"la Caixa" Foundation

Press release

"la Caixa" Foundation devotes more than 23 million euros to 33 new biomedicine and health research projects in Spain and Portugal

- **The fifth 2022 CaixaResearch Call for Proposals in Health Research will provide funding for 33 new cutting-edge biomedical research projects in the two countries, with grants of up to one million euros per project.**

- **The call is aimed at basic, clinical or translational research initiatives of excellence and great potential impact that address health challenges in the fields of cardiovascular, infectious and oncological diseases, and neuroscience, as well as projects to develop enabling technologies in these fields.**

- **The initiatives selected include, among others, projects to regenerate heart tissue after a heart attack; to decipher the impact of 'jumping genes' on tumour proliferation; to study how the gut microbiota influences loss of control of intake in obesity; to create a new technology to purify the air of respiratory viruses; and to develop therapeutic nanotechnology that can halt the progression of Parkinson's disease.**

- **The "la Caixa" Foundation CaixaResearch Call for Proposals is organised in partnership with the Fundação para a Ciência e a Tecnologia (FCT) of the Ministry of Science, Technology and Higher Education of Portugal, which subsidises 3 of the 13 Portuguese projects selected. The Luzon Foundation also cooperates by co-funding a project on amyotrophic lateral sclerosis (ALS).**

- **Since the programme was first launched in 2018, the organisers have devoted nearly 95 million euros to 138 research projects selected by a committee of international experts.**

Barcelona, 20 September 2022. Thirty-three promising new biomedical and health projects at research centres and universities in Spain and Portugal have

been selected in the 2022 CaixaResearch Call for Proposals in Health Research. In this way, "la Caixa" Foundation once again affirms its support for projects of excellence that can have a positive impact on the health of citizens.

The Foundation will devote a total of 23.1 million euros to these projects – 20 of them Spanish, 13 Portuguese – which will be implemented over the next three years.

The call, to which 546 proposals were submitted this year, aims to identify and promote initiatives of scientific excellence with the greatest potential value and social impact in basic, clinical and translational research, and innovation. All are aimed at resolving challenges in areas of the health field, such as infectious diseases (11 projects), neuroscience (9), oncology (8) and cardiovascular and related metabolic diseases (5). Several of the selected projects will develop biomedical technologies aimed at addressing some of these health challenges.

As regards the origin of the selected projects, 20 are from research centres and universities in different Spanish regions: Catalonia (9), Madrid (6), Andalusia (2), Valencia (2) and Galicia (1). The other 13 are from different centres in Portugal: 7 from the Lisbon Metropolitan Area; 3 from the Northern Region (Porto, Braga); 2 from the Central Region (Coimbra); and 1 from the Algarve.

The CaixaResearch Call for Proposals is organised in partnership with the Fundação para a Ciência e a Tecnologia (FCT), of the Ministry of Science, Technology and Higher Education of Portugal, which assigns 2.3 million euros to subsidise 3 of the 13 Portuguese projects selected this year. The call is also supported by the Luzón Foundation which, in cooperation with "la Caixa" Foundation, will co-fund a project on ALS.

The type of grants awarded ranges from funding of up to 500,000 euros over three years for projects submitted by a single research organisation to 1,000,000 euros over three years for projects submitted by consortia formed by 2-5 research organisations.

Since the programme was first launched in 2018, "la Caixa" Foundation has devoted 94.8 million euros to 138 innovative research projects with great social impact, 95 of them led by Spanish teams and 43 by Portuguese researchers, in what is the only call for proposals for health research grants in the Iberian Peninsula. All the projects are chosen every year by a committee of

international experts who evaluate the proposals, interview those shortlisted and select those with the highest quality.

"la Caixa" Foundation recently launched the latest CaixaResearch Call for Proposals in Health Research, to be decided in 2023. Interested researchers are invited to submit their applications for funding.

*** The annex accompanying this press release lists the titles of the 33 selected projects and the researchers and research centres leading them, as well as providing a brief summary of their goals.**

Further information:

"la Caixa" Foundation Press Department
Andrea Pelayo: 618 126 685 / apelayo@fundacionlacaixa.org
https://prensa.fundacionlacaixa.org/es/
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APPENDIX OF SELECTED PROJECTS IN THE CAIXARESEARCH CALL FOR HEALTH RESEARCH 2022

Understanding the role of new factors that cause genomic instability in cancer

Project leader: Andrés Aguilera
Institution: Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Universidad de Sevilla (Spain).

Description:
Genome instability, that is, alterations in the transmission of genetic information from one cell to another during cell reproduction, plays an eminent role in cancer origin. Generally speaking, cells are highly efficient at transmitting their DNA from one generation to the next; however, when there are failures in DNA repair, replication and DNA-to-RNA transcription, this can cause the information transmitted from one cell to the next to change dramatically at an abnormally high rate, with the accumulation of mutations and chromosomal rearrangements that can eventually affect the cellular gene expression programme, increasing the likelihood of affecting tumour suppressor genes or genes involved in metastasis.

In the project, the researchers will study the role played by RNA metabolism in chromosomal rearrangements at both genomic and molecular level, as these generate a high propensity for cancer. The aim is to identify the mechanisms of interaction between RNA metabolism and DNA repair functions that compromise genome integrity.

A new approach to combating antimicrobial resistance

Project leader: João Morais Cabral
Institution: i3S- Instituto de Investigação e Inovação em Saúde da Universidade do Porto (Portugal)

Description:
The rise in antimicrobial resistance, a natural process in which microorganisms develop resistance to the drugs used to treat them, is a serious problem and one of the greatest threats to global health. Combating antimicrobial resistance involves preventing the misuse and abuse of antibiotics and finding new approaches to combat bacterial infections, either by discovering new drugs or by finding ways to increase bacterial sensitivity to existing antibiotics.

This project focuses on finding and characterising fundamental biological processes in bacteria that are crucial for their viability. Specifically, the researchers will study bacterial proteins to determine whether they may be viable antibacterial targets that can be further explored to develop future clinical applications.

How to prevent the next outbreak of West Nile virus in Spain

Project leader: Jordi Figuerola

Institution: Estación Biológica de Doñana- Consejo Superior de Investigaciones Científicas (EBD-CSIC) (Spain)

Description:
Mosquito-borne infectious diseases, such as malaria, dengue fever and Zika, are a major threat to human health and the development of society. They are estimated to cause more than 700,000 deaths per year. Although for Europe has been practically free of pathologies of this type the last half century, West Nile virus (WNV) has re-emerged in the last decade and has increased its incidence and geographical distribution. In fact, the virus is endemic to Spain and caused 77 severe cases and 8 deaths, mostly in Andalusia, in 2020.

Until now, strategies aimed at managing these diseases have been based on trying to control the spread of the virus using biocides against mosquitoes when and where human cases of infection are detected.

However, rather than reacting to the appearance of cases of infection, the ARBOPREVENT project is aimed at preventing them in order to reduce the risk of transmission of WNV and other arboviruses among the human population. To this end, the researchers will generate early warning mechanisms to detect outbreaks several weeks before they occur so as to reinforce mosquito control, reduce the possible circulation of the virus and prevent it from spreading to humans.

The researchers will also map the distribution of the different mosquito species, identifying breeding areas and proposing strategies for controlling the mosquito population using methods compatible with environmental conservation.

How do cancer cells modify the surrounding microenvironment to their advantage?

Project leader: Elías Campo
Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) (Spain)
Consortium:

- Xose S. Puente, Fundación Universidad Oviedo (Spain)
- Holger Heyn, Centre de Regulació Genòmica-CRG (Spain)

Description:
Chronic lymphocytic leukaemia (CLL) is the most common haematological cancer among adults in the West, with an estimated incidence of 4-5 cases per 100,000 inhabitants per year. The disease may evolve in very different ways: while in some people it stabilises and does not require treatment, in others it progresses very rapidly and, despite treatment, eventually becomes resistant.

Although recent genomic and epigenomic studies, conducted at large scale, have revealed the complexity of the disease's mutations, they do not fully explain its diverse evolution. Recent new data point to the need to take into account, not only alterations in the genome, but also the influence of the tumour's microenvironment. On the one hand, the immune system attacks leukaemic cells, but at some point it weakens and this defence appears to be ineffective. On the other hand, cancer cells need stimuli to grow and survive, and these are provided by the non-tumour cells in their microenvironment.

This project will study how tumour cells are able to influence their microenvironment to their advantage, escaping the host immune system's response. The researchers will also seek to determine whether new genomic alterations can function as targets for therapies that modulate the response of the patients' immune system.

Innovative neuromodulation strategies to treat brain diseases

Project leader: Paulo Aguiar
Institution: i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal
Consortium:

- Liset Menendez de la Prida, Instituto Cajal, Consejo Superior de Investigaciones Científicas- CSIC (Spain)
- Joao Ventura, Universidade do Porto (Portugal)

Description:
Neurological diseases are one of the leading causes of death and disability worldwide. Their prevalence and incidence are also rising due to an ever growing and ever ageing world population. Current strategies to treat these pathologies mostly rely on pharmacological approaches. However, these tend to have numerous side effects and can become ineffective in the long-term.

Earlier studies have already shown that brain function is intimately related to the electrical activity of specific neuronal circuits. That is why recent initiatives have focused on precisely stimulating or modulating the electrical activity of neurons. Examples include deep brain stimulation used for Parkinson's disease and cochlear implants to alleviate hearing loss.

Despite the potential of these devices to stimulate the neuronal circuits, their development has been hindered by challenges such as the size of the devices themselves or the batteries they use. With NeuroSpark, the researchers in this project aim to develop and validate the first neuromodulation strategy based on electrical nanocomponents capable of emulating neuronal synapses. The goal is for this device to provide real-time adaptive control of neuronal activity. Its efficacy will be assessed, at first, in epilepsy models.

Towards a new treatment for autoimmune encephalitis
Project leader: Josep Dalmau
Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) (Spain).
Consortium:

- Thais Armangué, Fundació Privada per a la Recerca i la Docència Sant Joan de Déu, Spain

Description:
Anti-NMDA receptor encephalitis is a rare disease caused by the patient's own immune system attacking a brain receptor called NMDA. It is the most common encephalitis mediated by antibodies against a neuronal protein or receptor. It mainly affects young adults and children, causing psychiatric symptoms such as psychosis and neurological symptoms (seizures, memory loss, abnormal movements and even coma). After treatment, patients improve, but can continue to suffer from psychiatric and cognitive

disorders for months or years, generating a significant social, economic and family burden.

The cause of these long-lasting symptoms and how to treat them is currently unknown. Better knowledge of this stage could help to improve decision-making about the most appropriate treatment, as well as predicting the patient's prognosis more precisely.
In this project, the researchers will examine the alterations that occur in the brain through a study in which they will recruit patients, who will attend visits and undergo a series of tests, both in hospital and at home via mobile devices. The aim will be to identify biomarkers in blood and cerebrospinal fluid samples in order to find the optimal treatment for these patients, who will undergo online cognitive neurorehabilitation sessions.

The researchers will also use a new animal model of the disease in an attempt to better understand the cause of symptoms at molecular level, in the hope that this knowledge will open the door to designing new treatment strategies that can speed up patients' recovery.

Identifying new immune targets to treat cardiovascular disease

Project leader: Almudena R. Ramiro
Institution: Centro Nacional de Investigaciones Cardiovasculares Carlos III -CNIC (Spain)
Consortium:

- Dr. José Luis Martín Ventura, Fundación Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz (Spain)

Description:
Cardiovascular diseases are the leading cause of death worldwide, and the WHO estimates that 17.9 million people die from them every year. These deaths are mainly caused by atherosclerosis (the build-up of fat, cholesterol and other substances in the arteries) and abdominal aortic aneurysm, the two most common diseases of the arterial vessels. The immune system plays a key role in both diseases, as they are associated with a chronic inflammatory immune response involving both innate and adaptive immunity.

Due to this major role in causing cardiovascular diseases, the immune system is a highly attractive target for the development of early diagnostic tools and new treatments. However, this path has always been hampered by limited knowledge regarding which antigens trigger the immune response.

The research team has already identified an atherosclerosis antigen and in this project will attempt to identify new immune targets for both atherosclerosis and abdominal aortic aneurysm. The research will pave the way for implementing new strategies to restrict or enhance specific immune responses.

New approaches to heart tissue regeneration after heart attack

Project leader: Rui Benedito
Institution: Centro Nacional de Investigaciones Cardiovasculares Carlos III -CNIC (Spain)

Consortium:

- Mariona Graupera, Fundació Institut de Recerca Contra la Leucèmia Josep Carreras (Spain)
- Holger Heyn, Centre de Regulació Genòmica (CRG) (Spain)
- Rafael Kramann, University Hospital RWTH Aachen (Germany)

Description:
Myocardial infarction is the leading cause of death in the developed countries and the third most important in the developing countries. Most heart attacks are caused either by myocardial ischaemia or coronary artery occlusion. Seventy per cent of people survive heart attack, although how severely heart function is affected varies according to the extent of the infarct zone.

Both heart tissue and current therapies have very poor regenerative capacity, and this leads ultimately to high morbidity and associated health costs. The low regenerative capacity of heart tissue is caused to a large extent by the very limited activity of vascular cells in the infarct zone. This results in insufficient blood supply and also limits the capacity for healing and regeneration.

In this project, CNIC researchers aim to characterise and identify genetic pathways and pharmacological compounds that can activate these vascular cells in infarcted zones in order to effectively promote their growth and stimulate the tissue's regenerative properties, which could pave the way to discovering new strategies to prevent heart failure.

What influence does the environment have on cognitive abilities and their age-related decline?

Project leader: Ángel Barco
Institution: Instituto de Neurociencias, UMH-CSIC - Consejo Superior de Investigaciones Científicas (Spain)

Description:
Increasing life expectancy has inevitably led to a higher incidence of age-related diseases, which represents an enormous challenge to the health system. Great efforts are therefore focused on trying to prevent or delay age-related cognitive decline with the aim of increasing the quality of life in the later stages of life.

Both genetic inheritance and environmental conditions are known to influence cognitive ability. Environment enrichment is associated with better learning, better memory and healthier ageing, while environmental impoverishment is associated with the opposite effects. One of the possible mechanisms by which the environment influences our cognitive abilities, particularly early in life, are epigenetic changes in the brain.

In this project, the researchers will focus on the hippocampus, a brain area linked to cognitive abilities, with the aim of identifying and assessing the biological relevance of epigenetic changes in chromatin, the genetic material of the cell found in the nucleus, associated with differential performances in cognitive tasks.

A lymphoma-based organoid on a vascularised chip to advance in the design of personalised immunotherapies

Project leader: Patricia Pérez-Galán
Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) (Spain).
Consortium:
Kristina Haase, EMBL Barcelona (Spain)
Description:
Personalised medicine is essential to treat some cancers due to their enormous genetic heterogeneity. This is the case, for instance, of non-Hodgkin lymphoma, the most common haematological tumour. So far, samples taken from the patient's lesion and cultured in the laboratory have been used to try to predict the response to certain drugs. However, these in vitro models do not reproduce the tumour microenvironment (cellular, vascular and physical support), which is particularly important in the case of lymphomas due to the crucial role it plays in tumour survival and response to treatment.

In this project, the researchers aim to develop an organoid from the patient's tumour sample that recreates the immune microenvironment of the lymphoma, as well as its physical support, and to integrate it into a chip using state-of-the-art vascular models. This innovative lymphoma chip will make it possible to analyse the access of therapies to the tumour and to evaluate the response of lymphomas to different immunotherapies in a personalised way. This approach will also contribute to reducing the use of animals in biomedicine.

A new approach to improve the prospects of cancer immunotherapies

Project leader: Fran Supek
Institution: Institut de Recerca Biomèdica de Barcelona (IRB Barcelona) (Spain)
Consortium:
Ana Janic, Universitat Pompeu Fabra (UPF) (Spain)

Description:
Although immunotherapy has revolutionised cancer treatment, only around twenty per cent of patients currently benefit from it. Moreover, identifying these patient before treatment begins continues to be a major challenge.

One possible indication is the number of mutations, which predicts whether a tumour is treatable by immunotherapy. This suggests that the mutated proteins can be detected by the immune system. It is also known that human cells have a mechanism by which they can silence the expression of mutated proteins.

In this project, the researchers' hypothesis is that that switching off this mechanism in cancer cells would de-silence many mutations, causing more mutated proteins to be produced and rendering the tumour visible to the immune system and treatable by immunotherapy.

They will test this hypothesis using animal models of lung cancer and lymphoma. Their aim is to pave the way for future studies investigating the administration of drugs that inhibit this mechanism with a view to improving the prospects of immunotherapy.

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Towards the development of a new generation of antibiotics to combat antimicrobial resistance

Project leader: Alfonso Jaramillo
Institution: Instituto de Biología Integrativa de Sistemas (I2SysBio-CSIC) (Spain)

Description:
It is feared that antimicrobial resistance will cause more deaths than cancer by 2050. This is a serious global health problem that requires new strategies to systematically produce antimicrobial molecules against any bacteria.

Currently, most approaches to developing new antibiotics are based on screening potential natural molecules that already have antibiotic capacity or creating new molecules by randomly modifying existing ones and testing their potential antibiotic capacity against pathogens through a trial-and-error approach. But this strategy is slow, takes many years and enormous effort, and is not always successful. Moreover, in the meantime bacteria can combat this by developing new resistance due to their evolutionary capacity. Indeed, they have been shown to do this within hours in controlled environments.

The researchers will use evolution to create protein-based antimicrobial molecules. To enable this, they will develop a technology capable of accelerating evolution one million-fold compared to natural systems, making it possible to foresee mutations that could make bacteria resistant so as to adapt antimicrobial molecules to them. Moreover, the antibacterials they develop will not be able to evolve on their own and will be harmless to beneficial bacteria, resolving one of the undesirable effects of current antibiotics.

Towards a better understanding of how the immune system makes tailored responses to different pathogens

Project leader: Nuria Martínez
Institution: Centro de Biología Molecular Severo Ochoa, CBMSO-CSIC (Spain)

Description:
Every time we suffer from an infection, our immune system triggers a specific response according to the nature of the pathogen (viral, bacterial, helminth). This involves differentiating the immune system cells into different subtypes with specific defence functions, as well as the production of specific antibodies. The specificity of the response to each type of pathogen is the key to effectively combating the infection.

The success of this response depends partly on fine-tuned communication between immune cells. To date, this has been linked to physical contact between cells and the production of cytokines.

The researchers start out from the hypothesis that metabolic communication between one type of immune cells – B cells – and their neighbouring cells is what determines the specific response to each different pathogen.

In this project, they aim to identify how and when this communication occurs and how it is shaped by specific pathogens. This will pave the way to find new therapeutic strategies to control infections and autoimmune diseases, as well as to improve current vaccines.

Determining the impact of "jumping genes" on cancer proliferation

Project leader: José Tubio
Institution: Centro de Investigación en Medicina Molecular y Enfermedades Crónicas (CiMUS), Universidad de Santiago de Compostela (Spain).

Description:
The human genome has the same number of protein-coding genes as a simple worm. Thus, our complexity is explained by the way our genes are regulated. On this point, a significant fraction of our DNA is made up of fragments with the ability to move, so-called "jumping genes" or mobile elements: transposons and retrotransposons.

Retrotransposons can jump from one side of the genome to the other and cause loss of fragments of genetic material and scatter regulatory regions. Earlier studies conclude that retrotransposons are an important source of mutations in cancer, although the functional consequences of their activity are largely unknown.

In this project, the researchers will attempt to determine to what extent this mobilisation of retrotransposons causes changes in the context of the three-dimensional structure of the tumour genome and how this impacts on the function of cancer genes.

Prompt diagnosis of coronary heart disease to prevent early mortality

Project leader: Teresa Matias Correia
Institution: Centro de Ciências do Mar do Algarve (CCMAR) (Portugal)
Consortium:

- Rita G. Nunes, Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento (Portugal)
- Carlos Alberola-López, Universidad de Valladolid (Spain)
- Borja Ibáñez Cabeza, Centro Nacional de Investigaciones Cardiovasculares Carlos III -CNIC (Spain)

Description:
Coronary heart disease (CHD), which is the leading cause of death worldwide, occurs when blood flow to the heart becomes restricted. Early detection of this condition is of paramount importance for preventing life-threatening events.

At present, the most commonly used method for the early detection of CHD is coronary angiography. This test provides images of blood flow through the coronary arteries to the heart. The problem is that it is an invasive procedure, requires hospital admission and exposes patients to radiation, so it is not only expensive, but also rather impractical for routine screening.

There is an alternative to this: perfusion cardiac magnetic resonance imaging (perfusion CMR). Unlike angiography, this procedure is safe and non-invasive. The drawbacks are its limited image quality and incomplete heart coverage. Moreover, data interpretation is complex and requires highly trained staff. This has limited the widespread adoption of perfusion CMR.
To overcome these drawbacks, the researchers in this project will combine mathematical models of cardiac blood flow, perfusion CMR and image reconstruction to obtain unprecedented insights into heart health. The results from the project will contribute to improving the diagnosis and management of CHD and ultimately increase the survival rates, quality of life and safety of patients.

Can we grow older in a healthier way?

Project leader: Claudio Franco
Institution: Católica Biomedical Research Centre and Instituto de Medicina Molecular João Lobo Antunes (Portugal)

Description:
Life expectancy in the developed countries has doubled in the last century thanks, to a large extent, to advances in vaccines, antibiotics and health services. However, this substantial increase in longevity is accompanied by an equally significant increase in diseases associated with ageing, including cancer, cardiovascular and neurodegenerative diseases. Healthy ageing is therefore one of the main challenges facing modern society today, and a priority for biomedical research.

Ageing is a complex biological process that involves a significant decline in organ physiology and function. Recent studies have cast light on the crucial role that blood vessels play in ageing. For example, ageing is associated with a decline in the density of the vascular system, and preventing this decline leads to healthier ageing. However, the mechanisms that explain the association between alterations in the vascular system, ageing of the body and the onset of age-related diseases remain poorly understood.

In this project, the researchers will study the role of endothelial cells, which line the interior of blood vessels, in healthy ageing. Indeed, they have already identified a protein in these cells that acts as a crucial regulator of both ageing and age-related diseases.

A new treatment to prevent age-related macular degeneration

Project leader: Miguel Seabra
Institution: NOVA Medical School, Universidade NOVA de Lisboa, NMS|NOVA (Portugal)
Consortium:

- Antonio Cuadrado, Universidad Autónoma de Madrid, Spain

Description:
Age-related macular degeneration (AMD) is a retinal degenerative disease that causes a progressive impairment of the central vision. AMD is the leading cause of irreversible blindness in developed countries and is currently incurable. The disease is caused by

the death of a specific type of cells named photoreceptors, in the area of the retina responsible for high-resolution vision, the macula.

The researchers have already found strong new evidence that the NRF2 protein plays a key role in macula protection, preventing these cells from dying during AMD. Accordingly, in this project they will explore the protective role that NRF2 may play in AMD before it is irreversible and causes permanent damage. Laboratory-based studies will aim at selecting the best molecule that activates NRF2 and protects the retina. Simultaneously, these studies will be complemented by a clinical observational study in patients, who are prescribed an NRF2-activating drug already in clinical use. The results of this study could pave the way towards the development of a much sought-after AMD preventive treatment, as well as other chronic age-related diseases.

Towards a new therapeutic nanotechnology to combat the progression of Parkinson's disease

Project leader: Marta Martínez-Vicente
Institution: Vall d'Hebron Institut de Recerca (VHIR) (Spain)
Consortium:

- Julia Lorenzo, Universidad Autónoma de Barcelona (Spain)
- María Jesús Vicent, Centro de Investigación Príncipe Felipe (CIPF) (Spain)

Description:
Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's. It is a disease with no cure at present, and so far there are only treatments that alleviate some of the symptoms, but do not halt it or delay the progressive death of dopaminergic neurons, which is the main cause of the pathology. For this reason, there is an urgent need to develop new therapies aimed at halting this neurodegenerative process.

Recent studies in animal models have shown that restoring the function of the lysosomal enzyme GBA can prevent neurodegeneration and alleviate the symptoms of Parkinson's disease. A therapy has already been approved for use in humans that is capable of delivering the GBA enzyme. However, this potential therapeutic treatment has not been applicable to date in Parkinson's disease because the GBA enzyme cannot cross the blood-brain barrier to reach the central nervous system, where it can exercise its function.

To overcome this important limitation, the researchers in this project are developing an innovative technology based on polymeric nanoconjugates capable of delivering the GBA enzyme intranasally to the brain to slow neurodegeneration. This opens up a promising innovative approach to halting the progression of Parkinson's disease which also suggests a new pathway for the future application of this new nanomedicine to other neurodegenerative diseases.

Towards a better understanding of how the immune system responds to infections

Project leader: Esteban Ballestar
Institution: Institut de Recerca contra la Leucèmia Josep Carreras (Spain)

Description:
The immune system equips the body to fight infections. In most cases, it is highly effective and protects us from illness. However, some individuals are born with immunodeficiencies that make them much more susceptible to diseases caused by pathogens, either because their immune cells are insufficient or defective. Studying these individuals enables a better understanding of how the immune system works and how it organises its responses to potential attacks.

In this project, the researchers will generate a map of immune cells and the interactions between them. To this end, they will focus on a primary immunodeficiency, common variable immunodeficiency (CVID), which causes severe and recurrent intestinal and respiratory infections that require lifelong immune replacement therapy.

The goal is to obtain a better understand of the mechanisms underlying the challenges that these patients face in fighting infection. Another aim is to gain insight into how immune cell crosstalk orchestrates efficient responses to infection. All this, in order to provide new tools to improve the medical care and quality of life of patients with immunodeficiencies.

Towards a cure for long COVID

Project leader: Christian Brander
Institution: IrsiCaixa, Institut de Recerca de la Sida la Caixa (Spain)
Consortium:

- Simon Heath, CNAG-CRG, Centre for Genomic Regulation (Spain)
- Lourdes Mateu, Fundación FLS de Lucha contra el Sida, las Enfermedades Infecciosas y la Promoción de la Salud y la Ciencia (Spain)
- Joaquim Segalés, Institut de Recerca i Tecnologia Agroalimentàries – IRTA (Spain)

Description:
Ten per cent of COVID-19 infected individuals continue to experience symptoms months after infection. This illness, known as post-COVID-19 condition (PCC), can include severe neurological impairments such as brain fog and loss of memory, concentration or attention.

Although the reason for the persistence of symptoms is not yet known, several studies suggest that one of the possible causes could be alterations at epigenetic level, i.e., mechanisms that acts like on/off switches in genes. As in the case of HIV, the IrsiCaixa research team has observed that SARS-CoV-2 infection could be the cause of changes in these switches, which turn genes on and off and can alter the response of the patient's immune system, resulting in neurological alterations.

To determine the role of epigenetics in long COVID, the project team will assess whether there are alterations at this level, while also characterising potential neurological and immune system alterations. This will enable identification of the key affected genes involved in long COVID. To this end, the team will use an animal model of COVID-19 and test new therapeutic strategies aimed at reversing epigenetic dysregulation.

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A new way to treat brain metastases in breast cancer

Project Leader: Helena Florindo
Institution: Faculdade de Farmácia da Universidade de Lisboa (Portugal)
Consortium:

- Ronit Satchi-Fainaro, Universidad de Tel Aviv (Israel)

Description:
In 2021 breast cancer became the most common type of cancer globally, according to data published by the International Agency for Research on Cancer (IARC). Every year there are an estimated 132 cases per 100,000 inhabitants, most of them women. This type of primary tumour eventually generates brain metastases in 15-30% of patients. In fact, breast cancer is the second most frequent cause of brain metastases, which can appear even a decade after the primary tumour has been successfully treated. The prognosis when this occurs is poor.

Despite recent advances in cancer treatments, including immunotherapy, brain tumours and brain metastases remain urgent unmet medical needs. This is largely because the mechanisms by which cancer cells escape from their primary site of origin and nest and proliferate in another distant organ are not fully understood. Moreover, the way the immune cells control the communication between the brain microenvironment and tumour cells, which eventually leads to metastasis, is still not fully elucidated.

The project focuses on analysing the interactions established between the tumour, the vascular system and the immune system in metastatic brain cancers. The goal is to pave the way for the design of a new nano-immunotherapy that can regulate the brain's immune function so that it prevents and treats brain metastases.

A platform to rapidly develop and produce new biopharmaceuticals to treat emerging viruses

Project leader: Cláudio Manuel Soares
Institution: Instituto de Tecnologia Química e Biológica António Xavier (ITQB NOVA), Universidade NOVA de Lisboa (Portugal)
Consortium:

- Ana Salome Veiga, Instituto de Medicina Molecular-IMM (Portugal)
- Maria João Amorim, Católica Biomedical Research Center (CBR), Universidade Católica Portuguesa (Portugal)
- José Maria Valpuesta, Consejo Superior de Investigaciones Científicas (CSIC), (Spain)

Description:
The emergence of viral diseases such as influenza and COVID-19 threatens global health and socio-economic stability. For this reason, it is vital to be able to respond rapidly and effectively to viral threats and outbreaks. This requires targeted therapeutic solutions and, in this context, biopharmaceuticals can play a key role, precisely

because of their high potential specificity. However, their use requires rapid development and production strategies.

In this project, with a view to resolving this problem, the researchers aim to build an integrated platform able to design new molecules that are potentially active against a given threat and validate them in vitro. The platform, known as BioPlaTTAR, will accelerate the development of biopharmaceuticals for specific pathogens in emergency situations.

At first, the researchers will focus on the influenza and COVID-19 viruses. Their results could pave the way for new treatments to be used as an alternative to or in conjunction with small molecules and vaccines. In the future this platform can be adapted to new viral outbreaks. This will boost the competitiveness and self-sufficiency of Europe in the field of biopharmaceutical development.

Identifying new biomarkers for the progression of heart failure

Project leader: José Javier Fuster
Institution: Centro Nacional de Investigaciones Cardiovasculares Carlos III -CNIC (Spain)
Consortium:

- Nuria Lopez-Bigas, ICREA - Institut de Recerca Biomèdica (IRB Barcelona) (Spain)
- Antoni Bayés Genís, Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP) (Spain)
- Domingo Andrés Pascual Figal, Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (Spain)
- Manel Esteller Badosa, Fundació Institut de Recerca contra la Leucèmia Josep Carreras (Institut Josep Carreras) (Spain)

Description:
Until recently, the acquisition of mutations in blood-forming stem cells was thought to be relevant only to cancer. However, there is growing evidence that it is also a hallmark of ageing. Indeed, several human studies have shown that people carrying certain mutations in blood cells – a condition called clonal haematopoiesis – have high mortality rates, mainly due to cardiovascular disease.

Scientists have observed a potential connection between these mutations and the development of heart failure, a disease which develops when the heart does not pump enough blood for the body's needs.

MyoClonal is a collaborative project which will combine studies in humans and mice to further our understanding of the relevance of clonal haematopoiesis in cardiovascular disease. The researchers will conduct an in-depth study into the effect on heart failure of different acquired mutations in blood cells. The knowledge they generate will be used to improve the management of heart failure patients, who often require frequent hospitalisations and are at high risk of death.

Does gut microbiota play a role in the loss of intake control in obesity?

Project leader: Rafael Maldonado
Institution: NeuroPhar-MELIS, Universitat Pompeu Fabra (UPF) (Spain)
Consortium:

- Raül Andero Galí, ICREA - Institute of Neuroscience, Universitat Autònoma de Barcelona (UAB) (Spain)
- José-Manuel Fernández-Real, Institut d'Investigació Biomèdica de Girona, Universitat de Girona (Spain)

Description:
At present, four in ten people in the world are overweight or obese, and the incidence of these two conditions is increasing, particularly in developed countries, where they are reaching alarming levels and represent a serious public health problem.

These metabolic pathologies are often associated with complex alterations that lead to a loss of behavioural control that promotes weight gain. In this project, the researchers will study which environmental factors impact on brain function and lead to loss of appetite control. More specifically, they will focus on epigenetic mechanisms mediated by the gut microbiota.

The project results will generate greater understanding of these diseases and the role that behaviour plays, and will identify new biomarkers to identify the individuals that are most at risk of losing appetite control, as well as opening the door to the development of new therapies to treat obesity and overweight, and eating disorders.

How can we make vaccines effective for the entire population?

Project leader: Luis Graca
Institution: Instituto de Medicina Molecular (Portugal).

Description:
Vaccines are among the therapies with the greatest impact on human health, reducing mortality from infectious diseases. Although they are generally highly effective, they are less so in some population groups, such as the elderly. The reason for this is that the immune system loses its ability to respond to threats over time. An example of this is the flu vaccine, for which there are still high mortality and morbidity rates among this age group.

This project brings together experts in vaccines, nanoparticles and bioinformatics to explore a new strategy aimed at boosting the immune system's reaction so that vaccines do not lose their effectiveness. To this end, they will start from biological knowledge on the germinal centre and adjuvants and use nanoparticles to administer antigens and immunomodulatory compounds. This is a novel method of influencing antibody production that will also lead the researchers to a better understanding of molecular mechanisms that can help to increase vaccine efficacy.

How diet impacts the immune system in early life

Project leader: Manuela Ferreira
Institution: Centro de Neurociências e Biologia Celular da Universidade de Coimbra, (Portugal)

Description:
Infectious diseases remain one of the leading causes of death among children under five, while malnutrition has been shown to be a risk factor that worsens the prognosis. In view of this, there is an urgent need to attain a better understanding of how the intestine works and of the dialogue between the immune system and food ingested. This could pave the way for new preventive strategies, potential targets and effective treatments for gastrointestinal infections.
The project focuses on investigating one type of immune cell, intraepithelial T-lymphocytes, which are found in the intestinal epithelium (the lining of the gut) and act as the first line of immune defence and in regulation of the metabolism.

Despite many advances in recent years, the mechanism by which these lymphocytes develop, as well as their specific function, is still unknown. In this project, the researchers will focus on analysing the role of diet-derived retinoids – a type of chemical compound related to vitamin A and capable of regulating the growth of epithelial cells – on T lymphocytes, and on determining their function in the intestine in early life.

What is the role of senescent cells in breast cancer progression?

Project leader: Joaquín Arribas
Institution: Institut Hospital del Mar d'Investigacions Mèdiques, IMIM-Hospital del Mar (Spain)

Description:
Cancer is an age-related disease and a major contributor to the global health burden. Despite the ever-improving efficacy of treatments, a substantial percentage of tumours relapse, and patients often develop aggressive metastases. Accordingly, there is a continuing need to develop new therapies with more lasting effects.

Recent studies show that tumour relapse and the side effects of anti-cancer treatments are due to a large extent to the accumulation of senescent cells – damaged cells that stop growing but do not die, remaining active and releasing substances that produce harmful inflammation that promotes tumour progression.

In this project, the researchers will use experimental models to monitor and specifically eliminate these senescent cells. They will focus on breast cancer, the most common type of tumour in women. Their starting point is the hypothesis that eliminating these senescent cells during certain stages of tumour progression will contribute to the development of more efficient therapies to prevent tumour relapse and some deleterious side effects. They will also explore novel therapeutic strategies to eliminate senescent cells and find new, safer treatments.

How is perception altered in schizophrenia and other neuropsychiatric illnesses?

Project leader: Leopoldo Petreanu

Institution: Fundación Champalimaud (Portugal)
Consortium:

- Fundación Champalimaud

Description:

To perceive the world around us, our brain combines the sensory information it receives from sight with previously acquired knowledge. This is how we form a coherent picture of our environment and can make predictions to fill in gaps in the information that reaches our senses.
When this process malfunctions, it can cause us to perceive a reality that does not exist, as happens to some people with neuropsychiatric disorders such as schizophrenia. Hence the importance of understanding how the brain is able to combine prior knowledge with new information received by the senses and how predictions and expectations influence the world we perceive.

In this project, the researchers will attempt to experimentally bind a visual stimulus to patterns of neural activity in brain areas representing visual information in a mouse model of schizophrenia. They will then compare the results to those of healthy mice in order to identify how internal neural activity influences the brain's response to expected or unexpected stimuli. They will also attempt to determine whether activity in these brain regions can induce activation similar to that caused by sensory stimuli, even in the absence of such stimuli. These experiments will lead to new understanding of the role of expectation in how we perceive the world and of neuropsychiatric diseases themselves.

Towards more effective, less toxic treatments for acute lymphoblastic leukaemia

Project leader: Vera Sofia Correia Martins
Institution: Instituto Gulbenkian de Ciência (Portugal)
Consorcio

- Klaus-Michael Debatin, Ulm University Medical Center (Germany)

Description:
T-cell acute lymphoblastic leukaemia (T-ALL) is a very aggressive type of blood cancer that originates from a type of cells of the immune system, the T-lymphocytes. It affects mostly children, but can also occur in adolescents and adults. Although it is curable in 80% of children and 60% of adults, treatment causes severe secondary side effects. This means that, currently, 2 out of 10 children and 4 out of 10 adults diagnosed with T-ALL fail to respond to treatment. In addition, the disease re-emerges in some of the patients that initially respond well and for them the prognosis is poor.

Current therapies are clearly insufficient, and should become specific to avoid secondary side effects and relapse. Such technical advances require a better understanding of the mechanisms that trigger leukaemia, as well as disease relapse. Furthermore, biomarkers are also needed to identify, at the time of diagnosis, which patients will respond to the treatment offered and which will not.

To this end, the researchers propose an innovative approach that combines mouse and humanised mouse models to reveal the process whereby healthy immune cells

become cancerous, as well as to better understand how they resist treatment and reappear in relapse. In this project, they propose to identify and characterise the fundamental mechanisms that explain both the earliest events that trigger leukaemia, as well as those that enable relapse, thereby paving the way to developing novel and more effective therapies.

A new technology to clean respiratory viruses from the air

Project leader: Miguel A. Bañares
Institution: Consejo Superior de Investigaciones Científicas (CSIC) (Spain)
Consorcio:
Cristina Calvo, Hospital Universitario La Paz (Spain)
María Luz García García, Hospital Universitario Severo Ochoa (Spain)
Ana Iglesias-Juez, Instituto de Catálisis y Petroleoquímica, CSIC (Spain)
Antonio Alcamí, Centro de Biología Molecular Severo Ochoa, CSIC (Spain)

Description:

A huge variety of pathogens, such as SARS-CoV-2 and other human respiratory viruses, are found in the air in indoor spaces. Their main mode of transmission is by exposure to aerosols which, when breathed in, infect the host.

The SafeAir project is aimed at developing catalytic technologies to inactivate a wide range of infectious microorganisms. Specifically, it will create new air purifiers that use catalytic filters to inactivate viruses by oxidative stress, inhibiting their ability to infect human cells. The researchers will evaluate two types of technology: catalyst activation by light; and thermal catalyst activation assisted by microwave irradiation.

The new air cleaning system will not be a hazard either to human health or to the environment, as it will not generate undesirable secondary chemicals, and will not need to be regularly replaced.

Towards a better understanding of synapse disruption

Project leader: Ira Milosevic
Institution: Multidisciplinary Institute of Ageing, Universidade de Coimbra (Portugal)

Description:
The synapses between neurons are the main points for transmitting information from one cell to another and is the basis for the functioning of the central nervous system. To enable this, the nerve cells in the brain release signalling molecules or neurotransmitters. These cells also have mechanisms for recycling a part of these molecules, which tend to accumulate in homogeneously sized synaptic vesicles within the cell itself. In fact, it is these vesicles that enable synapses to maintain neurotransmission over many decades of life.

However, when the mechanism by which the cells form these vesicles is altered, they begin to accumulate pathological structures and accumulate endosomes, which are membrane and protein sorting organelles, at the synapses. This may promote

neurodegeneration and, ultimately, the premature death of these cells. In fact, alterations in this mechanism are behind many neurological diseases.

The researchers in this project will investigate selective aspects of cell membrane trafficking at synapses occurring in the hippocampus and cortex, with particular attention to synaptic endosomes.

What factors predispose to invasive pulmonary aspergillosis?

Project leader: Cristina Cunha
Institution: Instituto de Investigação em Ciências da Vida e Saúde (ICVS), Escola de Medicina, Universidade de Minho (Portugal)

Description:
Aspergillus is an airborne fungus present everywhere, both outdoors and indoors, and we breathe in its spores every day. In most healthy individuals, the fungus does not cause infection or health problems of any kind. However, some people – particularly those who are immunosuppressed because, for example, they have received a transplant, have a tumour, are in intensive care or even have COVID-19 – can develop invasive pulmonary aspergillosis, a disease that can be serious and life-threatening.

Globally, 30 million people are at risk of infection each year, although only 300,000 new cases of infection are diagnosed annually. But what is it that causes only certain people to become infected? Despite the fact that significant advances in combating this opportunistic infection have been made in recent years, both diagnosis and treatment of aspergillosis continue to be a serious medical challenge.

In this project, the researchers will investigate whether specific factors alter the balance between the host and its lung microbiota and predispose certain immunocompromised individuals to develop the disease. The results of the study can be used to improve both prevention, diagnosis and treatment of this serious complication and the prognosis of patients.

Exploring the role of nucleolar stress in amyotrophic lateral sclerosis

Project leader: Óscar Fernández-Capetillo
Institution: Centro Nacional de Investigaciones Oncológicas- CNIO (Spain)

Description:
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that leads to the progressive loss of motorneurons and for which there is no cure at present. It usually affects one person in 50,000 between the ages of 50 and 60. The prognosis after diagnosis is grim and patients die within three to four years. Although some treatments are available, they have little impact on life expectancy.

As ALS is polygenic in nature, in which several genes are mutated, it is difficult to identify a common mechanism that explains the disease. The first gene discovered to be mutated in this pathology is SOD1, which suppresses oxidative stress. Accordingly,

antioxidant treatments were first applied to treat the disease and current therapies focus on reducing oxidative stress. Unfortunately, however, these treatments have only marginal effects on patients' lifespan. However, besides SOD1, the function of many of the other genes found to be mutated in ALS patients points to problems related to RNA metabolism as the origin of the disease. In fact, one of the most universal markers of ALS is the accumulation of aggregates of TDP-43, an RNA-binding protein.

At the cellular level, a common consequence of mutations affecting RNA metabolism is the appearance of nucleolar stress, as the nucleolus is the cell organelle with the highest concentration of RNA. Indeed, alterations of the nucleolus have often been described in patients with neurodegenerative diseases. In this context, recent studies have shown that reducing nucleolar stress limits age-associated pathologies in animal models. However, the potential of this strategy to treat neurodegenerative diseases has not been investigated in depth. Accordingly, in this project, the researchers will explore the potential value of chemical and genetic strategies to modulate nucleolar function as a possible new therapy for the treatment of amyotrophic lateral sclerosis.