amphotropic Retroviral Packaging Vector. These vectors are optimised for packaging cassettes contained in Retroviral transfer plasmid
Canvax	Retroviral Packaging Vectors: ASSEMBLE Lentiviral Packaging System is optimised for viral packaging of 3rd generation lentiviral transfer vector/ transfer plasmid, which can be used in obtaining cell lines or gene therapy
Canvax	Recombinant Proteins: more than 80 recombinant proteins
Canvax	CaxBeadsTM Magnetic Particles: include a wide range of 20 ferromagnetic particles coated with different reactive groups such as C18, C4, C8, DEAE, etc. CaxBeadsTM Magnetic Particles have been optimised for many applications such as bioseparation, purification of DNA/RNA and proteins or immobilisation of target molecules in R&D
Canvax	GPCR ORF Clones: more than 180 GPCR (G protein-coupled receptor) optimised expression vectors for transfection in cell lines of interest
Canvax	Dual Reporter Plasmids: reagents for R&D, available in non-viral, retroviral and lentiviral format for cell transfection control
Canvax	pColiExpress® Glue Enzyme kits: a highly efficient, versatile and fast protein expression of E.Coli/ a highly efficient, versatile and fast system of DNA cloning vectors for protein expression of E.Coli
Canvax	Antibiotics for R&D: Ampicillin Sodium salt, Chloramphenicol, Kanamycin Sulphate, Carbenicillin Disodium Salt, Tetracycline Hydrochloride, Gentamicin Sulphate, Neomycin sulfate, Puromycin dihydrochloride and Hygromycin B
Canvax	Bst DNA Polymerase (Exonuclease Minus): allows DNA sequencing through the problematic secondary structures
Canvax	MagBeadsTM Plant Genomic DNA Isolation Kit: provides an effective, easy and convenient technique to isolate high quality DNA from plants. The kit uses an advanced technology for extraction based on paramagnetic beads
Canvax	MagBeadsTM Yeast Genomic DNA Isolation Kit: provides an effective, easy and convenient technique to isolate high quality DNA from yeast. The kit uses an advanced technology for extraction based on paramagnetic beads
Canvax	MagBeadsTM Plasmid Purification Kit: provides an effective, easy and convenient technique to isolate high quality DNA from cells of bacteria. The kit uses an advanced technology for extraction based on paramagnetic beads
Canvax	MagBeadsTM PCR Clean-up: provides an effective, easy and convenient technique to purify DNA and remove contaminants from reaction mixtures (e.g. PCR or labelling reactions)

Table 4. Products and services launched to market in 2015 by ASEBIO members (cont.)

Entity	Product name and purpose
Canvax	MagBeadsTM Bacteria G (+) Genomic DNA Isolation: provides an effective, easy and convenient technique to isolate high quality DNA from gram positive bacteria. The kit uses an advanced technology for extraction based on paramagnetic beads
Canvax	MagBeadsTM Bacteria G (-) Genomic DNA Isolation: provides an effective, easy and convenient technique to isolate high quality DNA from gram negative bacteria. The kit uses an advanced technology for extraction based on paramagnetic beads
Canvax	SNP Taq DNA Polymerase: Hot Start - Polymerase for SNP detection by allele-specific PCR and micro sequencing
Diomune	Consulting and R&D services: animal models of inflammation, cancer, etc. Knockout mice models and genomics and proteomics services (for R&D)
DREAMgenics	DG Reports: Online visualisation device and genomic data management that allows the optimal selection of genomic variants that cause the disease under study
Ecocelta Galicia	Fulvic acids: organic amendment stimulating power of plant roots. They posses the ability to chelate other nutrients, increasing its bioavailability (by the plant)
Era 7 Bioinformatics	Immunogenomics. New services integrating: TCR repertoire seq, BCR repertoire seq and NGS HLA sequencing
Farmasierra Laboratorios	NUTROBAL PLUS: food supplement made of combination probiotic formula, to fight acute diarrhea, traveler´s diarrhea and antibiotic-associated diarrhea
Ferrer	EPICUP: the first epigenetic diagnostic test based on the analysis of DNA methylation profiles, it helps the oncologist to identify the primary tumor in patients with cancer of unknown origin (CUP)
Fundacion MEDINA	Cancer biomarker discovery device
GENOMICA	New diagnostic kits CLART: Enhancement in new and existing cancer products
GENZYME	LEMTRADA: humanised monoclonal antibody indicated for the intravenous treatment in first line of Relapsing-Remitting Multiple Sclerosis (RRMS)
Gradocell Marketing y Distribución	Kit for Platelet-Rich Plasma (PRP) preparation by automatic closed system. Automated and quick separation blood phases, obtaining a high concentrated PRP.
IMMUNOSTEP	F(ab´)2 Polyclonal Rabbit Anti-Human Kappa Light Chains conjugated with fluorescein isothiocyanate isomer 1 (FITC) / Polyclonal Rabbit Anti-Human Lambda Light Chains, conjugated with R-phycoerythrin (R-PE) for use in flow cytometry for simultaneous detection and enumeration of kappa light chains and lambda light chains. The evaluation of cell surface Kappa/Lambda expression can identify clonally restricted B lymphocyte populations and thus can aide in the diagnosis of hematologic malignancy. Several B cell disorders are associated with decreased levels of Kappa/Lambda at the cell surface
Ingenasa	INgezim FVR Compac is an immunoenzymatic assay based on a Blocking or Competitive ELISA technique to detect antibodies specific to Rift Valley Fever Virus (RVFV) in ruminant sera samples
Ingenasa	INgezim AIE CROM: is based on Direct Immunochromatography technique which uses a monoclonal antibody (MAb) specific to protein Rp26 of Equine Infectious Anemia Virus (EIAV) in equine samples
Ingeniatrics Tecnologias	Flow Blurring Metal (FBM) Nebulizer
Institute for Research in Biomedicine Barcelona (IRB Barcelona) with the collaboration of Barcelona SuperComputing Center (BSC) and laboratories in the US and UK	Online tool for the simulation of nucleic acids, providing information on mechanisms that underlie DNA regulation and contributing to improvements in the design of drugs that directly or indirectly target DNA. The tool has potential applications in fields ranging from biomedicine to bionanotechnology
IRYCIS	New patented method to identify good responders to Interferon beta (INF-beta) therapy in Multiple Sclerosis (MS) before treatment initiation
IRYCIS	Cryotherapy-Dermatology device: customised selection of diameter for application of therapy in cases of malignant skin lesions
IRYCIS	Biomarker identification platform based on miRNAs expression from minimally invasive sampling method as a diagnostic tool for different diseases

Table 4. Products and services launched to market in 2015 by ASEBIO members (cont.)

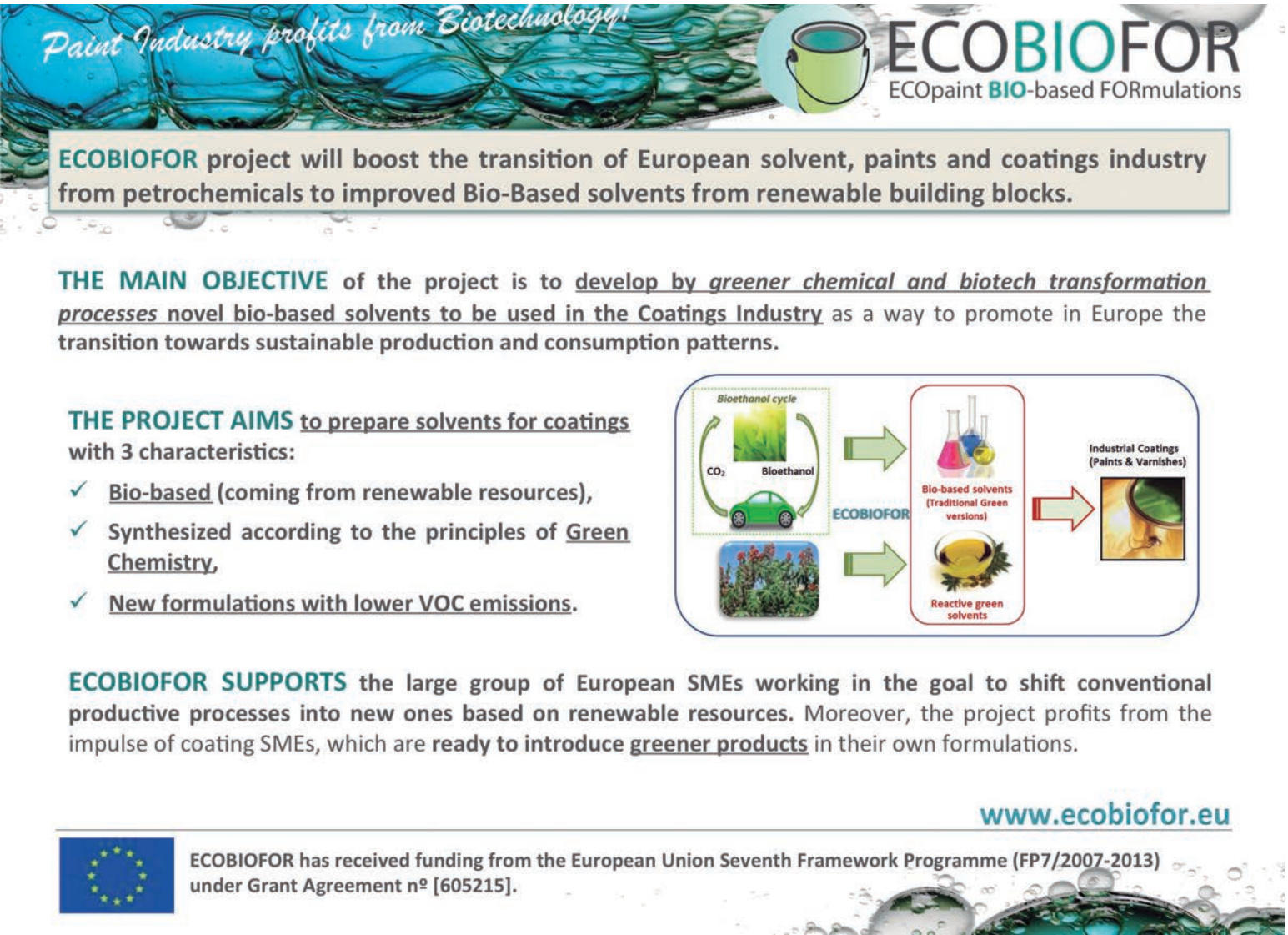
Entity	Product name and purpose
Laboratorios Rubió with the collaboration of Biosfer Teslab and the Pere Virgili Health Research Institute (IISPV)	Cardiovascular prediction test to work out the size and concentration of particles transported by LDL cholesterol
Life Length	Q-TRAP: measures telomerase activity in sera samples and cell cultures
Medinova Investigacion y Desarrollo	Development of medical research trials for pharmaceutical companies, biotechnology companies and Clinical Research Organizations (CROs)
Merck	RonaCare® SereneShield: strengthens the skin's defense system and helps prevent acne and skin redness
Merck	NeuroMerck: app that allows neurologist to stay up-to-date on demyelinating diseases
MSD	NOXAFIL 300 mg concentrate for solution for infusion is indicated for use in the treatment of the fungal infections and also for prophylaxis of invasive fungal infections
MSD	NOXAFIL 100 mg Gastro-resistant Tablets are indicated for use in the treatment of fungal infections and also for prophylaxis of invasive fungal infections
MSD	ATOZET 10 mg/80mg Film-coated Tablet for hypercholesterolaemia/ hypercholesterolemia
MSD	ATOZET 10 mg/40mg Film-coated Tablet for hypercholesterolaemia/ hypercholesterolemia
MSD	ATOZET 10 mg/20mg Film-coated Tablet for hypercholesterolaemia/ hypercholesterolemia
MSD	SIVEXTRO 200 mg powder for concentrate for solution for infusion for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults, also known as complicated skin and soft tissue infection (cSSTI)
MSD	KEYTRUDA® (pembrolizumab), 50 mg powder for concentrate for solution for infusion. Is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults
MSD	Sivextro (tedizolid fosfato) 200 mg Film-coated Tablet for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults, also known as complicated skin and soft tissue infection (cSSTI), first antibiotic administered once daily for 6 days
Myriad Genetics España	myHealth desk: online platform for the dissemination and knowledge of personalised medicine, specially in developments related to hereditary cancer
Nanomateriales y Polímeros	PolymBlend®: is a polymer blend which has been formulated with an optimum mixture of two high molecular weight static copolymers to produce materials with properties which are difficult to achieve with conventional polymers
Nanomateriales y Polímeros	Tiss®-Link: nonwoven nanofibre membrane made by electrospinning. It has a pre-actives surface (containing 3-atom spacer) for direct covalent immobilisation of biomolecules
Neiker-Tecnalia	Entzia: This new potato variety is characterised by a purple appearance and a high presence of antioxidant components, which gives it great nutritional value. It also has a considerable quantity of anthocyanins, a pigment with a great bioactive potential and beneficial effects for human health
Neiker-Tecnalia	Miren: This new potato variety performs very well during the cooking process, has a good flavour and a firm, smooth texture. Its concentration of carotenes is higher than that of the ordinary commercial varieties
NEOL BIOSOLUTIONS	Assessing of agricultural and industrial waste
Promega Biotech Ibérica	Maxwell® RSC ADN Whole Blood Kit: is used with the Maxwell® RSC Instrument to provide a simple method for efficient, automated purification of genomic DNA (gDNA) from 50-500µl of whole blood samples. The purified DNA can be used directly in a variety of downstream applications, including PCR and agarose gel
Promega Biotech Ibérica	UDP-Glo™ Glycosyltransferase Assay is a bioluminescent assay for detecting the activity of glycosyltransferases in many biological processes, including cell:cell interactions, cell signalling and bacterial cell wall biosynthesises
Promega Biotech Ibérica	6 x 5 LC-MS/MS Peptide Reference Mix: is a mixture of 30 peptides in a unique reagent designed to monitor liquid chromatography (LC), mass spectrometry (MS) instrument performance and assist in method development and optimisation

Table 4. Products and services launched to market in 2015 by ASEBIO members (cont.)

Entity	Product name and purpose
Promega Blotech Ibérica	GTPase-Glo™ Assay:assesses the activities of GTPases, GAPs and GEFs, which are components of the GTPase cycle
Promega Blotech Ibérica	Caspase-Glo® 1 Inflammasome Assay: is a homogeneous, bioluminescent method to selectively measure the activity of caspase-1, an essential component of the inflammasome
Promega Blotech Ibérica	The new BRET-based protein: protein interaction (PPI) assay uses NanoLuc® Luciferase as the BRET energy donor and HaloTag® protein, labelled with the NanoBRET™ 618 fluorophore, as the energy acceptor to measure the interaction of specific protein pairs. NanoBRET™ technology has been optimised for improved spectral overlap, increased signal, and lower background compared to conventional BRET assays
Promega Blotech Ibérica	The ADCC Reporter Bioassay is a bioluminescent reporter assay for quantifying biological activity on pathway activation by therapeutic antibody drugs in an ADCC mechanism of action (MOA) assay.
Promega Blotech Ibérica	Maxwell® RSC Circulating Cell Free Plasma, is used with the Maxwell® RSC Instrument to provide an automated purification of circulating cell-free DNA (ccfDNA) from human plasma samples. The instrument can process up to sixteen plasma samples in approximately 70 minutes, and the purified DNA can be used for the study of biomarkers in liquid biopsies
Promega Blotech Ibérica	NanoBit (‘NanoLuc Binary Technology’) is a structural complementation reporter designed for protein:protein interaction (PPI) studies in live and physiologically active cells. NanoBiT has two small subunits optimised for stability, low self-affinity and bright luminescence. If two proteins of interest are tagged with these subunits and then interact, the subunits come together to form an active enzyme. The proportional signal-to-activity and plate-based format make NanoBiT ideal for PPI studies, including high-throughput screening
Promega Blotech Ibérica	The Maxwell® RSC Plant DNA Kit is used with the Maxwell® RSC Instrument to provide an easy method for efficient, automated purification of genomic DNA (gDNA) from plant tissue samples. The Maxwell® RSC Instrument can process from 1 to 16 samples in under an hour, and the purified RNA can be used directly in a variety of downstream applications including RT-qPCR, gel electrophoresis, microarrays and Next Gen sequencing.
Promega Blotech Ibérica	Multimode Reader allows you to measure luminescence, fluorescence and absorbance in a simple configuration, through a touch tablet PC with more than 50 preloaded protocols. Very high sensitivity and wide dynamic ranges to facilitate interpretation of results.
qGenomics with the collaboration of IDIBAPS y el Hospital Clínic de Barcelona	Array qChip®Hemo: DNA chip or array to analyse the genome objective and provides a robust tool to determine genetic abnormalities in Chronic Lymphocytic Leukemia (CLL).
Sequentia Biotech	lncRNA pipe: This lncRNA pipeline mixes machine-learning techniques and analysis of sequence similarity to annotate lncRNAs in any genome or transcriptome of interest
Sequentia Biotech	Reconstructor: is an automatic in silico approach, which aims at the generation of a full genome sequence of an individual starting from the reference genome and resequencing data. Reconstructor pipeline is based on two main steps: Iterative read mapping and the novo assembly
Sequentia Biotech	SUPER-CAR: SUPER for Cancer Research is a novel pipeline focused on variant discovery and genotyping for cancer research
Sequentia Biotech	SUPER-MEN: SÚPER-MENdelian is a novel pipeline focused on variant discovery and genotyping of human Mendelian disease
Sistemas Genómicos	Preconception GeneProfile®: is a genetic test aimed at prospective parents to determine if they are carriers or not for certain hereditary diseases
Sistemas Genómicos	Epilepsy GeneProfile: With Epilepsy GeneProfile®, several pathologies can be studied such as early onset epileptic encephalopathy, frontal lobe nocturnal epilepsy, Unverricht-Lundbord disease, neonatal or childhood febrile seizures, generalised epilepsy with febrile seizures plus, Lafora type epilepsy, creatine deficiency, Ohtahara and Dravet syndrome as well as different syndromes associated with epilepsy. Epilepsy GeneProfile® also includes genes of metabolic response to the drugs used in the treatment of epilepsy
Sistemas Genómicos	BabyTest Plus: new screening test that permits the detection chromosomal abnormalities in the fetus from the 10th week of pregnancy

Table 4. Products and services launched to market in 2015 by ASEBIO members (cont.)

Entity	Product name and purpose
Sistemas Genómicos	DI GeneProfile®: contains a set of tests aimed at studying Intellectual Disability (ID) associated with different genetic diseases or as part of various syndromes through the analysis of 505 genes.
SYGNIS	kit TruePrime™ RCA : characterised by its extraordinary sensitivity, potential DNA amplification from small amounts (especially in the case of a single cell); as well as its ability to avoid external contamination at the time of amplifying DNA
SYGNIS	SunScript™ Reverse Transcriptase is the basis for a new line of Sygnis products based on the special features of in vitro evolution of human HIV-1 reverse transcriptase. All the futures makes SunScript™ Reverse Transcriptase the optimum enzyme for multiple applications to the study of the transcritome and gene expression analysis.
Universidad de Granada (UGR) with the collaboration of Laboratorio de Estudios Cristalográficos, Centro Pzifer-Junta de Andalucía-UGR de Genómica e Investigación Oncológica (GENyO)	Biocompatible and Biodegradable hydrogel for drug development
VIVEBIOTECH	Production of viral vectors deriving from Retrovirus (RV), Lentivirus (LV), Adeno-associated virus (AAV)
VIVEBIOTECH	Development of viral vectors and their gene therapy applications for clinical trials in humans
Vytrus Biotech	Plant Cell Biofactories™ (PCB): Technology platform that uses Totipotent cells, also known as Plant Stem Cells, as biofactories to produce highly innovative multi-asset ingredients



Strategic priorities

This section sets out the stated priorities of our members for 2016 and identifies how they have changed compared to the previous year.

As in recent years, internationalisation continues to be the biggest priority for ASEBIO members. Acquiring knowledge and / or technology, meanwhile, is now the second-highest priority for companies, increasing in importance by two points compared to the previous year. Acquiring other companies and reducing operations continue to be the lowest priorities in the biotech sector.

The priorities which have experienced the biggest changes are alliances with other biotechs and licensing in technology, both of which fell three places. Licensing out technology, on the other hand, rose three places.

table 5. Strategic priorities among Spanish biotechnology companies for 2016.

Position 2015	PRIORITY	Relevance 2016	Change from 2015	
1	Internationalisation	3.01	/=/	0
2	Acquiring knowledge and/or technology	2.71	▲	2
3	Launch of products to market	2.60	/=/	0
4	Entering into clinical phases/fiend trials/dose scaling	2.48	▲	2
5	Alliances with user companies	2.48	▼	-3
6	*Licensing out technology*	2.32	▲	3
7	Contracts or alliances with public institutions	2.21	/=/	0
8	Alliances with other biotechs	2.10	▼	-3
9	Expanding into other business areas	1.88	▼	-1
10	Refocusing product development	1.37	/=/	0
11	Hiring overseas professionals	1.34	▲	2
12	Refocusing R&D activities	1.25	/=/	0
13	Joint venture agreements	1.10	▲	1
14	*Licensing in technology*	1.03	▼	-3
15	Outsourcing production	0.92	/=/	0
16	Merging with another company	0.53	/=/	0
17	Reducing operations	0.47	▲	1
18	Acquiring another company	0.27	▼	-1

4.

INDUSTRIAL PROPERTY RIGHTS AND KNOWLEDGE GENERATION

4. Industrial property rights and knowledge generation

The data used for this Technology Watch Report was gathered using a method designed by Clarke, Modet & Co and Madrid Science Park following the OECD definitions for the biotechnology sector. This methodology has been specifically designed for this purpose and is continuously improved through the experience gained from studies on Industrial Property Rights conducted over the years.

The report has been compiled using data sourced from Thomson Reuters databases.

Other public databases used for data contrasting purposes include: the Spanish Trademark and Patent Office (SPTO), the European Patent Office (EPO), the United States Patent and Trademark Office (USPTO), Japan Patent Office (JPO) and the World Intellectual Property Organization (WIPO). All of them are open access and as statistics are based on patent publications, downloading the full documents referenced is also usually free of charge.

Patent applications published and patents granted

A total of 905 biotechnology sector patents were published in Spain during 2015 (results from search of published Spanish patents for bio sector, PCT, EP, US and JP, prioritising Spanish or Spanish agent and Spanish client), a small decrease of 7% compared to 2014, and a similar number to 2013, when 901 patents were published.

64% of patents published were patent applications and the remaining 36% were patents granted. Table 6 shows the breakdown according to the patent protection obtained (whether the patents are Spanish, European, US, Japanese, or international).

Figure 15 shows that the biggest proportion of published applications went through EPO and PCT, each accounting for 30% of the total, followed by applications to OEPM and USPTO. The distribution has remained practically the same since 2013.

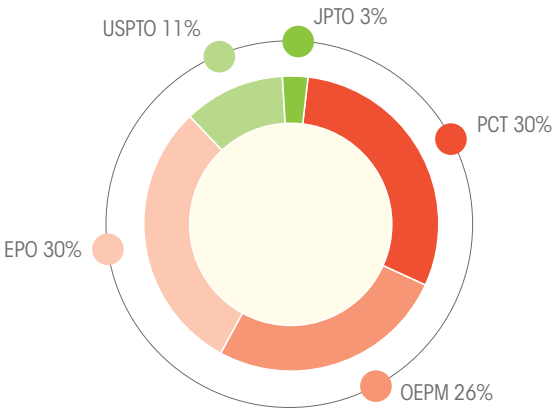
Figure 16 shows that the greatest proportion of patents granted was processed by the OEPM, with 57% of the total, the same percentage as the previous year. Compared to 2014, the number of US patents granted fell slightly, from 14% in 2014 to 13% in 2015.

Table 6. Patent applications and patents granted for Spanish biotechnology entities. 2015

Patents published 2015*	OEPM	EPO	USPTO	JPTO	PCT	TOTAL
Applications	148	176	64	17	174	579
Granted	186	79	38	23	(No aplica)	326
TOTAL	334	255	102	40	174	905

Source: Clarke, Modet & Cº- PCM.

Figure 16. Patent applications (2015)

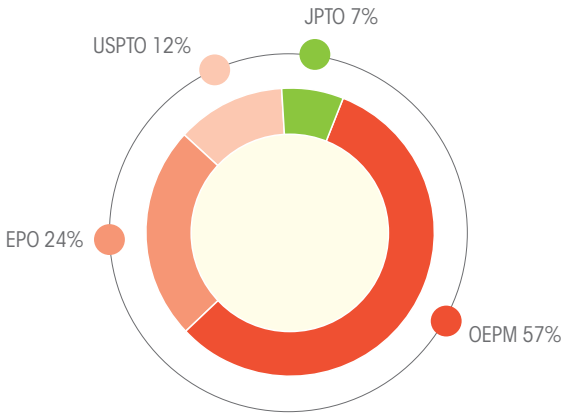


Source: Clarke, Modet & Cº- PCM.

Patent ownership in 2015

During 2015 the business sector ceased to be the biggest single agent in Spain, which it had been in 2014. Co-ownership became the main option, accounting for 33% of patents published, followed by the business sector (31%) and universities (21%). This trend in ownership is reflected both in the number of applications and patents granted (see Figure 17).

Figure 16. Patents granted (2015)



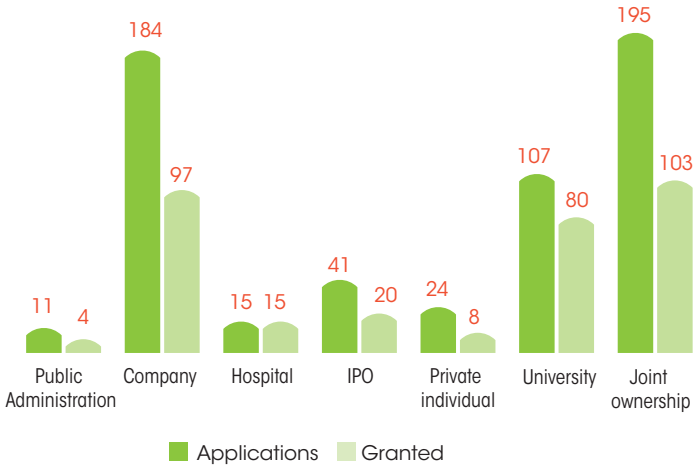
Source: Clarke, Modet & Cº- PCM.

Company patents in 2015

Over the course of 2015 a total of 152 biotechnology companies published patent applications or had patents granted, compared to 160 companies in 2014. These 152 companies published a total of 279 patents (11 less than in 2014).

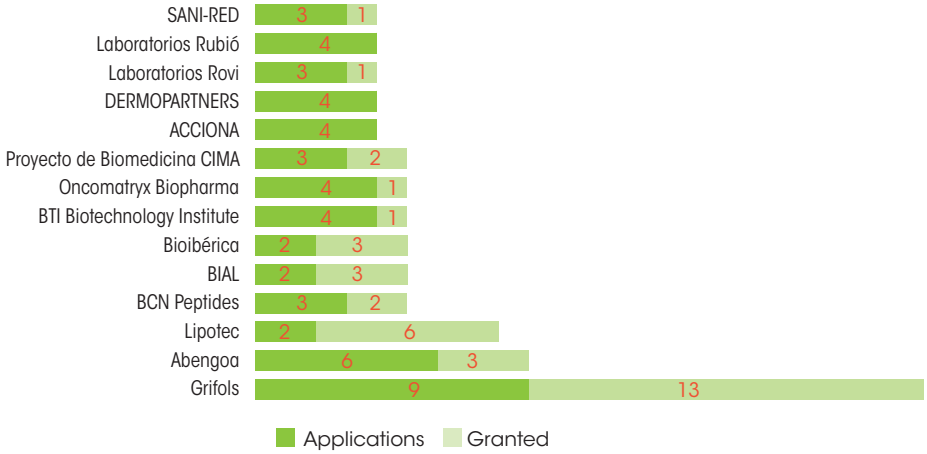
Grifols was the company that published the largest number of patents, followed by ABENGOA and Lipotec. This means that Grifols continues to head the raking (in 2014 it published 13 patents, in 2015 it published 22), ABENGOA has gone from publishing four parents in 2014 to nine in 2015, while Lipotec published 18 patents in 2014 and eight in 2015.

Figure 17. Ownership of patent applications and patents granted (2015)



Source: Clarke, Modet & Cº- PCM.

Figure 18. Companies filing patent applications and patents granted



Source: Clarke, Modet & Cº- PCM.

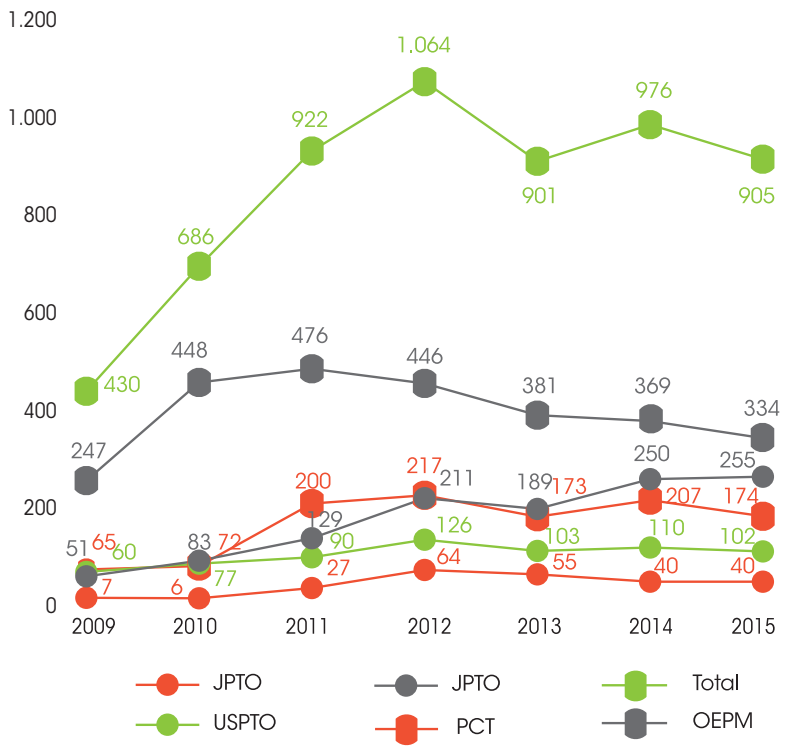
Industrial property in the Spanish biotechnology sector: 2009-2015

According to the data published over the last seven years, the number of patent publications in the biotechnology sector is clearly on an upward trend, with an increase of 110.47% during 2009-2015. This evolution reflects strong growth in the sector, while it also underscores the importance of industrial property in terms of recouping investments. Although growth did not match the 2009-2014 period, when it hit 126.98%. Compared to 2014 figures, the decrease was under 10%, both in terms of applications and patents granted. The upward trend seen the previous year was not sustained, probably due to the effect of the numbers seen in 2013, when the slowdown was particularly marked, specially in terms of applications.

The trend analysis shows the evolution of each application process over time.

Figure 19 tracks the evolution of biotechnology sector patents published in Spain, it shows the slight fall in the total number of publications in 2015 compared to 2014. The growth trends seen in 2014 have been reversed in all areas except in European patents, with the number of those patent publications having increased. This overall fall is clearly reflected in the fall seen in the number of OEPM patents published, which is partly balanced out by the rise in European patents.

Figure 19. Trends in published patent applications. 2009-2015



Source: Clarke, Modet & Cº- PCM.

Scientific output – biotechnology companies

Every year, ASEBIO carries out a study of publications in high impact journals by Spanish biotechnology companies and international research laboratories based in Spain that are members of ASEBIO.

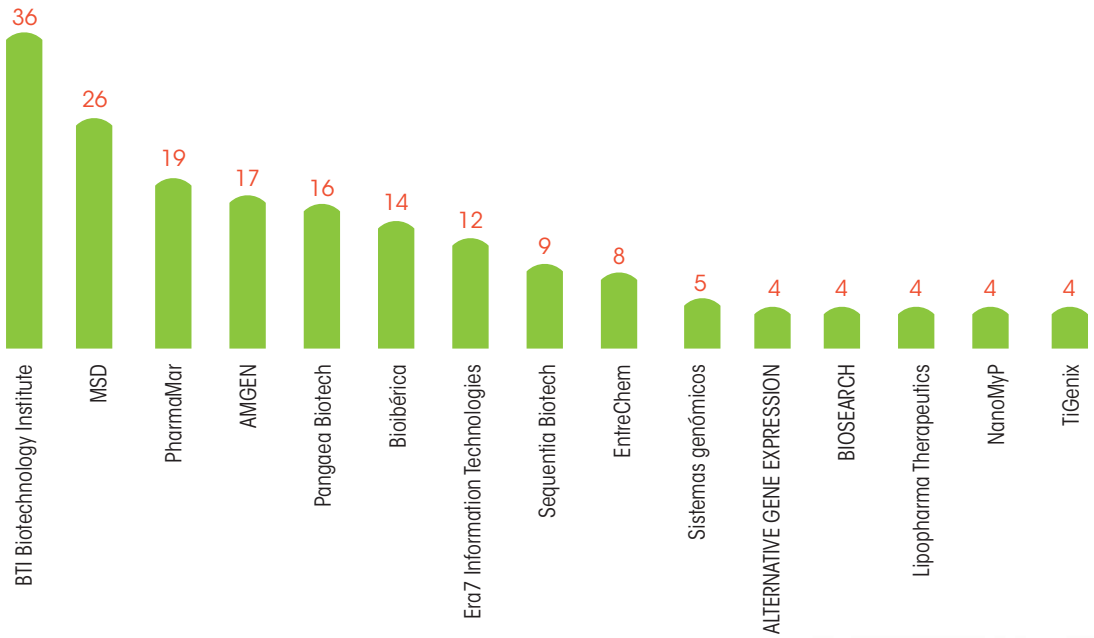
The study does not include press releases, conference posters, poster presentations, or publications by research centres or universities without links to studies for business projects.

During 2015 a total of 32 biotechnology companies published 205 scientific papers. Compared to the previous years (215 publications by 44 companies) it means a 4% drop in publications. Despite this decrease in the total number, companies have been more active, as 12 less companies have still managed to publish over 200 publications.

The companies with the most publications (Figure 20) are BTI Biotechnology Institute with 36 papers and MSD at 26 publications. They are followed by Pharmamar with 19 publications, AMGEN with 17, Pangea Biotech at 16, Bioibérica with 14 and Era7, which published 12 papers.

Although not officially part of this analysis due to not being companies, it is worth noting that the Institut Químic de Sarriá (IQS) published 27 papers while the Fundación MEDINA published 15 papers.

Figure 20. Number of scientific publications by ASEBIO member companies in 2015



Source: ASEBIO.

5.

HEALTH – RED BIOTECHNOLOGY

5. Health – red biotechnology

Spanish biotechnology has demonstrated its global competitiveness over the past year. Significant transactions involving large international pharmaceutical companies and specialised funds have recently been announced. This demonstrates that Spanish biotechnology is on a par with that of other countries in terms of the science developed.

New products and services developed through biotechnology have opened up great opportunities in therapeutic areas such as oncology and immunology, but also in other less prevalent areas and for diseases that until now have have been incurable. The coming developments and challenges for Spanish companies will demonstrate that biotechnology is able to carry on innovating, and to do so, we must reaffirm our commitment to the therapeutic value of innovation, not only in terms of costs and ensuring that R&D policies are not limited to funding, but also that they must be linked to the development innovation systems such as collaboration networks.

ASEBIO also believes that patients should be present at all stages of the innovation process. We must explore how far we can go to detect potential drugs and the impact they may have on health services. Clearly, we must provide early access to medicines while maintaining patient safety as a priority and also work on the long term funding of innovation.

Molecular diagnosis and personalised medicine

In Spain there is a disparity in the processes of the different autonomous communities and a lack of transparency in the criteria of access to the market of in vitro diagnostic tests (IVD), which hampers dynamism in the Spanish market and delays patient access to them. As a result, the Personalised Medicine and Advanced Diagnostics working Group at ASEBIO, with the coordination of Insights in Life Sciences (ILS) presented the White Book: "The current situation of market access for in vitro diagnostic tests in Spain" which is part of the strategy of ASEBIO to facilitate market access for innovative products and services and shows that there are significant differences in the process of market access for in vitro diagnosis tests in Spain compared to France and the UK.

Over the last year, our members have developed new products and services. We will detail some of them here:

SYGNIS launched TruePrime™ RCA kit, a product that uses a novel multiple displacement amplification method to amplify single or double-stranded circular DNA molecules through rolling circle amplification (RCA). The company also began to sell a new line of products under the name SunScript Reverse Transcriptase™, a novel, engineered reverse transcriptase (RT) with RNA and DNA-dependent polymerase activity. **SYGNIS** announced a non-exclusive worldwide license agreement for Double Switch technology with Thermo Fisher Scientific. **SYGNIS** AG granted Thermo Fisher non-exclusive global rights to develop and commercialise products and services for the detection and analysis of protein interactions in vivo based on its proprietary Double Switch technology to researchers working in the field of proteomics.

Neuron Bio has registered a patent for the diagnosis of Alzheimer's disease. It is based on the identification of a range of biomarkers, permitting reliable diagnosis of Alzheimer's in patients and anticipation to the progress of the disease before clinical symptoms such as dementia appear, thus improving the efficacy of current methods. It will allow the identification of suitable individuals to participate in trials, reducing costs and evaluating its effect evolution of the disease, thus increasing the probability of success for new treatments.

Sistemas Genómicos, meanwhile, which in 2015 was awarded the CE mark for all of its diagnostic kits, presented Babytest Plus, the first Non-Invasive Prenatal Diagnosis (NIPD) screening test that permits the detection of chromosomal abnormalities in the foetus from the tenth week of pregnancy. The company also launched Preconception GeneProfile®, a genetic blood analysis for prospective parents to determine whether they are carriers of certain hereditary diseases. They also presented DI GeneProfile®, the best test in the market for the diagnosis of Intellectual Disability (ID), associated with different genetic diseases.

In 2015 the liquid biopsy in metastatic colorectal cancer was released. VHIO was the first centre of excellence to incorporate this technique, which can determine the RAS biomarkers (KRAS and NRAS) via liquid biopsy in patients with metastatic colorectal cancer. This was the result of an agreement with **Merck, SL,** and Sysmex Inostics.

AB-Biotics began the trial of the pharmacogenetic test Neurofarmagen®, which helps identify the most appropriate medication for each neuropsychiatric patient, with 18 Spanish hospitals. The company also announced a new license agreement of the product with CompanionDx Reference Lab, LLC for exclusive distribution and sale in the US. In addition, in 2015 AB-Biotics reached agreement for the promotion and distribution of their products in China, Israel, the Middle East, Australia and New Zealand.

BIOMEDAL and LABCO launched a test to evaluate the effectiveness of gluten-free diets (GFD) to identify cases of accidental ingestion of gluten or detect when the patient is not properly following a diet outlined by a specialist.

Myriad Genetics Spain launched myHealth desk, an online platform for the dissemination and knowledge of personalized medicine and particularly of developments related to hereditary cancer. Made up of leading institutions in oncology, it seeks to position itself as the most advanced platform for genetic counselling in the country.

Laboratorios Rubió and Biosfer Teslab created a cardiovascular prediction test, a pioneering product in Europe, to calculate the size and concentration of particles transported by LDL cholesterol.

Ferrer, the pharmaceutical company, announced the launch of EPICUP, the first epigenetic diagnostic test based on the analysis of DNA methylation profiles, it assists oncologists in the identification of the primary tumor in patients with cancer of unknown origin (CUP). this tool offers a high degree of accuracy, making EPICUP a good complement to the diagnostic methods currently used.

Pangaea Biotech and LABCO launched a non-invasive test capable of detecting genetic material in blood in lung cancer patients. The test allows oncologists to monitor treatment response in real time and, when necessary, switch drugs.

Developing therapies for human health

Oncology

It was a historic milestone in Spanish biotechnology: **Roche**, the Swiss multinational and one of the world leaders in the pharmaceutical sector, paid 15 million euros to **Oryzon** for the rights to its ORY1001 molecule, which has great potential in the treatment of a type of leukemia. If clinical trials in human patients with ORY1001 are successful, Roche could pay **Oryzon** 400 million euros. The agreement has given the Spanish company enough financial muscle to accelerate development and its goal is to become a leading international company in epigenetic medicine and the development of biological therapeutic solutions in the oncology field and for neurodegenerative diseases. **Oryzon** has opened a subsidiary in Boston (US) and its goal is to attract new investors for listing in the NASDAQ index. In addition to the patent issued to Roche, the company has 16 more molecules in development.

Palobiofarma reached an agreement for the transfer of rights to its PBF-509 drug for the treatment of lung cancer to the Swiss company Novartis. The transaction, valued at 13 million euros is a new sign of the amount of activity in the industry. The European Commission authorised the use of VECTIBIX® (PANITUMUMAB) by Amgen, as first-line treatment in association with FOLFIRI chemotherapy in adults with metastatic colorectal cancer (mCRC) with non-mutated RAS (wild-type).

IRB Barcelona developed a computational tool, DSysMap (Disease-mutations Systemic Mapping) that allows a greater understanding of the genetic causes of complex diseases such as cancer, Alzheimer's and diabetes.

The Spanish National Cancer Research Centre (CNIO) was at the forefront, as it so often is, of developments in the fight against cancer. Researchers from the **CNIO** have discovered a new strategy to fight cancer. The scientists blocked the shelterin protein TRF1 in cancer cells, disrupting telomere protection and preventing immortal proliferation of cancer cells. TRF1 removal induces an acute telomere uncapping, which results in cellular senescence or cell death. They have seen that this strategy kills cancer cells efficiently, stops tumor growth and has bearable toxic effects.

In 2015 **Roche** succeeded in bringing Gazyvaro® to Spain, after the new drug designed to combat chronic lymphocytic leukemia (CLL) received funding authorisation from the Ministry of Health. Patients receiving the drug have a 61% reduction in the risk of progression or death compared to the current standard treatment.

The Medina Foundation presented a natural agent to suppress PI3K pathway, which plays a key role in cancer metabolism, either by contributing to cell cycle progression, or reducing apoptosis and increasing metastatic capabilities of cancer cells.

Celgene, showed that Lenalidomide, registered under the name Revlimid, can improve progression-free survival by 8.7 months, compared with 5.2 months of therapy chosen by the specialist, in patients with mantle cell lymphoma in relapse or refractory (LCM), as shown by the study "MCL-002" (SPRINT), which is in phase II, multicenter, randomized and open. In addition, **Celgene** announced the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the EMA on the extension of indication of subcutaneous azacitidine (Vidaza) for the treatment of patients over 65 with acute myeloid leukemia (AML) that are not candidates for hematopoietic stem cells.

The European Community approved KEYTRUDA® (pembrolizumab), an anti-PD-1 therapy by **MSD** for the treatment of unresectable or metastatic advanced melanoma in adults. This is one of the first treatments of a new generation of immunotherapies,

which works by blocking the PD-1 pathway. This approval, which allows commercialisation in the 28 member states of the European Union, is based on data from three clinical trials in more than 1,500 patients with advanced melanoma, both as first-line treatment and for patients who have previously undergone treatment. This product was also designated as a "major therapeutic advance" by the FDA for the treatment of advanced colorectal cancer.

In June 2015, **PharmaMar** announced the start of a phase III study for the anticancer agent PM1183 (CORAIL) in patients with platinum-resistant ovarian cancer (PROC). The pivotal study is a randomized, open-label, and international multicenter trial designed to evaluate the activity and safety of PM1183 compared with investigator's choice of topotecan or pegylated liposomal doxorubicin (PLD) in patients with PROC.

YONDELIS® (trabectedin) has been approved in 2015 by the US Food and Drug Administration (US FDA) and by the Japanese authorities for soft tissue sarcoma (STB). Under license agreements, Janssen Products holds the rights to develop YONDELIS® (trabectedin) in the US and rest of the world except for Japan, where Taiho Pharmaceutical has the rights to develop and commercialize the drug, and Europe where **PharmaMar** develops and markets YONDELIS® (trabectedin).

FinaBiotech, and EMD Millipore Corporation (USA) signed a non-exclusive license for a hybridoma developed by **FinaBiotech** which secretes an antibody that binds to an antigen, the ß-F1-ATPase protein, which is involved in cell metabolic activity.

Merck announced that the Committee for Orphan Medicinal Products (COMP) of the EMA gave a positive opinion for the designation of avelumab, anti-PDL1 monoclonal antibody as an orphan drug in Merkel metastatic cell carcinoma (MCC), a rare and aggressive type of skin cancer.

Autoimmune and inflammatory diseases

The following **CIBER** integrated projects of excellence are funded by the **ISCIII**: the identification of novel modulators of chronic inflammation in prevalent diseases, a multidisciplinary approach for understanding obesity, metabolic syndrome type 2 diabetes and fatty liver diseases, and the molecular links between diabetes and neurodegenerative disorders. These projects are funded with two million euros in the National Sub-Programme for Knowledge Generation of the Strategic Action in Health (AES).

Spherium Biomed started a clinical trial to evaluate the efficacy and safety of SP13004 in the prevention and treatment of oral mucositis associated with chemoradiation in head and neck cancer.

In 2015 **TiGenix** began the process of authorization from the EMA for the commercialisation of Cx601 for Crohn's disease, indicated for the treatment of complex perianal fistulas in patients with this condition. During the same year the primary target in its pivotal phase III trial of Cx601 was achieved.

Infectious diseases

In 2015 **MSD** prepared three new launches in order to expand the antimicrobial arsenal with the deployment of Sivextro, designed for the treatment of ABSSSI infections caused by methicillin-resistant staphylococcus aureus (MRSA), followed by Zervaxa (another antibiotic) and Keytruda (a monoclonal antibody for metastatic melanoma).

The "SEPCELL" project led by **TiGenix** was awarded 5.4 million euros from the H2020 program to perform the Phase Ib / IIa trial of Cx611 as an add-on therapy to the standard of care in patients with severe sepsis.

Nervous system diseases

"NeuroM" (**Merck Spain**) was launched in 2015, it is an app that allows neurologists to stay up-to-date on demyelinating diseases such as multiple sclerosis. The aim of the app is to provide valuable content and resources for Neurologists, such as access to scientific journals, news, opinion and relevant training in the area of demyelinating diseases.

The Japanese Patent Office (JPO) granted **Neuron Bio** the patent for "Neuroprotective, hypocholesterolemic and antiepileptic compound", which protects the NST0037 molecule as a product and in its use for the prevention and treatment of various diseases of the Central Nervous System, among them Alzheimer's disease. **Neuron Bio** also patented two new molecules in Spain: NST0076 and NST0078. These two compounds penetrate into the brain with high efficiency to avoid neuronal death. In 2015, **Neuron Bio** was granted an epilepsy patent in the US, where it opened a subsidiary based in Boston. The patented compound is derived from simvastatin, which offers improved effects in the treatment and prevention of epilepsy and seizures.

A new compound of animal origin, isolated from the porcine brain and completely developed by **Bioiberica**, has achieved positive results in slowing down the progression of Alzheimer's in seven animal studies. The compound is PRJ212, which has a novel mechanism of action based on neuroprotection that could prevent memory loss in patients at the mild stage.

Oryzon, listed on the continuous market, received approval for its Clinical Trial Application from the Spanish Drug Agency (AEMPS) to initiate a Phase I clinical trial for ORY-2001 for the treatment of Alzheimer's disease. ORY-2001 is Oryzon's second molecule that will move to clinical development. Ory-1001, its previous molecule, is still in testing with acute leukemia patients.

Ferrer initiated the Phase II clinical trial of Lorediplon in patients with primary insomnia. **Ferrer** successfully completed a clinical trial with Lorediplon that demonstrated dose related clinical benefits in measured sleep

parameters that were either comparable to or exceeded zolpidem in terms of the maintenance and quality of sleep that subjects achieved.

nLife Therapeutics successfully performed one study with efficacy in an alpha-synuclein overexpression model of Parkinson's disease (PD) with elderly monkeys.

Almirall presented new clinical evidence confirming the effectiveness, safety and tolerability of Sativex in patients with spasticity symptoms in Multiple Sclerosis (MS). Sativex ® is the only prescription medication indicated as complementary therapy to treat symptoms of moderate to severe spasticity that do not respond to other antispasmodic treatments.

Rare Diseases

The Government of Spain approved a Royal Decree for the creation of a State Register of Rare Diseases, which establishes the basic regulation and proper coordination of the records and information systems of Autonomous Communities. This tool makes it possible to maintain a census of patients, know the incidence and prevalence of Rare Disease and guide health planning and management of these diseases. Also in 2015, CIBERER, part of the ISCIII, launched "MAPER", an interactive map that aims to provide reliable and up-to-date information on all research projects on rare diseases developed in Spain.

Alexion Pharmaceuticals announced that the European Medicines Agency's Committee for Medicinal Products for Human Use (EMA/CHMP) adopted a positive opinion, recommending the granting of a commercialisation authorisation for Strensiq (asfotasa alpha) and Kanuma (sebelipasa alpha). The proposed indication for Strensiq is for a long-term enzyme replacement therapy in patients with pediatric-onset hypophosphatasia (HPP) to treat bone manifestations of the disease. The proposed indication for Kanuma is for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase deficiency (LAL-d).

InKemia launched its second spinoff called Myogem Health Company, S.L. (Myogem), aimed at the development, manufacture and commercialisation of products aimed at improving the health of people affected especially by rare diseases. Joint research by IQS, the University of Valencia and IUCT allowed Myogen to license active compounds against myotonic dystrophy.

SOM Biotech and the Vall d'Hebron Research Institute (VHIR), successfully completed the phase IIa proof-of-concept trial in humans to evaluate the efficacy and safety of an innovative oral therapy for transthyretin amyloidosis (ATTR), a rare disease that affects the peripheral nervous system and heart.

The team from the Centre for Biological Research at **CSIC**, part of **CIBERER**, obtained orphan drug designation by the EMA for bazedoxifene acetate, currently used in osteoporosis, for use in hereditary hemorrhagic telangiectasia (HHT), a rare disease that causes bleeding that impairs the quality of life of patients.

Ability Pharmaceuticals Received a positive opinion from EMA for Orphan Drug Status of ABTL0812 in Pediatric Cancer Neuroblastoma. ABTL0812 is finalising its first phase I / Ib clinical trial orally in patients with advanced solid tumors.

After obtaining the approval of the AEMPS, **Sanifit** began a clinical trial phase Ib / IIa, double-blind, randomised, placebo-controlled study to evaluate the safety, pharmacokinetics and pharmacodynamics of SNF472 in dialysis patients. SNF472 is an experimental drug for the treatment of calciphylaxis and cardiovascular disease in patients with dialysis, it works by blocking the progression of cardiovascular calcification in this population with renal failure.

BCN Health conducted a market access study for orphan drug status for the treatment of Cerebrotendinous xanthomatosis, a rare metabolic disease with a prevalence of 4 / 100,000.

Advanced Therapies

The European Patent Office granted European Patent EP2292736 to **TiGenix** for stem cells compounds derived from adipose tissue. The patent, named "Identification and isolation of multipotent cells derived from non-osteochondral mesenchymal tissue" covers stocks specified expanded multipotent cells derived from adipose tissue and its therapeutic uses, such as pharmacological compounds derived from these cells. **TiGenix** also obtained a patent in the US for the use of stromal cells derived from adipose tissue in the treatment of fistulas. For this purpose, it was associated with Lonza as their CMO for the supply of Cx601 in the phase III trial in the US. TiGenix also announced that it had completed enrolment for its phase I / II clinical trial in acute myocardial infarction (CAREMI study).

3P Biopharmaceuticals announced that it had made a drug cell therapy based on allogeneic cardiac stem cells (AlloCSC-01) for Coretherapix. The safety and efficacy of this cellular drug is currently being studied in the first human clinical trial for early treatment (one week) of acute myocardial infarction. This clinical trial is being conducted by Coretherapix with the participation of six Spanish and European hospitals.

Ferrer and **Histocell** presented preclinical results of NeuroSave (FAB117-HC), a new advanced therapy for traumatic spinal cord injury. The drug, made from a type of adult stem cells specially designed to promote the recovery of spinal cord injury (HC016 cells) showed positive results when administered in the acute phase directly in the injured/damaged area spinal cord.

Histocell, meanwhile, obtained a patent in the US for its HC016 cellular therapy product, obtained from adult stem cells from adipose tissue and allogeneic origin. The product is

manufactured following a proprietary protocol of **Histocell**. The technology used helps to enhance the resistance / strength and survival of these cells in cytotoxic environments, improving anti-inflammatory properties as well as protective and tissue regenerative properties.

Bioinformatics

In 2015, the **IRB Barcelona** succeeded in developing a theoretical methodology to better understand the behaviour of biomacromolecules and, in particular, nucleic acids, in a wide spatiotemporal scale, focused on biomedical and bionanotecnologics applications. In 2015 the institute was commissioned to coordinate the European H2020 project in bioinformatics, worth three million euros, to bring order to the emerging field of three-dimensional genomics through the "Multi-scale genomics complex" project.

Era7 Bioinformatics increased its portfolio of services incorporating a line of Immunogenomics. The services included in this new line are: TCR repertoire seq, BCR repertoire seq and NGS HLA sequencing.

Dermatology

Almirall presented a study on the prevalence of actinic keratosis (AKs) in Spain. It aims to estimate the rate of standardised prevalence of actinic keratosis in outpatient population aged ≥45 years in Spain, treated in hospital dermatology services or requiring consultation.

Bioiberica launched AQUASORB® a line of products for atopic dermatitis and psoriasis, the formula incorporates an innovative ingredient in dermatology called chondroitin sulfate, which also binds sphingolipids, omega-3, hyaluronic acid and vitamins B7, B3 and B2, which have been scientifically shown to reduce inflammation and irritation, provide itching control and improve skin hydration.

Cosmetics

Navarre **Bionanoplus** company participated as a partner in the European project "SKHINCAPS" (SKin by Innovative Healthcare NanoCAPsuleS), funded by the H2020 with the goal of developing high value-added products in the dermocosmetic field. Bionanoplus will be responsible for nano encapsulating the different actives using its innovative patented technology, which permits the industrial production of nanoparticles both easily and safely.

Ingeniatrics obtained a new patent in the US in the field of cosmetics, titled "Nozzle insert device and methods for dispensing head atomizer", it is a patent based on the new Flow Blurring technology related to nozzle devices and methods for creating atomized sprays and more particularly to modular nozzle insert devices for use in dispensing head atomizers on liquid product containers.

Bionos Biotech launched an assay to determine the protective capacity of a final product or ingredient against oxidative stress under physiological conditions. **Bionos** has developed a new technique to determine the antioxidant activity capacity of a cosmetic product or ingredient through quantification of cellular metabolites involved in the antioxidant protection system in a quick, rigorous and economic manner.

Vytrus Biotech was granted a new patent for innovative activity: broad spectrum protection against solar radiation (UV/VIS/IR). This new activity protects dermal fibroblasts from oxidative stress induced by solar radiation and infrared radiation and protects the increase of levels of MMP-1 induced by the infrared radiation.

Merck presented new ingredients to protect skin from threats that may damage it, such as the secretion of sebum, pollution, ultraviolet radiation (UV), exposure to toxic substances and air conditioning.

Vaccines

Sanofi Pasteur MSD reported that the Gardasil 9® vaccine, nine-valent HPV vaccine, had received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the EMA. The company also announced that the results of tests to establish the framework had stablished the safety, immunogenicity and effectiveness of the current quadrivalent vaccine and future nine-valent vaccine for the prevention of HPV.

CNB-CSIC researchers in Madrid developed a safe and effective vaccine against severe acute respiratory syndrome or SARS, a severe and potentially fatal disease, which was first detected in China in 2002 after an outbreak that caused about 800 deaths. The new version solves the safety problems of the previous prototype and continues to provide full protection against the disease in mice tests.

Others

The Spanish company **mAbxience**, which opened a plant in Leon, announced they were investigating six biosimilars during 2015.

The National Health System included in the reimbursement the drug Prolia® (denosumab) by **Amgen**, indicated for treatment to increase bone mass in men with osteoporosis at high risk of fracture. The repayment of this new indication is a step forward to address an almost unknown disease in men that produces complications that lead to reduced of quality of life and high economic and social costs.

Bionaturis announced it will open a subsidiary in the Chinese region of Jiangsu after signing a strategic agreement with the Administrative Committee of Industrial Development for High Technology, in order to develop and distribute their products in the Asian market.

2015 witnessed the expansion of the **Merck** biotechnology plant in Tres Cantos, with an investment of 15 million euros and an increase in staff of 20%, with which it aims to increase its production capacity by 50% and improve energy efficiency.

6.

AGRIFOOD - GREEN BIOTECHNOLOGY

6. Agrifood - green biotechnology

Functional foods

AB-Biotics and the multinational pharmaceutical company Sanofi reached an agreement through which **Sanofi** launched AB-Kolicare, a probiotic developed by AB Biotics. This probiotic is indicated for baby colics and through two different strains of probiotics it reduced average crying by 67.5 percent after 14 days of treatment.

The **CSIC** presented studies on rats of a wheat variety which is genetically engineered to silence the expression of the gliadin proteins that affect people with celiac disease. Once this first phase concludes the testing in humans will begin, in collaboration with the Reina Sofía Hospital.

The "Primicia" project started, with the support of CDTI and led by the company Tutti Pasta. Others participating in the project include Natacy and the **IMDEA Institute**. The objective is to bring products to market that are effective in controlling chronic inflammatory diseases through nutrigenomics.

"Smartfoods", another project financed by CDTI, is coordinated by Laboratorios Ordesa and in also involves the company **Biopolis** and the **CSIC**, among others. It will aim to make smart food combining several bioactive ingredients with different functionalities to simultaneously act against a larger number of targets involved in one pathology. The project will be investigated in the areas of probiotics, prebiotics, bioactive peptides and structured lipids, in addition to in vitro studies, in vivo animal models and clinical trials using various omics sciences.

According to an interventional nutrition study conducted by **Bioiberica** in collaboration with the Technological Centre of Nutrition and Health at the University Rovira i Virgili, Reus, consuming milk fortified with Mobilee®, Bioiberica's functional ingredient for joints, improves knee strength. Mobilee® is a patented ingredient, rich in hyaluronic acid, polysaccharides and collagen approved as Novel Food by the European Commission and the GRAS status in the US.

Biosearch Life ended the POSTBIO project "New applications of probiotic strains and derived compounds with biological activity". The company worked on the development of new probiotic products with functional and innovative technological features that allow its use in cancer diagnosis, minerals or cardiovascular health supplements. Biosearch Life also presented the results of its study on its probiotic strain Lactobacillus fermentum CECT5716 to reduce breast pain in women during lactation. These problems have been linked to an imbalance in the natural microbiota in breast milk in which for a number of different factors certain bacterial groups begin to proliferate, with potential pathogens such as staphylococci.

While working on the "Neofood" project it is participating in, **Neiker**-Tecnalia successfully identified and isolated a collection of microalgae species belonging to the Thraustochytrids family, which have large amounts of lipids and docosahexaenoic acid (DHA). DHA influences visual and neurological development and ingesting it helps to prevent degenerative health problems.

IMDEA Institute announced its collaboration with the SFC-SQM Madrid Association to conduct a clinical trial in patients with Chronic Fatigue Syndrome (CFS) and Multiple Chemical Sensitivity syndrome (MCS). The trial is to develop a line of research to advance the understanding of the molecular mechanisms of these diseases, and how to utilise personalised nutrition as a therapeutic complement.

The Health Research Institute at La Fe University Hospital and Polytechnic coordinates an ambitious international project, "Innovative Approach for Self-Management and Social Welfare of Cystic Fibrosis Patients in Europe: Development, Validation and Implementation of a Telematics Tool-MyCyFAPP Project", to customise the treatment of cystic fibrosis (CF), based on the development of an application for mobile devices that allows the self-adjusting of medication in accordance with specific diets on any given day.

Biomedal launched the in-vitro iVYDAL Diagnostics® brand to serve the human diagnostics market, working on a series of innovative products for the diagnosis and monitoring of celiac disease. The main product is iVYLISA GIP (marketed by LABCO Quality Diagnostics as Gluten Detect), a test to detect traces of gluten in dregs which allows detection of gluten for a gluten-free diet (GFD).

Animal health

VetGENOMICS launched a pilot test for the identification of dog excrement through DNA analysis and the SNP (Single Nucleotide Polymorphism) technique. The project, called "caniD" identifies which animal the excrements come from and at the same time provides information on the possibility of the animal having parasites, which poses a risk to both the animal and the health of citizens.

AZTI with **Biopolis** researchers, among others, coordinates the LIFE "Enviphage" European project to identify bacteriophages to control pathogenic microorganisms in fish farms without affecting communities in aquaculture bacteria's and intestinal environment.

Bioiberica reached a strategic alliance with Centauri, the Galician biotechnology company, which specialises in advanced stem cell therapies for animal health, to launch a cellular therapy service aimed primarily for dogs, horses and cats with osteoarthritis. The therapy involves removing abdominal fat cells from the animal, which Centauri expands and then reapplies to the animal to regenerate their tissues. As raw materials **Bioiberica** used: porcine intestinal mucosa, pig and cattle cartilage, cockscomb and shellfish chitin.

ArtinVet announced it will develop an injectable hydrogel to be applied for the regeneration of bone and joint in pet injuries. It is also expected that it will launch ServiSkin, an artificial skin to treat dogs with very large wounds that works by regenerating the skin of the animal.

The Technological Corporation of Andalusia (CTA) will contribute to the financing of the "Bovihealth" project, an initiative in which the **Bionaturis** COVAP Group is participating. The Bovihealth initiative aims the development peptides to be used as health and growth promoter in cattle, to reduce the use of traditional antibiotics in this type of livestock.

Bionaturis also announced the addition of six new biotech drugs/ molecules to its product portfolio. Five are aimed at the veterinary sector and more specifically high incidence livestock and pet diseases, such as atopic dermatitis, osteoarthritis (or osteoarthritis) and various types of cancer.

Diomune designed a novel and effective alternative to current treatments for canine Leishmaniasis, an auto vaccine that enhances the immune response of the animal, improving its clinical outcome, reducing the severity of clinical signs, and eventually allowing it to recover quality of life. It is an immunomodulatory treatment, prepared from a sample from the dog in question. Once Leishmania is inactivated, the autovaccine is prepared using antigen processing techniques to obtain a set of epitopes that will increase Th1 type response. The treatment involves a primary immunisation and a prime-boost vaccine 15 days after immunisation.

Environment

Kimitec Group, which owns **Agrocode Bioscience**, participates in the "Bloster" project for biopescide production from the valorisation of endemic plants and organic waste from food industries.

NEIKER announced that it would be joining the 4 per 1000 international project, a French initiative to guarantee food production and combat climate change. The aim of this initiative is to get more carbon-rich soils, for which it proposes to increase annually by 4 per 1,000 carbon stored in forest and agricultural soils. Thus, soil fertility will increase and, consequently, agricultural production will also go up.

Agriculture

The Biotech company **Sequentia** announced the launch of a Green Non-coding Database (GreeNC). It is a repository of Long non-coding RNAs (lncRNAs). lncRNAs are functional non-translated molecules longer than 200 nucleotides with diverse roles, recorded in 37 species of plants and six algae.

The same company, **Sequentia Biotech**, announced that together with the Department of Agricultural Sciences of the University of Naples Federico II, they had succeeded in sequencing a new variety of wild potato, native to South America, Solanum commersonii, with great adaptability to harsh environments and resistance to pathogens and pests.

Researchers at the Institute of Subtropical and Mediterranean Horticulture La Mayora (joint centre of the University of Malaga and the **CSIC**) and the Andalusian Institute of Research and Agricultural and Fisheries Training (IFAPA) managed to increase the vitamin C content of tomatoes by 15% using a strawberry gene. To this end, they selected the strawberry gene involved in the production of ascorbic acid and which produced D-galacturotano reductase protein.

Eurosemillas announced its participation in the genomics research project "Citruseq- Citrusgen". The project objective is to develop genomic and biotechnological tools to facilitate the generation and selection of new lines and varieties of citrus. Eurosemillas is evaluating 6,000 genotypes generated in this project. For the analysis of the main parameters of fruit quality, such as acidity, sugar content, flavonoids, essential oils, etc., they are using NIRS (Near Infrared Reflectance Spectroscopy).

Neiker-Tecnalia, conducted a study of the genetic structure of Phytophthora infestans, which causes potato mildew, and for the first time in Spain identified the existence of the genotype Blue13 (13_A2). The identification was carried out through genotyping with microsatellite markers (SSR). Blue13 Phytophthora infestans is the most aggressive genotype currently present in Europe and has been detected in potato fields in the provinces of Alava, Orense and Tenerife.

Neiker also created two new potato varieties of high nutritional value. The first, Entzia is characterised by a high presence of antioxidant components and a large quantity of anthocyanin pigment. It shows a bioactive potential and great beneficial effects for human health. It also has a high concentration of iron, zinc, potassium and magnesium. The second variety, Miren, has a concentration of carotenes which is higher than that found in the usual commercial varieties.

Bayer CropScience presented the first melon toad skin varieties obtained from their native improvement program at at the Experimental Station La Palma in Cartagena (Murcia). These new varieties, Salzillo Hispano F1 and F1, are adapted specifically to the production areas of Murcia and incorporate resistance to powdery mildew, the most endemic disease in the area.

As for GMO crops and according to the International Service for the Acquisition of Agri-biotech Applications (ISAAA), in 2015 Spain cultivated 107,749 hectares of Bt maize, which represents an increase of 18% compared to that registered in 2014 (131,538 hectares). This puts Spain in the 17th position worldwide in number of hectares of GMO crops.

According to estimates of the Ministry of Agriculture, Food and Environment (MAGRAMA), the total area of GMO varieties grown in Spain in 2015 has reached 107,749.24 ha. which includes varieties registered in the catalogue of the EU and APC (Interim Marketing Authorization) of Spain. By region, Aragon remains the region with the highest number of cultivated hectares 42,611.76 ha. followed by Catalonia (30,790.41 ha.) and Andalusia (1470.59 ha.).

7.

INDUSTRIAL / WHITE BIOTECHNOLOGY

7. Industrial / white biotechnology

Biotechnology applications for energy production

The US Patent and Trademark Office informed Inkemia IUCT of the granting of the patent "Process for manufacturing biofuels", which will be valid until 2033. The second generation Hydrotreated Vegetable Oil (HVO) can be obtained from waste glycerin produced in conventional biodiesel plants. It is listed as an advanced biodiesel and according to European Regulations, by 2020, it will be obligatory to mix up to 7% of this type of biodiesel with current petrol diesel.

Neol Bio, a subsidiary of Neuron Bio, patented a method for converting agricultural waste oils for industrial use. This is a patent for the production of oils from agricultural residues, such as wheat straw and sugarcane bagasse, based on the use of the microorganism Neoleum®. Oils obtained using this technology will serve as the basis of biofuels and other bioproducts through sustainable processes and using organic waste as raw material not involved in the food chain.

The TECNALIA-VTT, which collaborates in the "AERTOS Biobased Economy" project involving eight major European technology centres, presented the results of the valuation of a type of lignin, characterised by its high cellulose content. The lignin used in this bioprocess is characterised by containing a concentration of around 50% cellulose and is obtained from lignocellulosic materials by enzymatic hydrolysis, monosaccharides required for production by fermentation of second generation bioethanol.

The ITAKA initiative (Initiative Towards sustAinable Kerosene for Aviation), in which SENASA participates, the **Camelina Company** Spain and Compañía Logística de Hidrocarburos is aimed at the use of sustainable camelina crops as raw material to develop a new biofuel. The biofuel developed by ITAKA has already been successfully tested in twenty flights Amsterdam-Aruba by the Dutch company KLM and by Iberia in a Madrid-Barcelona flight. The budget is 19 million euros.

Abengoa was selected by Fulcrum Bioenergy to build the first biorefinery that uses gasification technology to convert municipal solid waste (MSW) into synthetic crude, which will be transformed into fuel for aviation. Thirteen projects by five biotech companies associated with ASEBIO were selected in the first phase of innovative public procurement tenders-for value of 3.7 million euro project.

"CLAMBER" (Castilla La Mancha Region Bioeconomy) is an initiative of the Junta de Castilla La Mancha in collaboration with ASEBIO and co-funded by the European Commission through Feder funds. In addition, the Government of Castile-La Mancha approved the process to build the biorefinery that will host the "clamber" project in Puertollano (Ciudad Real), for which a budget of 700,000 euros was made available.

The main objective of CLAMBER is to position the Castile-La Mancha region among the European leaders in the bioeconomy or industrial biotechnology, which seeks to obtain bioproducts as an alternative to petroleum-based products (plastics, fuels, lubricants, dyes ...) frm renewable and sustainable sources (new crops and waste vegetable or animal origin).

CLAMBER, with a total budget of 20 million euros, is being deployed in two major actions: 1) The implementation at the petrochemical complex of Puertollano of a demonstrator biorefinery plant that can be used by research groups and companies for scaling industrial bioprocesses and 2) funding for research projects in this field related to the impact of agricultural and industrial sectors which form the basis of the economy of the region. The projects of these five biotechs (**Camelina Company Spain, Biopolis, Neol Biosolutions, Natac** and Zurko Research) address various areas, all aimed at developing new bioindustries in Castile-La Mancha that will generate high value added products from various waste residues: bioplastics from whey (a residue from the Manchego cheese industry); Omega 3 for food, cosmetic or pharmaceutical use from wheat straw; various pharmaceutical components using waste products from the wine and oil industries; biofertilizers from livestock waste and other biobased products (fuels, lubricants, solvents etc.) by transforming various agricultural and industrial waste. Another project will explore the possibility of harvesting camelina, an oil plant, for the production of aviation fuel and other industrial uses.

In December 2015 the Government approved a Royal Decree to promote the use of

biofuels with the overall objective of by 2020 making up 20% of total energy energy consumption, while 10% of the fuels used in the transport industry must come from renewable sources. At this meeting it was reported that in 2014, the percentage of renewable energies used in Spain was 17.4%. The Royal Decree also stablishes minimum biofuel use for transport, which gradually rises from 4.3% in 2016 to 8.5% in 2020, for instance in 2017 it is 5%, then 6% in 2018 and 7% in 2019. There are minimum yearly targets for the sale or consumption of biofuels. In addition, for the calculation of the 2020 target, the use of first-generation biofuels is limited to 7%, while the Government must establish, by 2017, an indicative target for advanced biofuels.

According to the Study of Macroeconomic Impact of Renewable Energy in Spain of the Association of Renewable Energy (APPA), in 2014 the total contribution to GDP of the biodiesel and bioethanol sectors was 417.7 million euros, of which 309.7 million were of direct contribution and 108.0 million of induced contribution. The total contribution to GDP has increased in real terms by 40.1% compared to the previous year, representing a change in the downward trend observed in the previous three years. This same study indicates that the consumption of biofuels in Spain in 2014- 1.169.978 tons, including biodiesel, bioethanol and Hydrotreated Vegetable Oil (HVO), contributed to reducing emissions of greenhouse gases (GHGs) in transport and prevented equivalent of more than 1.7 million tons of CO2 emissions into the atmosphere.

Biopolymers and bioplastics

According to a report by the Institute for Bioplastics and Biocomposites of the University of Applied Sciences and Arts of Hannover, data collected in cooperation with IFBB (Institute for Bioplastics and Biocomposites) and Nova-Institute, the global production capacity of bioplastics will increase from 1.7 million tonnes in 2014 to about 7.8 million in 2019. By sector of application, packaging remains the largest consumer of bioplastics with almost 70% of the total market for bioplastics. This study also indicates that within five years 80% of bioplastics will be produced in Asia and Europe will be left with less than 5% of production capacity.

NanoMyP company launched PolymBlend®, a polymer blend formulated with an optimum mixture of two high molecular weight statistic copolymers to produce materials with properties which are difficult to achieve with conventional polymers. In addition, it can be used for the formulation and preparation of polymeric films using other techniques (spin coating, knife coating, curtain coating, etc.) as well as for the preparation of thin coatings, porous membranes and other products.

Researchers from the **CSIC** and the University of Malaga have created a biodegradable plastic from tomato skin which can be used as an alternative to packaging made from petroleum. The viscoelastic, waterproof and protective properties against fluid loss and parasite attack, makes it especially useful for producing plastics.

Bioprocesses and other bioproducts

Inkemia IUCT group and **Biochemize** participate in the European "CARBAZYMES" project which aims to open the door to the development of biocatalytic routes for the synthesis of bulk chemicals and APIs in high demand and thus pioneer environmentally friendly processes for much needed products which are particularly relevant for Europe's sustainable future and competitive ability in the global industry.

In addition, **Inkemia** obtained the US patent "Compositions for degreasing metal surfaces" that protects new solvents obtained from (non-fossil), renewable raw materials for use in several applications such as degreasing metal, widely applied in industries such as the automotive, aerospace, metal tools, industrial machinery and other metal industries.

During 2015 **Neol Bio** filed three patents, all based on the use of genetically improved variants of the Neoleum® microorganism; the first consisted of a new method of production for fatty alcohols, which uses residual raw matirials not in competition with human nutrition, consumes less energy, is more efficient and produces less pollution. The second patent involved a new method of producing an oil with a high oleic acid content, and the third consisted of a new production method of very long chain fatty acids (arachidic, erucic, gondoic and nervonic) having a wide industrial use in cosmetics, lubricants and as additives for plastics.

Vytrus Biotech announced the launch the Plant Cell Biofactories™ (PCB) Technology Platform, which uses the technology of plant stem cells as biofactoriesto generate highly innovative multiactive ingredients. Since plant stem cells contain a large quantity of proactive essential substances (amino acids, lipids, carbohydrates, vitamins) that perform in a synergic way along with the derma-cosmetic active principles of interest, contributing to improved effectiveness of the product.

GAIKER-IK4 co-leads the European "NANOREG" project intended to investigate the application of REACH legislation to nanomaterials and develop a methodology to identify, evaluate and manage the risk involved in using nanomaterials and thereby prevent potential risks to the operator, consumer and environment during the life-cycle of this type of materials. **GAIKER** will coordinate the work package of in vitro toxicity to investigate whether existing methodologies can be adapted to the toxicological assessment of nanomaterials.

8.

FINANCIAL ENVIRONMENT

8. Financial environment

Sanifit, the biopharmaceutical company specialised in treatments for calcification disorders, was the subject of the biggest financial operation in the Spanish biotechnology sector, raising 36.6 million euros in a financing round led by Ysios Capital with the participation of the pharma investment funds, Lundbeckfond Ventures and Baxter Ventures. This capital expansion also included La Caixa, Forbion Capital Partners, Gilde Healthcare, Edmond de Rothschild Investment Partners, además de business angels.

The figure from the acquisition of Alkahest by **Grifols** was just short of that number, at 33.5 million euros. That operation means Grifols now owns 45% of the US company. Grifols will also provide 11.2 million euros to finance the development of plasma products while Alkahest will receive milestone payments and royalties from sales by Grifols.

TiGenix was involved in a number of high profile opeations over the course of 2015. First, a capital injection by Grifols, the parent company, for a total of 25 million euros in convertible bonds. Later in the year another round of capital expansion involving several investros raised 8.2 million euros.

In July 2015 **TiGenix** acquired 100% of Coretherapix capital for 18.6 million euros; an upfront payment of 1.2 million euros in cash, 6.1 million in **TiGenix** shares and 11.3 in future payments linked to milestones in product development and royalties on net sales and other amounts from other products in the Coretherapix pipeline that are brought to market.

Finally, towards the end of 2015 TiGenix filed for an IPO for to be listed on US NASDAQ stock market index.

Minoryx Therapeutics completed a Series A funding round of 19.4 million euros. **Ysios Capital** led the round, which was also supported by **Caixa Capital Risc** and international investors including Kurma Partners, Roche Venture Fund, Idinvest Partners, Chiesi Ventures and Health Equity.

Following the 2014 agreement between Roche and **Oryzon**, which included milestone payments, **Oryzon** received 3.5 million euros upon finishing the multiple ascending dose (MAD) Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of ORY-1001 in patients with relapsed or refractory acute leukemia.

Before listing on the Spanish stock exchange, **Oryzon** also raised 16.5 million euros in a capital expansion round through the sale of 4.9 million new shares at 3.39 euros per share. This operation means new shareholders now include the CEO of US company Active Motiff and the Institut Català de Finances (ICF).

Its listing on the Spanish stock exchange was coordinated by Solventis AV, taking place on the 14 December 2015. Founders Carlos Buesa and Tamara Maes agreed to a twelve-month lock up on their shares.

Palobiofarma signed a 13-million-euro licensing agreement, giving Novartis the exclusive global rights to develop, manufacture and market the product known as PBF-509.

Plant Response Biotech identifies and develops new molecules and genes regulating plant responses to biotic and abiotic stresses. The agrobiotechnology company raised 5.7 million euros in a financing round led by Monsanto Growth Ventures, the venture capital group at **Monsanto** Company. The operation also involved La Caixa, Middleland Capital and Novozymes.

Towards the end of the year, **Sygnis** announced the completion of a cash capital increase which raised 5.6 million euros. A total of 2,962,552 shares were placed with existing shareholders in a rights issue, as well as with new investors in a subsequent private placement.

Histocell, which specilaises in regenerative medicine and cell therapy, concluded a capital increase in 2015 which raised 2.5 million euros. The operation included the participation of Histocell's major shareholders, including Orza AIE, Geroa and Elkarkidetza, Capital Risk Management, based in the Basque Country and the IMQ Group. Other investors included BI fund of Seed Capital Bizkaia and private investors. The round of financing was aimed at placing Reoxcare, an advanced wound dressing with antioxidant properties for the treatment of hard-to-heal skin wounds, on the international market.

The 2015 completion of the merger between Natraceutical and **Reig Jofre**, which included the issuing of new shares by Reig Jofre, led to the creation of Spain's fifth biggest laboratory.

2015 also saw the completion of the reverse merger between Zeltia and PharmaMar, in

which the oncology division PharmaMar absorbed its parent company Zeltia, which was then rebranded PharmaMar.

After the merger was concluded a share swap took place of one **PharmaMar** share for each Zeltia share. The new company announced an expected IPO on the US NASDAQ index for the end of 2016.

In October 2015, Neol Bio, a division of **Neuron Bio**, was listed on the MAB, becoming the fifth biotech company to start trading on the index. GVC GAESCO acted as Registered Adviser and carried out a 1.55 million capital increase prior to the listing.

Almirall reached an agreement to acquire 100% of Poli Group Holding, the holding company of Poli Group, which is made up of three operating companies (Taurus Pharma GmbH, Polichem S.A. and Polichem S.r.l). Poli group nhas a portfolio of 16 proprietary drugs, with a focus on dermatology but which also includes gynaecology and respiratory products.

Venture Capital

Columbus Venture Partners, a venture capital fund specialised in biotechnology, was founded in September 2015. Its senior investment team is made up of professionals from the healthcare industry, venture capital, pharma and biotech sectors. In April 2016 the company launched Columbus Innvierte Life Science FCR fund, within the framework of the INNVIERTE programme run by the Centre for the Development of Industrial Technology (CDTI). The objective of the fund was to raise 50 million euros for investment in biotechnology sector companies.

In March of 2016, **Caixa Capital Risc** announced the launch of Caixa Innvierte Start FCR, a new 20-million-euro fund designed to finance innovative companies in their early stages of development with cash injections totalling from 500.000 euros up to two millon euros. This fund was also created in the framework of the INNVIERTE programme by the Centre for the Development of Industrial Technology (CDTI).

Caixa Capital Risc was one of the most active investors in 2015, having participated in 19 operations with bio companies, commiting around 17.8 million euros. These included the capital increases for **Sanifit** and two for **Minoryx Therapeutics**, Aelix, **PlantResponse Biotech**, **Inbiomotion**, Transplant Biomedicals and Biótica.

Inveready, for it's part, participated in capital increases for InnoUp Farma, Ediagnostic, Zera Intein Protein Solutions, Agrasys, Oncostellae, Cuantum Medical Cosmetics and Oncovision.

It it also worth noting that **Ysios Capital** participated in three operations for **Sanifit**, **Minoryx Therapeutics**, and Aelix, committing investments worth a total of 12.9 million euros.

In November 2015 the CDTI, through the INNVIERTE programme, announced the allocation of 90 million euros to finance the creation and launch of new technology companies emerging from the research area. A contribution of 38.5 million euros by the INNVIERTE programme was announced in March 2016, with the rest to be provided by other investors, including Caixa Innvierte Start FCR and Columbus Innvierte Life Science FCR.
In July 2015 the CDTI also initiated the process of finding investors for a new private equity fund with the objective of supporting Spanish mid-cap companies in the biotechnology, biohealth and food sectors, among others. In April 2016, the CDTI announced the activation of the 400-million-euro fund, to which it contributed 100 million through the INNIVIERTE programme, while the remaining 300 came from national and international private investors, the European Investment Bank and the European Investment Fund. Investments by the fund, known as the N+1 Private Equity Fund III, range from 35 to 75 million euros and will support growth and internationalisation processes of high potential Spanish SMEs and mid-cap companies with technological and industrial capabilities.

In 2014 **Iproteos** became the first Spanish company to use crowdfunding to acquire funds to develop a drug for cognitive impairment. During 2015 some biotech companies have made use of the same strategy to obtain alternative financing through crowdfunding.

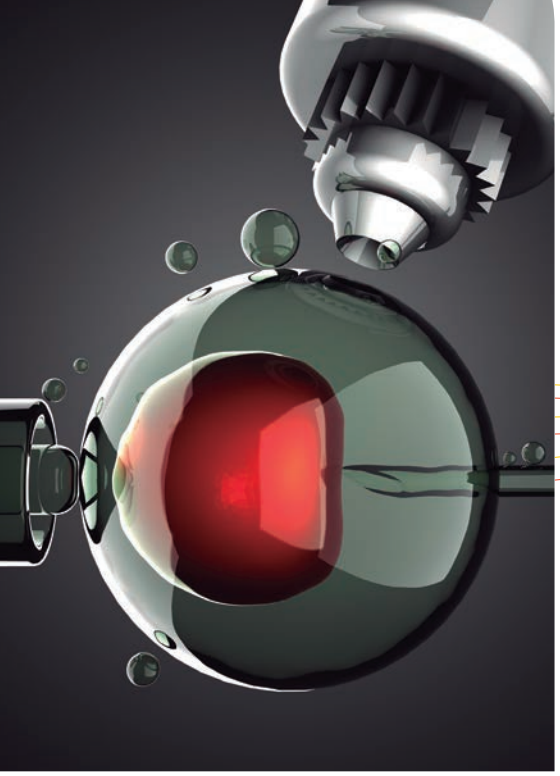
Universidad Carlos III de Madrid launched Crowd-UC3M, a reward-based form of crowdfunding in which investors are involved in the development of the project by benefitting from the advances attained. To this end, 13 projects were selected, each with a minimum and an optimal budget.

Mind The Byte, a bioinformatics company, raised double the expected amount through equity crowdfunding, a different form of crowdfunding in which contributions to capital later become shares. The company raised 234,310 euros from 115 private investors. Inkemia, which already owned 5% of Mind The Byte stock, contributed 18,000 euros in order to maintain its shareholding.

SOM Biotech, meanwhile, launched a crowdfunding campaign to investigate five pediatric rare diseases.

9.

INTERNATIONALISATION



9. Internationalisation

Spanish Biotechnology in the World

Key Indicators on Biotechnology – OCDE

In 2015 the OECD updated its "Key indicators on Biotechnology" statistics, which compare a number of variables in OECD countries. Some statistics for important countries such as the UK and Japan are not given in the study and data collection methods may vary from country to country. For this reason, it is recommended that OECD data is not used as a country ranking but as a source of information on trends in the sector at the internation level.

Number of firms active in biotechnology: According to this study, in 2013 there were 554 biotechnology companies in Spain, meaning Spain was only behind France, the US and Germany but ahead of countries including Italy, Israel and South Korea. That is an increase of 162% compared to the number of companies on record in 2006. However, despite these positive numbers, the fact remains that Spain lost 68 companies in a single year (in relation to the 622 companies of 2012).

Biotechnology R&D expenditure: 40.8% of R&D investment in biotechnology (2013) in Spain is carried out by small and medium sized companies, one of the highest percentages among OECD countries, which reflects the large number of SMEs in the sector. In countries with a more mature biotechnology industry, such as the US, Denmark and Switzerland, the number rarely reaches 10%.

Percentage of dedicated biotechnology firms by application: Another interesting point raised by the OECD report is found in the breakdown by type of company. For health and industrial biotechnology Spain is average among OECD countries with 69.8% and 17.2% of companies working in these areas. Spain stands out, however, for the large proportion of its companies working in food biotechnology (26.7%) and agriculture (18.9%), the highest percentage in the OECD, while environment, at 17% of companies, comes in second highest. These numbers show that although our biotechnology sector is similar to that of other countries, it is also specilised in subsectors which in Spain are already very developed industries, such as the food and environment areas.

SCImago Country Rank

In 2014 Spain continued in tenth place in terms of scientific output (all areas of knowledge).

In areas related to biotechnology, ranking positions included ninth in Chemistry, tenth in Medicine, eleventh in Biochemistry, Genetics, Molecular Biology, Neuroscience and Pharmacology, as well as Toxicology and Pharmaceutics, twelfth in Immunology and Microbiology.

GEN Cluster Ranking

In its first appearance in the Top 10 European Cluster ranking by GEN Magazine (Genetic Engineering & Biotechnology News) Spain is placed eight in Europe for scientific and industrial capacity in biotechnology.

Table 8. Total expenditure on biotechnology R&D *

	Total biotechnology R&D expenditure in millions of US dollars PPP*	Year
United states	26.893,0	2012
France	3.267,9	2012
Switzerland	2.560,0	2012
Japan	1.230,1	2010
South Korea	1.354,4	2013
Germany	1.201,8	2014
Denmark	1.082,2	2013
Spain	**756,6**	**2013**
Belgium	660,8	2011
Holland	420,2	2010

Source: OCDE.

** Purchasing power parity*

The 2016 ranking is as follows:

1. Germany
2. United Kingdom
3. France
4. Holland
5. Italy
6. Switzerland
7. Denmark
8. Spain

In terms of Spain, GEN underlines that the country is home to the third largest number of companies in Europe and sixth in terms of financing for R&D.

However, it is ninth both in terms of patents and jobs, as well as thirteenth in venture capital financing.

Foreign Direct Investment in Spain

Since the end of 2014, when Oryzon signed the first big investment agreement of a Spanish company by an international big pharma player (Roche), the Spanish biotechnology sector has witnesses seven-figure investments by venture capital funds and international pharmaceutical companies, and Spanish investors such as Ysios Capital Partners, which has often led financing rounds, as has Caixa Capital Risc.

This unprecendented development has put Spain on the international biotechniology map, while also bringing together the great scientific quality of Spanish biotechnology proyects. We expect to see the sector continue to attract foreign investment.

All venture capital operations have taken place in collaboration with Ysios Capital Partners and Caixa Capital Risc, which highlights the key role played by Spanish funds in attracting international venture capital funds. The biggest agreements have involved seven companies in the sector, six of them ASEBIO members:

Table 12. Main investment involving Spanish companies and international investors

Date	Spanish biotechnology company	National / international investor	Country	Capital raised
April 2014	Oryzon Genomics	Roche	Switzerland	16.000.000 €
September 2015	Sanifit	Ysios Capital Partners	Spain	36.600.000 €
		Baxter Ventures	US	
		Forbion Capital Partners	Holland	
		Lundbeckfond ventures	Denmark	
		Edmond de Rothschild Investment Partners	France	
		Caixa Capital Risc	Spain	
October 2015	Minoryx	Ysios Capital Partners	Spain	19.400.000 €
		Roche Ventures	Switzerland	
		Caixa Capital Risc	Spain	
		Kurma Partners	France	
		Idinvest Partners	France	
		Chiesi Ventures	US	
		Health Equity	US	
October 2015	Palobiofarma	Novartis	Switzerland	15.000.000 €
January 2016	Aelix Therapeutics	Ysios Capital Partners	Spain	11.500.000 €
		Caixa Capital Risc	Spain	
		Johnson & Johnson	US	
April 2016	Stat Diagnostica	Ysios Capital Partners	Spain	25.000.000 €
		Kurma Partners	France	
		Boehringer Ingelheim	Germany	
		Caixa Capital Risc	Spain	
May 2016	Ability Pharmaceuticals	SciClone	US	

Source: ASEBIO.

Internationalisation Survey

This section details the conclusions of the internationalisation survey for biotechnology companies. It is carried out by ASEBIO, now for the eigth consecutive year.

A total of 79.3% of the companies surveyed considered internationalisation to be "essential" for their business activities. In combination with companies which consider internationalisation to be "important" we can account for a total of 93% of respondents, just like in previous years. This clearly demonstrates the commitment of the sector to internationalisation as an integral part of the business model. If fact, 71% of companies decided to internationalise their activites from the moment of launch.

14% of companies is yet to initiate its internationalisation process. However, 50% of these companies declares internationalisation to be a near term objective which they have not chosen not to start on principaly either because they want to consolidate their project in the Spanish market before expanding overseas or due to a lack of financial resources.

According to the internationalisation survey, 86% of respondents participated in international activity during 2015, a similar percentage to 2014. Overseas activities by our members are shown on Figure 9.

52% of ASEBIO member companies now have a specific international department, which marks a decrease from the 60% of the previous survey.

Favoured markets for biotechnology firms are again those in which the sector has matured enough to provide greater business and investment opportunities, such as the EU and North America (accounting for 80% of respondents). Some way behind is Japan (46.81%), Brazil (36.96%), South Korea (35.71%), Israel (29.55%) and, in contrast with the previous year, other Latin American markets have lost ground in terms of commercial priorities.

Again, a lack of financial means is cited as the main obstacle to setting out on internationalisation processes, according to 73.85% of companies. A percentage that has, however, steadily fallen every year: 79% (2014), 85% (2013), 91% (2012) and 100% in 2009. Other impediments continue to include a lack of training, according to 27.69% of respondents, as well as language barriers (18.46%).

Finally, 92.19% of ASEBIO members who took part in the survey think that the internationalisation process of the biotechnology sector will continue to gain momentum, while 7.81% believe that internationalisation will stay the same or lose strength.

Table 9. Main international activityby ASEBIO members in 2015

Participation in events and fairs	80.00%
Alliances with overseas companies	63.08%
Exporting products or services	60.00%
Licensing out	47.69%
Overseas expansion	36.92%
Investment in brand, communication and marketing	33.85%
Hiring internationalisation professionals	27.69%
Licensing in	18.46%

Source: ASEBIO.

Overseas Expansion

37 ASEBIO member companies have an international presence across 45 markets and 5 continents. The number of overseas subsidiaries has increased to 141, with the US playing host to the largest number, a market in which 21 ASEBIO members are present.

The geographical distribution remains practically identical to 2014, with the majority of subsidiaries being in Europe (the EU and Switzerland account for 48% of the total) and Latin America, with 26% of the total:

Europe	48%
Latin America	26%
US/Canada	18%
Asia/Oceania	9%

Table 11 shows the countries in which our member companies are present and the number of subsidiaries.

Table 10. Subsidiaries of ASEBIO member countries around the world

US	21	Chile	3	Guatemala	1
Germany	10	Holland	3	Honduras	1
Portugal	9	Poland	3	Japan	1
Italy	8	Costa Rica	2	Malasia	1
UK	8	Uruguay	2	Malta	1
France	7	Australia	1	Monaco	1
Mexico	7	Austria	1	Panama	1
Brasil	5	Bolivia	1	Paraguay	1
Colombia	5	South Korea	1	Peru	1
Canada	4	Denmark	1	Czech Republic	1
Belgium	4	Ecuador	1	Dominican Republic	1
China	4	El Salvador	1	Singapore	1
Sweden	4	UAE	1	Thailand	1
Switzerland	4	Eslovaquia	1	Turkey	1
Argentina	3	Greece	1	Venezuela	1

Source: ASEBIO.

Table 11. Biotechnology companies which are ASEBIO members and countries in which they have a direct presence

Company	Country
ABENGOA BIOENERGÍA NUEVAS TECNOLOGÍAS	US, Holland, France, Brazil
AGAROSE BED TECHNOLOGIES	US
ALMIRALL	Canada, US, Mexico, Portugal, UK, France, Italy, Switzerland, Belgium, Holland, Germany, Denmark, Austria, Poland
ASPHALION	Germany
AZIERTA Contract Scientific Support Consulting	Colombia
Bioibérica	Poland, Brazil, US, Italy
Bioncotech Therapeutics	US
Bionure Farma	US
Bioraw	Malta, China
Biotechnology Institute	Germany, Italy, Portugal, UK, Mexico, US
Cytognos	Holland
ERA 7 Bioinformatics	US
ESTEVE	Portugal, Italy, Germany, Sweden, Turkey, Mexico, US, China
GENETADI BIOTECH	Mexico
Genomica	Sweden, China
GRIFOLS	Czech Republic, UAE, France, Germany, Italy, Poland, Portugal, Eslovaquia, Sweden, Switzerland, UK, Canada, Mexico, US, Argentina, Brazil, Chile, Colombia, Australia, Japan, China, Malasia, Singapore, Thailand
Grupo Ferrer	France, Germany, Belgium, Greece, Portugal, US, Mexico, Honduras, Dominican Republic, Panama, Bolivia, Paraguay, Guatemala, El Salvador, Costa Rica, Colombia, Venezuela, Ecuador, Peru, Brazil, Uruguay, Argentina, Chile
Grupo Noraybio	France, Italy
Grupo Reig Jofré	Monaco, Sweden, Belgium, Portugal, UK, US.

Table 11. Biotechnology companies which are ASEBIO members and countries in which they have a direct presence (cont.)

Company	Country
Insights in Life Sciences (iIS)	UK
INKEMIA IUCT Group	Brazil, Colombia
Intelligent Pharma	UK, US, Germany, Canada
Inveready	US
Laboratorios LETI	Germany, Portugal, US
Laboratorios Rubió	Portugal
Lipopharma Therapeutics	US
maBxience	Switzerland, Uruguay, Argentina
NATAC	US, Chile
ORYZON	US
PharmaMar	US, Italy, Germany, France, Switzerland, Belgium, UK
Pharmaphenix	Soutyh Korea, US
Praxis Pharmaceutical	Portugal, France, Colombia
Progenika Biopharma	US
Sequentia Biotech	Italy
Sermes CRO	UK
Sistemas Genómicos	Mexico, Canada, Costa Rica
Sygnis Biotech	Germany

Source: ASEBIO.

International Alliances

ASEBIO identified a total of 54 international alliances during 2015

The geographical distribution is similar to that of other years, with a decrease of alliances in Latin America and North American countries. There has been an 8% increase in alliances in European countries, however.

These figures include all formal agreements between any Spanish company or institution and international entities involving an explicit agreement for a shared objective of any nature (R&D, production, sales or other areas).

10.

Biolatam 2015

10. Biolatam 2015

Biolatam was initially conceived as a biannual event planned to take place on odd-numbered years, but since Biolatam 2015 it has become an annual event aimed at facilitating relationships between international companies, investors, institutions and research centres working on biotechnology and related areas. For Biolatam 2015, ASEBIO organised the event with EBD Group, as well as PROCHILE and ASEMBIO, who were the local partners. It took place in the city of Santiago de Chile, the capital of Chile (at the CentroParque Convention and Conference Centre) on the 16 and 17 of November 2015.

Biolatam 2015 combined a partnering system, conference programme, commercial fair and networking event. The programme centred on: advanced therapies, biosimilars, bioeconomy/biofuels, diagnosis and Treatment of infectious diseases, venture capital, animal health, medical technologies, personalised medicine, cosmetics, foods and food biotechnology, biodiversity/bioprospecting, aquaculture, market access and cluster policy.

Participation numbers were satisfactory, with over 342 attendees, 250 companies and institutions from 20 countries. There were over 400 bilateral meetings organised through the partnering system and 189 products were offered for licensing.

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11.

WHO IS WHO? – ASEBIO MEMBERS

Business members

3P Biopharmaceuticals, S.L.

AB BIOTICS S.A.

AbbVie

Abengoa Bioenergy

Ability Pharmaceuticals, S.L.

Agarose Bead Technologies

AC-Gen Reading Life

Agroaxis

Agrocode Bioscience

Alexion Pharma Spain, S.L.

ALGAENERGY, S.A.

ALGENEX (Alternative Gene Expression S.L.)

Alma Management & Execution

Almirall, S.A.

AMADIX

Amgen, S.A.

Anapharm Europe

Aptatargets

Aptus Biotech

Aquilón cyl, S.L

Araclon Biotech, S.L.

Archivel Farma, S.L.

Artinvet Innovative Therapies, S.L.

Ascil Biopharm

Asphalion

ALTHIA

Ayming

Azierta

Bayer CropScience NV

BBD Biophenix

BCN Health

Betanzos HB

BIOCHEMIZE SL

Biocross

Biofina Diagnostics

Biogen Idec Ibérica, S.L.

Biogenetics

Biohope

Bioibérica, S.A.

Bioimag Soluciones de Contraste S.L

Bioingenium, s.l.

Biokit Research & Developments, S.L.U.

BioMarin Europe Ltd. Sucursal en España

Biomedal, S.L.

Bionanoplus, S.L.

Bionaturis Group

Bioncotech Therapeutics, S.L.

Bionet Ingeniería

Bionos Biotech S.L.

Bionure

Biopolis, S.L.

Bioraw

Biorizon Biotech, S.L.

Biosearch S.A.

Biotools B&M Labs, S.A.

Bosques Naturales, S.A.

Bristol Myers Squibb

BTI Biotechnology Institute

Caixa Capital Risc

Camelina Company España, S.L.

Canaan Research & Investment

Canvax Biotech S.L.

Capital Cell

Celgene

Celgene Institute of Translational Research Europe (CITRE)

Centro de Estudios Superiores de la Industria Farmacéutica

CRB Inverbío, S.G.E.C.R

Curaxys

CYTOGNOS, S.L

DENCELLS BIOMEDICAL INSTITUTE S.L

Diomune S.L.

DREAMgenics, S.L.

Ecocelta Galicia

EntreChem, S.L.

Enzymlogic

Era7 Information Technologies

Esteve

EuroGalenus Executive Search

Eurogenetics

Ferrer

Ferrer inCode, S.L.

Fibrostatin, S.L.

Formune S.L.

Freshcut

Galchimia

Gendiag

Genera Biotech

Genmedica Therapeutics

Genomica S.A.U

Genzyme

Gilead Sciences, S.L.

GP-PHARM, S.A.

GRADOCELL,S.L.

Gri-Cel SA

Grifols Engineering, S.A.

Grifols, S.A.

Grupo BioSerentia

Grupo Farmasierra

Health in Code

Histocell, S.L.

Hoffman Eitle

Iden Biotechnolog

Immpulso Medical Sciences, S.L.

Immunostep, S. L

Inbiomotion SL

Ingeniatrics

Ingulados

InKemia IUCT group

Inmunología y Genética Aplicada, S.A. INGENASA

Innoqua Toxicology Consultants, S.L.

Innovaxis

Insights in Life Sciences (iIS)

Instituto de Medicina Genómica (IMEGEN)

Instituto Empresarial de Biotecnología

Integromics, S.L.

Intelligent Pharma S.L.

Inveready

Iproteos

Kymos Pharma Services, S.L.

Labgenetics, S.L.

Laboratorio CIFGA

Laboratorios LETI, S.L. Unipersonal

Laboratorios Rubió

Lean GxP Support S.L

Life Length

Life Science Praxis, S.L.

Lifesequencing

Lilly

Lipopharma Therapeutics

Logista Pharma

Lonza Biologics Porriño, S.L.

mAbxience

Making Genetics

Master Diagnostica, S.L.

MeDiNova Investigación y Desarrollo SL

Merck, S.L.

Merck, Sharp & Dohme de España, S.A. (MSD)

Metas Biotech S.L.

Miltenyi Biotec

Minoryx Therapeutics

MONDRAGON Health

Monsanto Agricultura España, S.

Myriad Genetics España, S.L.U

n-life Therapeutics

Nanoimmunotech

nanoMyP (Nanomateriales y Polímeros, S.L.)

Nanotherapix S.L.

Natac Biotech, S.L.

NEOL BIOSOLUTIONS SA

Neural Therapies

Neuron Bio

Newbiotechnic, S.A.

Nimgenetics, Genómica y Medicina, S.L.

Noray Bioinformatics, S.L.U. - NorayBio

Noray Biosciences Group (Noray BG)

Novo Nordisk

Omakase Consulting, S.L.

One Way Liver, SL. (OWL)

Operon, S.A.

Oryzon Genomics S.A.

OSASEN SENSORES, S.L.

Palobiofarma

Pangaea Biotech

Parexel Internacional

Pevesa, S.L.

PHARMA BIO SEGUROS

Pharmamar, S.A.U.

Pharmaphenix

Phytogen Medical Foods

Plant Response Biotech S.L.

Plebiotic

PONS Patentes y Marcas

Praxis Pharmaceutical, S.A.

Progenika Biopharma, S.A.

Promega

ProRetina Therapeutics, S.L.

ProtoQSAR

qGenomics

Raman Health Technologies

Recombina

Repsol

Research Toxicology Centre

RJ Biotech Services

Roche Farma

Sanifit

Sanofi Pasteur MSD, S.A.

Sartorius Stedim Spain, S.A.U.

Science & Innovation Link Office (SILO)

Secugen, S.L.

Seprox Biotech

Sequentia Biotech

Sermes CRO

Sigma-Aldrich Química, subsidiaria de Merck

Sistemas Genómicos, S.L.

SmartLigs

SOM Biotech SL

SPECIFIC PIG S.L.

Spherium Biomed S.L

Stacks Consulting e Ingeniería de Softwware

STAT-Diagnostica & Innovation, S.L.

Stem Center, S.L.

StemTek Therapeutics, S.L.

SYGNIS

Sylentis, S.A.U.

Teraclón IDF, S.L.

The Zebrafish Lab

Thrombotargets Europe, S.L.

Tigenix SAU

Valoralia I+D

Vaxdyn

VCN Biosciences

Venter Pharma, S.L.

Vertex Pharmaceuticals Spain

Vetgenomics, S.L.

VidaCord, S.L.

Vitagenia HealthCare

Vivacell Biotechnology España, S.L.

Vivia Biotech, S.L.

Vivotecnia Research, S.L.

VLP Bio

Vytrus Biotech

Ysios Capital Partners SGEIC, S.A

Zeclinics

Other organisations

Agencia de Innovación y Desarrollo de Andalucía IDEA

Agencia Estatal. Consejo Superior de Investigaciones Científicas, CSIC

Banco Español de Algas

BioBasque, la Bioregión Vasca

Biocat

BIOIB (Cluster biotecnológico wde las Islas Baleares)

Centro de Investigación Médica en Red (CIBER)

Centro Nacional de Investigaciones Oncológicas, CNIO

Centro Tecnológico LEITAT

Federación Española de Enfermedades Neuromusculares

Fundacion Española para la Ciencia y la Tecnología

Fundación Española de Hematología y Hemoterapia (FEHH)

Fundación GAIKER

Fundación Imdea Alimentación

Fundación MEDINA (Centro de Excelencia en Investigación de Medicamentos Innovadores en Andalucía)

Fundación para la Investigación Biomédica de Andalucía Oriental (FIBAO)

Fundación para la Investigación Biomédica Hospital Universitario 12 de octubre

Fundación Parque Científico Tecnológico Agroalimentario Aula Dei (Fundación PCTAD)

Fundación Parque Tecnológico de Ciencias de la Salud de Granada (PTS)

Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI)

Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud

Fundación Pública Andaluza Progreso y Salud

Fundación Vasca de Innovación e Investigación Sanitarias

GENMIC: Grupo de Investigación de Genética y Microbiología

Gobierno de La Rioja. Dirección General para la Innovación

Grupo de Investigación BioFarma de la Universidad de Santiago de Compostela

Institut de Recerca Biomèdica de Lleida (IRBLleida)

Instituto de Biomedicina de Sevilla (IBIS)

Instituto de Investigación Biomédica (IRB Barcelona)

Instituto de Investigación Biomédica (IRB Barcelona)

Instituto de Investigación Sanitaria La Fe

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asebio

Diego de León, 44 - 2° dcha.
E-28006 Madrid (SPAIN)
www.asebio.com

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