

The unique know-how and cross-disciplinary expertise of CNB's scientists and technologists provides excellent opportunities to transfer leading-edge knowledge and technologies to society and industry. The purpose of the CNB Knowledge Transfer Office (KTO) is to facilitate the process of innovation by:

raising **awareness** among CNB's researchers about the potential socioeconomic impact of their research and facilitating their implication in technology development and innovation,

enhancing the **visibility** of the CNB as a source of transferrable knowledge and partner for industry in the development of innovative technologies, and

potentiate the centre's innovation **capabilities** across all aspects of knowledge protection, commercialisation and entrepreneurship.

Innovation

KNOWLEDGE TRANSFER MANAGER

Cristina Merino Fernández (since June 2017)

Ana Sanz Herrero (until March 2017)



Awareness

The CNB Knowledge Transfer Office (KTO) organises innovation events to foster the entrepreneurial spirit of CNB scientists and familiarise them with the basic principles and benefits of knowledge transfer. Activities in the 2017-2018 period included round tables and workshops on News on European RTD Funds (Eurostars, Eureka, SME Instrument), Wizard of OTT (Technology Transfer Office) and the centre's Course on Introduction to Research. The KTO participated in the 1st RAFTS4BIOTECH Industrial Event, the Round Table: IPR in different scientific fields within the 100xCiencia.2 conference: Co-creating Value in Scientific Research.

Furthermore, with the aim of showcasing success stories of spin-off companies promoted by scientists from academia, the KTO and the CNB Science Communication and Outreach Office teamed up to organise guided tours to the biotech company NIMGenetics.

Visibility

To enhance the visibility of CNB's technology offer, the KTO has established contacts with stakeholders in the public and private sectors, including INNOMADRID, AINIA, ASAJA, San Carlos Hospital, Infanta Leonor Hospital, TTO-CIRCLE, business angles (WOMENANGELS), investors, REDTRANSFER. KTO has also participated in meetings, seminars, and congresses related with innovation (Innovatia 8.3: Women and Entrepreneur Universities, wegate, ESOF, EIT-HEALTH, FarmaForum, Biospain).

Furthermore, in close collaboration with CNB's Science Communication and Outreach Office, the KTO disseminates the capacities and expertise of CNB scientists in the media and social networks.

Capabilities

The CNB KTO works in close collaboration with the CSIC Deputy Vice-presidency for Knowledge Transfer, covering all aspects of innovation management from the protection of intellectual property to the development and commercialisation of new technologies.

CONTRACTUAL RESEARCH

The KTO supports and manages contractual relations between the CNB and partners in industry. In the 2017-2018 period, these contracts have generated revenues of 2.4 M€.

Major areas of collaboration and industrial partners include:

- Detection of gluten in food (Damm, R-Biopharm, Ingenasa, Operon)
- Production and study of recombinant bacteria, antibodies and proteins for diagnostic and therapeutic purposes (Mediagnost, Biopolis, Synlogic, Genmed, G2 Therapies, eBioscience, Millipore, Alergovet, Ingenasa, Protein Alternatives, Bacmine, Sanofi-Aventis, Bioncotech, Thrombotargets, Landsteiner)
- Vaccine development (Sanofi-Aventis, Labopat, Syva, Ceva Santé Animale)
- Development of applications for clinical analytics (Immunostep)
- Improvement of crop production and resistance to pathogens (Plant Response Biotech, Plant Bioscience Limited, Globachem, Agro Innovation International, Electro Transformación Industrial)
- Electron microscopy and image analysis (FEI Electron Optics, Thermo Fischer Scientific)
- Biotech consulting (Lab Safety Consulting, Elzaburu)

Furthermore, the KTO is in charge of managing Material Transfer Agreements (MTA) with other research institutions and companies all around the world, in which the CNB acts as the material provider in almost half of them. These agreements reflect on the international reputation of the CNB as a provider of leading-edge materials for research in the life sciences.

PUBLIC-PRIVATE RTD ALLIANCES

The KTO is in charge of collecting information about skills, results and activities of research at the CNB with the aim of identifying potential partners for technology transfer and opportunities for joint research projects.

Furthermore, the office also provides CNB researchers relevant and timely information on funding opportunities for



public-private research projects and assists them in grant preparation, contractual and follow-up issues. During the past two years, CNB scientists presented 5 innovative projects in the framework of private-public partnership funding schemes, such as the Retos Colaboración, INTERCONECTA or AECC programmes, and GlaxoSmithKline's Discovery Fast Track Program.

INTELLECTUAL PROPERTY PROTECTION

The KTO provides support in all aspects of intellectual property protection of research results, identifies appropriate business partners for outsourcing the development of new technologies, supervises the activities of license holders, and oversees the payment of royalties.

ENTREPRENEURSHIP

The KTO helps to identify business opportunities and provides advice on the creation of spin-off companies. In 2017 and 2018, the office supported 3 initiatives for the creation of technology-based companies.

TECHNOLOGY OFFER

Patents available for licensing are summarised below. Companies interested in a patent license or investors for the creation of a technology-based company are being sought.

OUTCOME OF THE SUPPORT PROVIDED BY THE KTO IN 2017-2018

Technological support contracts



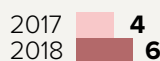
Confidential disclosure agreements



R&D contracts



License agreements



Material transfer agreements (material provider)



Material transfer agreements (material receptor)



Public-private research grants



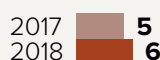
Co-ownership agreements



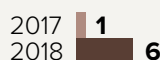
Inventions

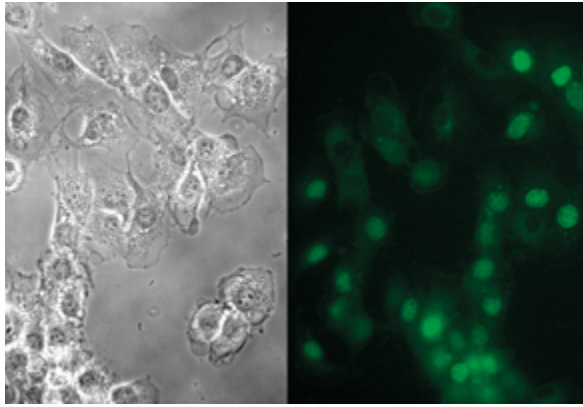


Priority patent applications

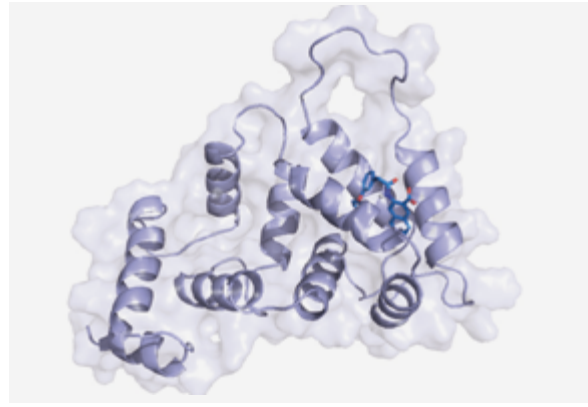


International patent applications





110 INNOVATION



New anti-inflammatory molecules based on natural products of bacterial origin

CSIC and the Autónoma University of Madrid have discovered anti-inflammatory properties in a natural peptide that has its origin in the bacterial cell wall. The structure of this peptide, which differs from the canonical peptidoglycan structure, is only observed during intracellular infections.

CNB INVENTORS

Francisco García del Portillo
Estel Ramos Marquès
Gadea Rico Pérez

APPLICATION NUMBER AND PRIORITY DATE

P201831219, 14/12/2018

MAIN INNOVATIONS AND ADVANTAGES

- The peptide may have less side effects than other steroid-based anti-inflammatory agents.
- It can be potentially used to reduce inflammation in autoimmune disorders and infections caused by other intracellular pathogens.

KChIP2 modulating compounds and their use for the treatment of cardiovascular pathologies

Dr José Ramón Naranjo's research group has developed new compounds able to activate the KChIP2/Kv4 interaction without directly affecting Kv4 channels or other potassium currents.

CNB INVENTOR

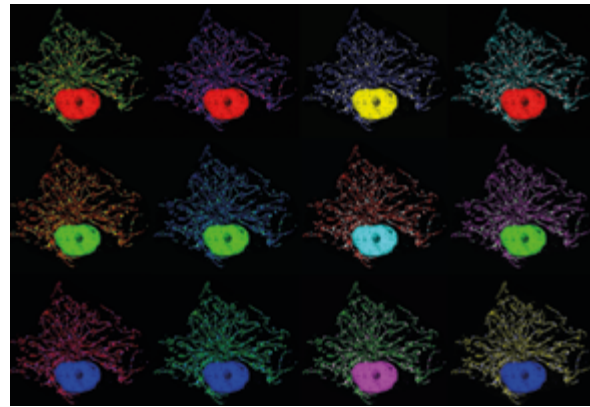
José Ramón Naranjo Orovio

APPLICATION NUMBER AND PRIORITY DATE

EP18382890, 04/12/2018

MAIN INNOVATIONS AND ADVANTAGES

- KChIP2 is the main accessory subunit of Kv4 channels. It is expressed in the heart and regulates voltage-dependent potassium currents (I_{To}) through the interaction with Kv4 potassium channels. The I_{To} current is essential to control cardiac excitability and is reduced in various cardiac pathologies.
- The new KChIP2 modulating compounds activate the KChIP2/Kv4 interaction without interfering with Kv4 channels or other potassium currents.
- These compounds could potentially be useful to treat cardiac pathologies, such as cardiac hypertrophy, arrhythmias, infarct or ischemic failure.



INNOVATION 111

OPTOBIOTICS: novel antibacterial proteins activated by blue light

The group of Dr Rafael Giraldo has developed a chimeric protein that, when expressed in bacteria, changes its structure upon absorption of blue light, which results in the generation of protein aggregates (amyloids) that inhibit bacterial growth.

CNB INVENTOR

Rafael Giraldo Suárez

APPLICATION NUMBER AND PRIORITY DATE

EP18382882.1, 03/12/2018

MAIN INNOVATIONS AND ADVANTAGES

- A synthetic protein (LOV2-WH1) is activated as an anti-microbial by a physical, harmless stimulus: blue light.
- Blue light absorption by LOV2-WH1 stimulates the assembly of anti-bacterial protein particles.
- Mobilisation of LOV2-WH1 through vectors/bacteriophages would enable its usage against a broad spectrum of bacterial pathogens.
- LOV2-WH1 is amenable to photo-therapy approaches, aiming to combat bacterial skin infections or to decontaminate pathogens from surfaces.
- In mixed bacterial populations assembled in an industrial bioprocess, optogenetic activation of LOV2-WH1 can be used to selectively eliminate a specific subpopulation once it has accomplished its task.

New method for detection of fluorescent proteins in cells

Dr Francisco Iborra's research group, in collaboration with scientists from the Autónoma University of Madrid and IMDEA Nanoscience, developed a new method for detection of fluorescent proteins in cells.

CNB INVENTOR

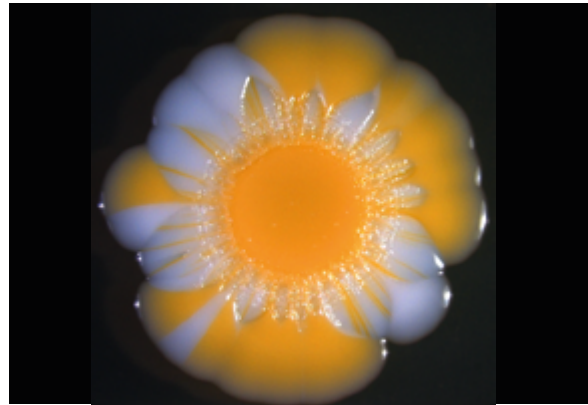
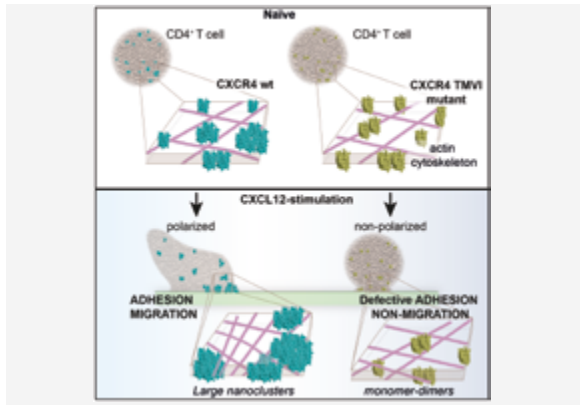
Francisco José Iborra Rodríguez

APPLICATION NUMBER AND PRIORITY DATE

201830775, 27/07/2018

MAIN INNOVATIONS AND ADVANTAGES

- The new method for the detection of fluorescent markers in cells provides high resolution images with less phototoxicity than other approaches available so far.
- The new method is based on the use photoactive nanoparticles and optical tweezers.



112 INNOVATION

Therapeutic targets in chemokine receptors to select useful compounds for the treatment of pathologies that intervene in chemokine responses

CNB researchers have identified a molecular target in the transmembrane VI (TMVI) region of the chemokine receptor CXCR4. This target is now being used to design and detect selective compounds that modulate/antagonise chemokine-mediated function by altering receptor oligomerisation. Antagonists of receptor oligomerisation block cell movement towards chemoattractant gradients, which renders this target potentially useful for altering immune cell infiltration in tissues during autoimmune and inflammatory diseases or metastasis. As CXCR4 is also the main coreceptor for T-tropic HIV-1 viruses, these antagonists may be useful to block HIV-1 infection and to reduce the viral load of AIDS patients.

CNB INVENTORS

Mario Mellado García
José Miguel Rodríguez Frade
Laura Martínez Muñoz
César Augusto Santiago Hernández

APPLICATION NUMBER AND PRIORITY DATE

PCT/ES2018/070484, 05/07/2018

MAIN INNOVATIONS AND ADVANTAGES

- The invention provides a novel approach for the screening of compounds that are potentially useful for the treatment of pathological conditions triggered by chemokine signalling, such as inflammatory and autoimmune diseases, cancer or HIV-1 infection.
- The identification of molecular targets in chemokine receptors/chemokine complexes provides a completely new and effective approach to antagonise specific chemokine responses, opposed to classical strategies based on ligand binding blockade that have failed so far to obtain drugs for clinical purposes.
- The invention has been tested in *in vivo* experiments using a murine model for neutrophil homing to the bone marrow.

Mol. Cell 2018 70:106-119

Overcoming resistance to Beta-lactam antibiotics in Bacterial species

New use of statins for overcoming resistance to beta-lactam antibiotics in bacterial species synthesising isoprenoids using the mevalonate synthetic pathway.

CNB INVENTOR

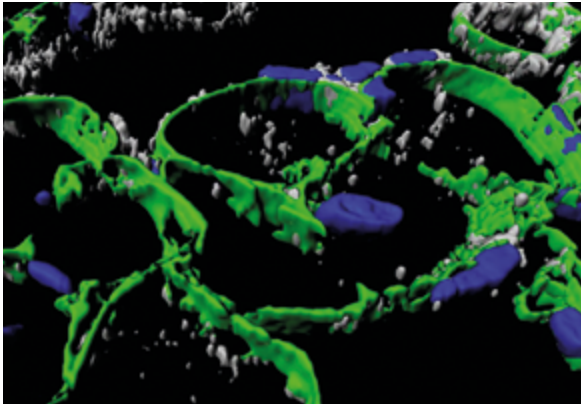
Daniel López Serrano

APPLICATION NUMBER AND PRIORITY DATE

EP17382734, 02/11/2017

MAIN INNOVATIONS AND ADVANTAGES

- This method can be used to eliminate Methicillin-resistant *Staphylococcus aureus* (MRSA) infections that are resistant to multiple antibiotics, which cause hard-to-treat infections in hospitals that sometimes become lethal to the patient. As there are limited strategies to eliminate these infections, this method represents an outstanding possibility to treat patients with complicated infections.
- This method can be used to recycle conventional antibiotics that were discarded because of the spread of antibiotic resistance. Due to the lack of new antibiotics and the necessity to increase the arsenal to fight antibiotic resistance of bacterial infections, recycling conventional antibiotics to fight new multi-drug resistant infections is a promising strategy to reduce the number of infection in clinical settings.



INNOVATION 113

Construction of an attenuated influenza virus and its use as vaccine

Drs Ana Falcón and Amelia Nieto have developed an influenza A virus that contains an amino acid change in the PB2 subunit of the viral polymerase that attenuates the virus *in vivo*, but replicates efficiently in cultured cells. The virus accumulates high amounts of defective viral genomes (DVGs) within its viral particles, and the content of DVGs is related with the antiviral response. Accordingly, the mutant virus elicits an efficient stimulation of the host-response, both in cell cultures and in infected mice. Mice infected with this mutant virus do not lose body weight, indicating that the virus is not pathogenic, although it replicates efficiently in the lungs.

CNB INVENTORS

Ana María Falcón Escalona
Amelia Nieto

APPLICATION NUMBER AND PRIORITY DATE

PCT/ES18/070566, 21/08/2017

MAIN INNOVATIONS AND ADVANTAGES

- The invention applies reverse genetics to generate an attenuated Influenza virus that contains a point mutation in a subunit of the viral polymerase that is stable in the circulating viruses.
- The mutant virus is not pathogenic in mice but replicates efficiently in the lung where it elicits an effective antiviral response.
- These properties make the PB2 mutant virus an ideal candidate for vaccine development.

Bacterium for conversion of plant biomass waste into valuable chemicals

Dr Victor de Lorenzo's group is developing KT2440 strains of robust stress-resistant and safe (GRAS-certified) *Pseudomonas putida* that are able to utilise plant biomass-derived sugars – glucose, cellobiose, and xylose – and convert them into valuable bioplastics, polyhydroxyalkanoates (PHA) and the platform chemical xylonate. Xylonate can be used as a complexing agent, chelator, or a precursor for co-polyamides, polyesters, hydrogels, 1,2,4-butanetriol, ethylene glycol or glycolate, and may also provide a cheap, non-food derived alternative for D-gluconic acid, which is widely used (about 80 kton/year) in industry.

CNB INVENTORS

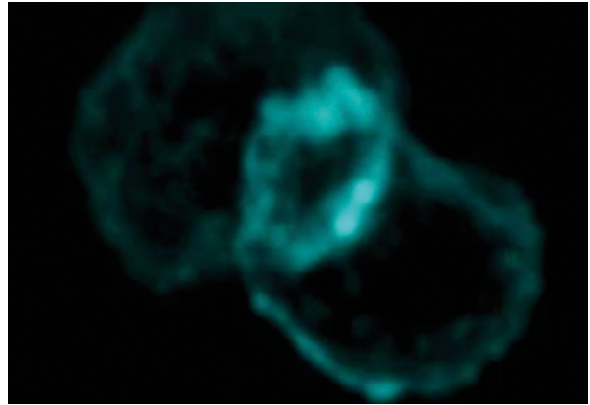
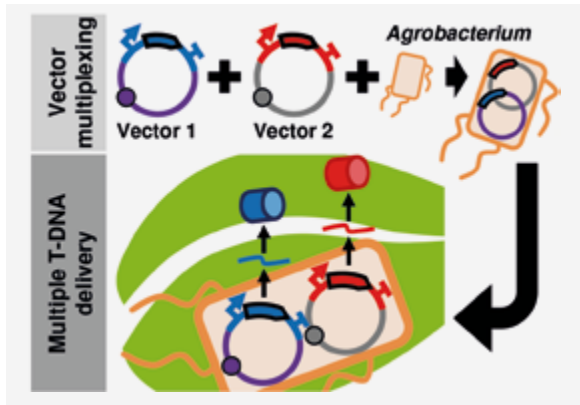
Pavel Dvorak
Víctor de Lorenzo Prieto

APPLICATION NUMBER AND PRIORITY DATE

PCT/EP2018/068347, 06/07/2017

MAIN INNOVATIONS AND ADVANTAGES

- Engineered strains with reduced genome show better physiological vigour, higher ATP and NADPH availability, higher resistance to oxidative stress, and more stable heterologous gene expression when compared with wild-type *Pseudomonas putida*.
- The new *Pseudomonas putida* strain EM42 β grows rapidly on cellobiose, converts this sugar into PHA and, in addition, oxidizes xylose to xylonate. Thus, two desirable bioproducts are obtained in parallel.
- Xylonate is also produced from xylose with high yield (up to 0.97 g g⁻¹) by non-growing *Pseudomonas putida* whole cells which can be recycled to reduce process cost.
- An engineered *Pseudomonas putida* strain that can co-utilise xylose with glucose and cellobiose is already available, and new strains that can co-utilise multiple plant biomass-derived sugars and convert them into valuable chemicals are under development.



114 INNOVATION

Next-generation binary T-DNA vectors for (plant) synthetic biology

Researchers at the CNB and the Polytechnical University of Valencia have jointly developed an expression vector system that provides a flexible framework for plant biotechnology and synthetic biology applications. The system includes novel mini binary vectors with compatible origins. Vectors have been used successfully in plant transient and stable expressions, CRISPR/Cas9-targeted genome mutagenesis, and for genetic circuit component and viral expression vector delivery.

CNB INVENTORS

Fabio Pasin
Juan Antonio García Álvarez
Carmen Simón Mateo

APPLICATION NUMBER AND PRIORITY DATE

PCT/ES18/070421, 12/06/2017

MAIN INNOVATIONS AND ADVANTAGES

- Compactness: the reduced size (< 3.8 kb) of the vectors facilitates cloning and reverse genetic studies.
- Flexibility: vectors autonomously replicate in *Escherichia coli* and *Agrobacterium*.
- Stability: vectors include bacterial terminators that avoid transcriptional read-through to T-DNA cassettes and help to stabilise large/complex inserts.
- Scalability: vectors are suitable for standard as well as high-throughput cloning methods (e.g. Golden Gate, GoldenBraid, and Gibson assembly)
- Standardisation: vectors meet current plant synthetic biology standards and allow the use of publicly available DNA parts libraries.
- Compatibility: vectors can be multiplexed with binary vectors commonly used by plant scientists for multi T-DNA delivery in a two-vector/one-strain expression approach.

Transphagocytic T cells as anti-cancer immunotherapy

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

CNB INVENTOR

Esteban Veiga Chacón

APPLICATION NUMBER AND PRIORITY DATE

Patent filed in USA, Canada, Australia and EU, 7/8/2015

MAIN INNOVATIONS AND ADVANTAGES

- The invention can be used to prevent/treat tumours and/or stimulation of an immune response against tumour antigens.
- tiCD4+ T cells (trained by bacteria) are newly defined antigen-presenting cells that can be useful as a cancer immunotherapy tool.
- tiCD4+ T cells mediated antigen presentation potently cross-prime naive CD8+ T cells.
- tiCD4+ T cells mediated antigen presentation generates central memory C8+ T cells with very low levels of PD-1.
- The anti-tumour activity of tiCD4+ T cells has been tested in mouse melanoma models. The invention can be applied for melanoma and other highly immunogenic tumours.

