8

INNOVATION

The CNB is one of the few CSIC research institutes that operates its own Technology Transfer Office (TTO), in close collaboration with the CSIC Deputy Vice-presidency for Knowledge Transfer.

CNB researchers work to unlock the secrets of living things and to apply their research results to the development of new, safer, more effective compounds and technologies to improve our health, agriculture and environment. The TTO facilitates the transfer of this knowledge to society.

The TTO helps CNB scientists obtain funding from innovation and public/private project programmes. As an example, five CNB projects were presented to the first call of the "Fondo Para el Patrocinio de la Ciencia y la Innovación", a programme promoted by the FUAM and the CSIC. Two CNB projects were pre-selected, one of which, proposed by Dr Roberto Solano, was funded for applying their patented technology to render tomato plants resistant to biotrophic pathogens.

The TTO assists researchers in exploring new ways to secure research funding. In 2015, the group led by Dr Cristina Risco participated in a project at PRECIPITA, the crowdfunding platform of the Spanish Foundation for Science and Technology (FECYT).

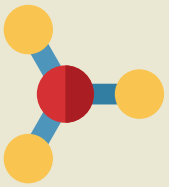
The TTO fosters collaboration between CNB researchers and pharmaceutical companies. A joint endeavour of Dr Isabel Mérida's group and the University of Santiago de Compostela was one of six projects selected by GlaxoSmithKline in 2015 for its Discovery Fast Track Program, from 378 proposals from around the world. This initiative aims to discover lead compounds for the development of new anti-cancer drugs.

TECHNOLOGY TRANSFER MANAGER

Ana Sanz Herrero

Material transfer agreements (MTA)

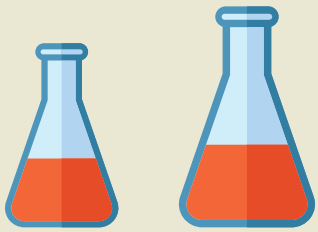
In 2015 and 2016, 54 and 35 MTAs were signed, respectively; the CNB was the material provider in 12 of them in 2015, and in 9 in 2016. These agreements reflect the value of materials developed at the CNB for scientists around the world.



2015	2016
54	35
12 CNB AS MATERIAL PROVIDER	9 CNB AS MATERIAL PROVIDER

Confidential disclosure agreements (CDA)

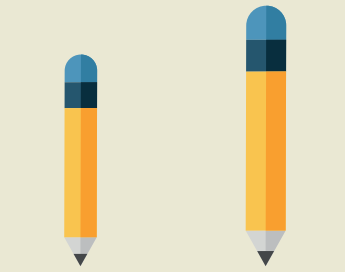
Five CDAs were signed in 2015, and 18 in 2016. This increase shows the commitment of the TTO to early promotion of the centre's technology offer.



2015	2016
5	18

R&D and technological support contracts with industry

Over the past two years, 29 contracts were signed with companies as the result of direct negotiations with the TTO, adding approximately 0.4 million euros annually to the centre's budget.



2015	2016
13	16

Inventions

In the 2015-2016 period, CNB researchers filed 12 new invention disclosures. After analysing their patentability, seven led to new patent applications; two have already been extended to international (PCT) patent applications.

2015	2016	
5	7	INVENTIONS
6	1	PRIORITY PATENT APPLICATIONS
1	1	INTERNATIONAL PATENT APPLICATIONS

Biological materials licensing agreements

During the past two years, the TTO was very active in identifying and transferring CNB biological materials (antibodies, proteins, mouse models, etc.) through license agreements:

- **RNA from transmissible gastroenteritis coronaviruses (TGEV)**, developed by Dr Luis Enjuanes's group.
- **13 monoclonal antibodies to human hormones**, generated by Drs Leonor Kremer, Mario Mellado, José Miguel Rodríguez Frade and Carlos Martínez-A.
- **CCR6 knock-out mice** from Dr Carlos Martínez-A's group.
- **Polyclonal antibodies to Meis1 and Meis1/2**, developed by Drs Juan Pablo Albar and Miguel Torres.

Monitoring previous license agreements

A patent from Dr Vicente Rubio's group to render plants more tolerant to abiotic stress generated returns over the past two years through a 3-year evaluation contract by a multinational seed company with the licensee company (Plant Bioscience Ltd).

The CNB spin-off company Proteobotics also renewed its license option for a patent that protects a method for the identification of proteins from mass spectrometry data (this patent has been granted in Europe and the USA).

A patent on monoclonal antibodies against the human CCR9 chemokine receptor (developed by Dr Leonor Kremer's group) was licensed in 2014 to the company SunRock Biopharma; meanwhile, patent applications have been filed in Europe, the USA, Canada, Japan and Korea.

The company is now evaluating the therapeutic potential of these antibodies for treatment of CCR9-expressing tumours in animal models.

Dr Kremer's group obtained funding from the Spanish government to collaborate with the company in further development of these antibodies into marketable therapeutics.

Fostering innovation through innovation events

The TTO organizes innovation seminars to bring CNB researchers in contact with companies, promote the centre's capabilities and technology offer, familiarize CNB researchers with intellectual property protection issues, and foster the entrepreneurial spirit of CNB scientists.

In 2015 and 2016, the CNB participated in the **Global I+T** Event together with 12 universities and research centres.

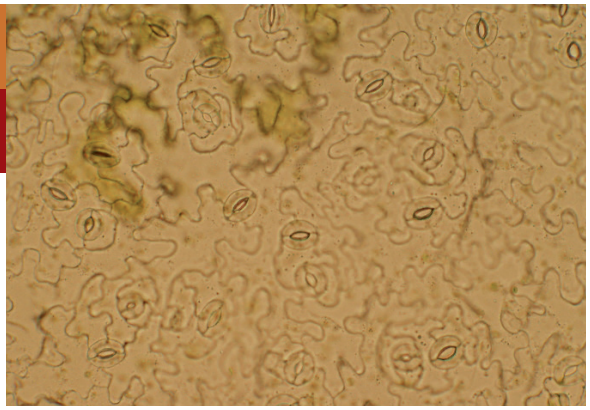
This innovation event was organized by eGauss Holding to connect companies, investors and start-ups with researchers, providing a unique forum in which to discuss the many facets of innovation from different angles.

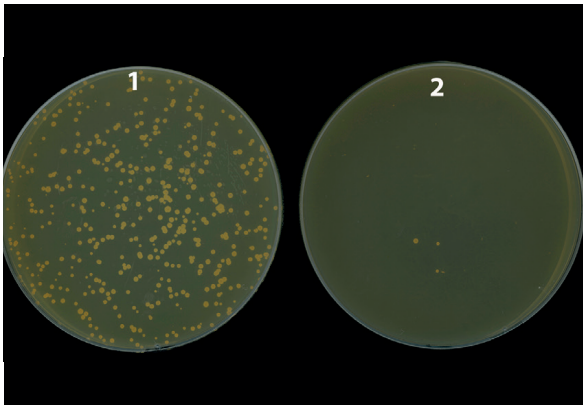
The TTO also organized **GSK and MRC Technology Seminars** on collaboration programmes with academia; these seminars were followed by one-to-one meetings with scientists.

On the occasion of the **World IP Day 2016**, the TTO organized a round table with three speakers from different biotech industries, who shared and discussed the relevance of IP matters with their audience.

Promoting and training in entrepreneurship

Seminars aimed at promoting and training CNB researchers in entrepreneurship included the following events: "Practical workshop about the Business Model Canvas for CNB scientists" (January 2015), "Thinking about entrepreneurship" (July 2016) and "From science to business" (October 2016).





TECHNOLOGY OFFER
PATENTS AVAILABLE FOR LICENSING

Plants resistant to biotrophic pathogens without increasing susceptibility to necrotrophs

Despite efforts to obtain broad-spectrum resistance to pathogen infections in plants by manipulating the master defence hormone pathways (jasmonic acid (JA) and salicylic acid (SA)), these approaches have failed so far due to the known antagonism between these two pathways. The research group led by Dr Roberto Solano has developed plants in which JA insensitivity is restricted to guard cells of stomata, resulting in plants with increased resistance to biotrophs, but without the trade-off of enhanced susceptibility to necrotrophs.

RESEARCH GROUP

Dr Roberto Solano Tavira

APPLICATION NUMBER AND PRIORITY DATE

EP16382513, 7/11/2016

PRESENT SITUATION

Companies are being sought from the agro-biotechnology industry interested in a patent license.

MAIN INNOVATIONS AND ADVANTAGES

Combining inactivation (non-functional) or deletion of the Jas domain of a *JAZ* gene with specific expression of the modified JAZ sequence at the stomata guard cells leads to increased plant resistance to biotrophs, without enhanced susceptibility to necrotrophs; this is because JA insensitivity is restricted to guard cells and does not affect mesophyll cell defence.

REFERENCE

Gimenez-Ibanez *et al.* New Phytol. 2017; 213: 1378-1392

Genetic hypervariable strains of actinobacteria

Dr Jesús Blázquez's research group, in collaboration with the Andalusian Public Health System, the University of Seville, and the University of Sussex, has developed a method to produce hypermutable actinobacterial and archaeal strains. The group identified a DNA repair system in Actinobacteria and Archaea, which is completely different from the mismatch repair system (MMR) described for most living beings. Its inactivation increases the mutation rate of *Streptomyces coelicolor* and *Mycobacterium smegmatis* from 100-1000 times that of the wild-type strain, as well as the recombination rate of divergent DNA sequences (homologous hyper-recombination). This innovative method is useful for the production of genetically hypervariable Actinobacteria (such as *Streptomyces*, *Mycobacterium* and *Bifidobacterium*) and some archaeal species (such as *Pyrococcus*, *Thermococcus* and *Halobacterium*), from which is possible to isolate specific strains with biomedical and/or biotechnological applications.

RESEARCH GROUP

Dr Jesús Blázquez Gómez

APPLICATION NUMBER AND PRIORITY DATE

P201531949 and P201531950, 31/1272015

INTERNATIONAL PCT APPLICATION

PCT/ES2017/070002, 2/1/2017

PRESENT SITUATION

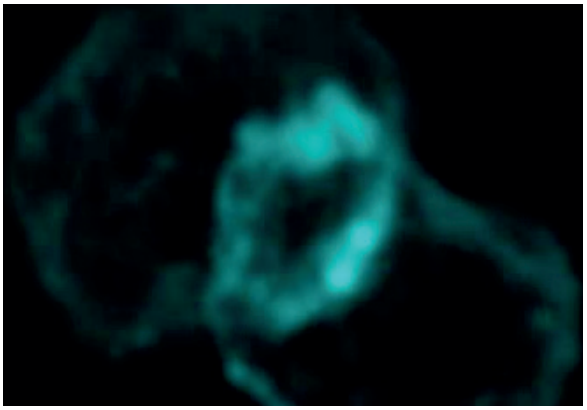
Companies interested in a patent licence and/or collaboration agreement to develop and exploit this technology are being sought.

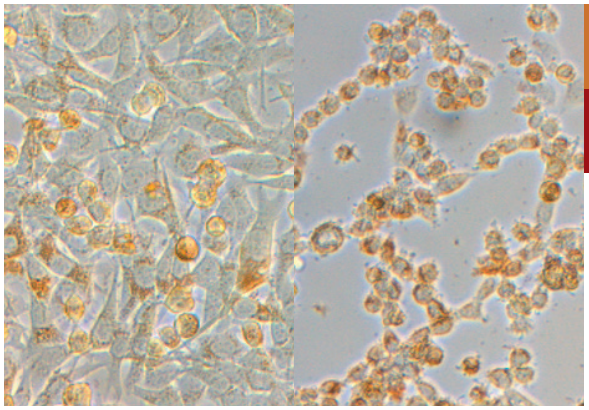
MAIN INNOVATIONS AND ADVANTAGES

The invention can generate bacterial strains that overproduce secondary metabolites (such as antibiotics, antitumour compounds, immunosuppresors, antihelminthics, antifungals, herbicides, insecticides), bacterial strains adapted to environmental or industrial conditions (temperature, pH) or strains that overproduce new metabolites by fusing metabolic pathways.

REFERENCE

Castaneda-Garcia *et al.* Nat Commun. 2017; 8: 14246





TECHNOLOGY OFFER
PATENTS AVAILABLE FOR LICENSING

Transphagocytic T cells as anti-cancer immunotherapy

Dr Esteban Veiga's research group, with scientists from the Centre of Molecular Biology Severo Ochoa (CBMSO-CSIC), the Autonomous University of Madrid and the Health Research Institute of La Princesa University Hospital, developed a new method for anti-cancer immunotherapy based on transphagocytic lymphocytes (tiCD4+ T cells).

RESEARCH GROUP

Dr Esteban Veiga Chacón

APPLICATION NUMBER AND PRIORITY DATE

P201531177, 7/8/2015

INTERNATIONAL PCT APPLICATION

PCT/ES2016/ 070597, 8/8/2016

PRESENT SITUATION

International PCT application has been filed. Companies interested in a patent licence or investors for creation of a start-up are being sought.

MAIN INNOVATIONS AND ADVANTAGES

- The invention can be used to prevent/treat tumours and/or stimulation of an immune response against tumour antigens.
- CD4+ T cells are newly defined antigen-presenting cells that can be useful as a cancer immunotherapy tool.
- The invention can be applied for melanoma and other highly immunogenic tumours.
- The anti-tumour activity of tiCD4+ T cells is even greater than the activity of dendritic cells.
- A single injection of transphagocytic T cells was sufficient to protect mice against growth of an aggressive melanoma, while the dendritic cell-based vaccine required more doses and did not yield comparable results.

REFERENCE

Cruz-Adalia *et al.* Cell Host Microbe 2014; 15: 611-622

Device to induce hyperthermia in cells through magnetic nanoparticles

Dr Domingo Barber's research group has developed an instrument to generate a controlled alternating magnetic field to induce hyperthermia in cells through magnetic nanoparticles.

RESEARCH GROUP

Dr Domingo Barber

APPLICATION NUMBER AND PRIORITY DATE

P201431531, 17/10/2014

INTERNATIONAL PCT APPLICATION

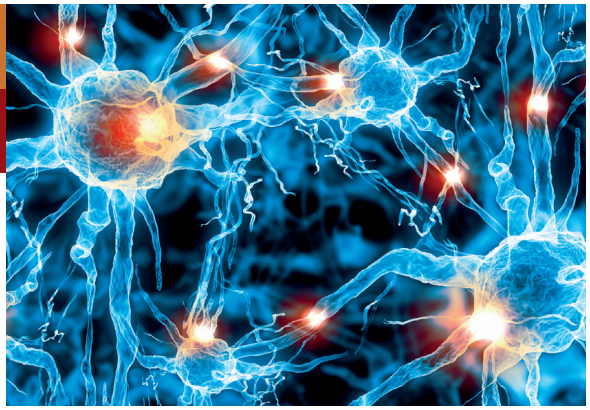
PCT/ES2015/070753, 15/10/2015

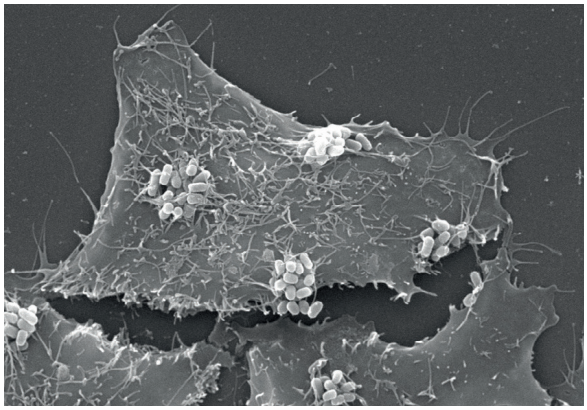
PRESENT SITUATION

Companies interested in a patent license are being sought.

MAIN INNOVATIONS AND ADVANTAGE

- A unique non-contact-based method for precise measurement (to 0.01ºC) of the temperature reached by the nanoparticles inside cells.
- Frequency and amplitude of the magnetic field can be programmed automatically by the scientist. It allows changes in parameters such as frequency, amplitude, pulse code modulation, or a mixture of these, all digitally controlled in real time.
- User-friendly software for data capture, representation and analysis to control parameters of the magnetic field and nanoparticle temperature.
- Compact, easy-to-use equipment. It requires no parts exchanges over a wide frequency and potency range, making it a perfect instrument for hyperthermia research.
- It can also be used in materials science to analyse the heating properties of materials and nanoparticles (SAR curves).





TECHNOLOGY OFFER
PATENTS AVAILABLE FOR LICENSING

Novel compounds to modulate DREAM activity

Dr José Ramón Naranjo's research group, in collaboration with scientists from the Institute for Chemical Medicine (IQM-CSIC), the Autonomous University of Madrid and the Centre for Network Biomedical Research on Neurodegenerative Diseases (CIBERNED), have developed compounds with a nuclear structure derived from phenylacetamide with the capacity to modulate the neuronal calcium sensor DREAM, for use as preventive or therapeutic compounds for treatment of diseases with altered DREAM levels.

RESEARCH GROUP

Dr José Ramón Naranjo

APPLICATION NUMBER AND PRIORITY DATE

P201431898, 22/12/2014

INTERNATIONAL PCT APPLICATION

PCT/ES2015/070923, 9/2/2016

PRESENT SITUATION

Companies interested in a patent license are being sought.

MAIN INNOVATIONS AND ADVANTAGES

The concept of DREAM as a therapeutic target is novel and the development of different series of compounds able to bind to and modify DREAM activity could open new avenues for treatment of DREAM-related neurodegenerative disorders.

Engineered bacteria to deliver intracellular single-domain antibodies into human cells

Dr Luis Ángel Fernández's research group has developed non-invasive *Escherichia coli* bacteria bearing functional molecular syringes assembled by a Type III protein secretion system (T3SS). These bacteria can secrete and translocate single-domain antibody (sdAb) fragments with full capacity to bind to their cognate antigens to the cytoplasm of human cells. They have shown their functionality by formation of antigen-sdAb complexes in the cytoplasm of infected cells. The use of live bacteria has great potential for *in vivo* delivery of therapeutic proteins.

RESEARCH GROUP

Dr Luis Angel Fernández Herrero

APPLICATION NUMBER AND PRIORITY DATE

P200700644, 12/03/2007

INTERNATIONAL PCT APPLICATION

PCT/ES08/070045

PRESENT SITUATION

Spanish patent has been granted (12/03/2007). US Patent has been granted and published as US 8,623,349 B2 (Jan 7, 2014). Companies interested in a patent license are being sought.

MAIN INNOVATIONS AND ADVANTAGES

- Non-invasive *E. coli* cells with a Type III protein secretion system remain extracellular and can inject specifically the desired single-domain antibodies.
- Intracellular sdAb levels (105-106 molecules/cell) are appropriate for modulating the activity of regulatory and cell signalling proteins. Injection of sdAb does not require bacterial invasion or transfer of genetic material, and thus differs from other approaches that must transfer the protein-encoding gene by viral infection or transfection.

REFERENCE

Blanco Toribio *et al.* PLoS One. 2010; 5: e15227