PRESS RELEASE

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Photos: Christa Rhiner, Carlos Ribeiro, Alfonso Renart, Luís Moita, Maria Mota, Pedro Sousa-Victor, Mariana Pinho

CaixaResearch Health Research Contest awards 7 researchers at CF, IGC, iMM and ITQB NOVA

Seven Principal Investigators from four institutions - the Champalimaud Foundation (CF), Gulbenkian Institute of Science (IGC), Institute of Molecular Medicine (iMM) and Instituto de Tecnologia Química e Biológica António Xavier (ITQB NOVA), members of the COLife alliance - have secured funding to advance research in neuroscience, ageing, and parasitology from the CaixaResearch Health Research Contest 2023.

For this edition of the contest, 11 groundbreaking biomedical and health projects spearheaded by research institutions and universities in Portugal were selected. This funding underscores the commitment of the "la Caixa" Foundation to champion projects of unparalleled excellence that stand to significantly benefit public health.

Listed below is more information about the seven awardees from the four COLife institutes and their projects.

Christa Rhiner (CF)

Unveiling buried core repair circuits in the brain

The central nervous system constantly integrates local and peripheral cues within closely linked cellular networks. The response of the brain to injury is complex, involving a web of interconnected cell types that engage in intricate communication. The balance of these multifaceted interactions can either pave the way for healing and repair or shift towards widespread impairment and persistent pathology.

"In our *BrainImpact* project, we aim to decipher the altered cellular dialogue that occurs in the brain post-injury", says Project Leader Christa Rhiner. "Our goal is to identify and understand the critical words that these cells exchange with each other in order to promote repair". Amidst

dominant inflammatory responses, the inherent complexity of the mammalian brain impedes the rapid and efficient decoding of cellular cross-talk. To overcome this hurdle, *BrainImpact* employs fruit flies as a model. “Their simpler structure enables us to quickly test the function of numerous injury-regulated genes and identify factors that drive pro-regenerative processes”, affirms Rhiner.

“Based on the identified mechanisms in the fruit-fly, we'll then study and manipulate the most promising targets within the injured mouse brain, a context more analogous to humans”. New tools developed by our collaborators at the Achucarro Basque Neuroscience Center will make it possible to test the impact of key repair factors on brain circuits and recovery of cognitive and motor behaviour following brain injury” continues Rhiner. The diverse methodologies honed within *BrainImpact* will enable Rhiner and colleagues to gauge the impact of repair factors across various scales—from genetic and cellular dimensions to network dynamics and behavioural outcomes. This approach is poised to shed light on novel molecular and cellular repair circuits, potentially pinpointing molecules that could enhance brain plasticity and prevent long-term brain impairment post-injury.

"Securing funding for this project will allow us to map out vital brain repair programmes that are conserved from flies to mammals. We're excited to assess their capacity to enhance outcomes after brain injuries, from the cellular to the organismal level”, adds Rhiner.

Bio: Christa Rhiner pursued her studies in Biology at the University of Bern and Lausanne in Switzerland. She earned her PhD from the University of Zurich in 2007, with her thesis centred on nervous system development in *C. elegans*, supervised by Michael Hengartner. During her postdoctoral research, she delved into genes mediating cell competition in *Drosophila* and mice with Eduardo Moreno’s team at the National Cancer Institute (CNIO) in Madrid. Subsequently, Christa took on roles as a lecturer and senior investigator at the Institute of Cell Biology in Bern, where she began her exploration into neuronal fitness and injury-induced brain plasticity using *Drosophila* as a model. Since 2017, she has been leading the Stem Cell and Regeneration group at the CF in Lisbon. Her research there focuses on neural stem cell regulation, repair pathways, and the interplay between the brain and body following brain tissue damage.

Carlos Ribeiro (CF)

From metabolic space to neuronal space: mapping how nutrients and the microbiome affect brain function and behaviour

What we eat has a strong impact on how we feel and behave. The microbiome, a community of microorganisms living in our bodies, especially in our gut, influences brain function, as recent discoveries have revealed. “For example”, notes Carlos Ribeiro, “we have shown that specific gut bacteria can strongly affect an animal's dietary preferences. Yet the mechanisms through which nutrients and the gut microbiome affect brain function and behaviour remain elusive. A key challenge is that we do not know *where* and *how* they alter the chemistry of neurons and, subsequently, behaviour”.

In this project, Ribeiro and his team will employ a novel technology known as spatial metabolomics in fruit flies to:

1) Find out where and how food and gut bacteria influence brain chemistry.
2) Test how changes in brain chemistry mediate the effects of food and microbiome on behaviour.
3) Understand how these chemical alterations in the brain modify sensory information processing.

This endeavour will provide new insights and technologies to explore how nutrients and the microbiome shape brain function in health and disease.

“Biology is about spatial organisation”, says Ribeiro. “Especially in the brain where neurochemicals have very different effects depending on where in the brain they act. Changes in diet and the composition of our gut microbiome alter the brain’s neurochemistry. But until recently, we had no way to find out where these changes happened. Leveraging a groundbreaking technology developed by our collaborators at the European Molecular Biology Laboratory in Germany, we aim to visualise where in the brain molecular shifts occur due to dietary and microbiome changes. This will open new frontiers in dissecting how diet and the microbiome change brain function and behaviour”.

Bio: Carlos Ribeiro, a founding Group Leader in the CF’s neuroscience programme, was born to immigrant parents in Switzerland. He earned his PhD from the University of Basel’s Biozentrum, where he pioneered 3D live time-lapse confocal imaging to study *Drosophila* embryo development. As an EMBO Postdoctoral fellow at the Research Institute of Molecular Pathology (IMP) in Vienna, he initiated a groundbreaking research programme on brain-body interactions and behaviour shaped by reproductive and nutrient states. Ribeiro was instrumental in advancing the study of behavioural nutrient homeostasis in *Drosophila*, demonstrating how flies adjust their nutrient preferences based on internal states. His interdisciplinary work, bridging behaviour, neuroscience, metabolism, and the microbiome, has unveiled conserved

mechanisms governing food choices and their impact on life-history traits. His lab at the CF has also innovated technologies like flyPAD and optoPAD, positioning *Drosophila* as a key model for studying nutritional homeostasis and physiology. He has taken on broader international leadership roles and is currently Secretary General of the Federation of European Neuroscience Societies.

Alfonso Renart (CF)

Understanding how people with autism spectrum disorder perceive the intensity of sensory stimuli

The most commonly recognised symptoms of Autism Spectrum Disorder (ASD) pertain to social interaction and communication. However, up to 90% of individuals with ASD also exhibit atypical sensory experiences. Research into these sensory atypicalities offers a promising avenue for translational studies, given that methods used to measure behavioural responses to sensory stimuli and the architecture of sensory systems in the brain, are conserved between humans and rodent animal models. Yet, there has been a lack of directly comparable behavioural paradigms to investigate sensory issues in ASD.

Recent findings indicate that ASD patients violate Weber's Law (WL), a universal principle governing perception across sensory modalities and species. Building on their prior work, which employed psychophysics in rats and humans along with mathematical analysis to propose a mechanistic foundation for WL, the goal is to develop quantitative phenotypic markers that can shed light on the physiological mechanisms underlying sensory deficits in ASD.

"In this project, we will quantify the behaviour of human ASD patients and multiple rat genetic models of ASD using identical psychophysical tasks," explains Project Leader Alfonso Renart. "Our goal is to identify rat ASD models that quantitatively replicate the WL violations observed in human ASD patients. Employing state-of-the-art data analysis methods and theoretical frameworks, we will then infer the mechanistic origins of these violations in both species. Concurrently, we will explore the neural underpinnings of WL in control rats through targeted loss-of-function experiments and neural population recordings. This will help us understand the brain circuits responsible for this universal law of perception and identify potential sites of sensory dysregulation in ASD."

This ambitious endeavour leverages quantitative behavioural analysis as a potent tool for both diagnosis and understanding the aetiology of mental disorders, and seeks to make

groundbreaking contributions to fundamental and translational brain research. "The funding from the Caixa Health research grant will enable us to conduct a comprehensive and systematic evaluation of sensory functioning in both ASD individuals and animal models. We aim to discover precise, cross-species behavioural markers linked to ASD, opening the door to a mechanistic understanding of certain facets of this condition," adds Renart.

Bio: Alfonso Renart completed undergraduate studies in Physics and went on to earn a PhD in Computational Neuroscience, both at the Universidad Autónoma de Madrid. Following postdoctoral research at Brandeis University in Xiao-Jing Wang's lab and at Rutgers University under Kenneth Harris, Renart became the Group Leader of the Circuit Dynamics and Computation Lab at the Champalimaud Foundation. The lab employs a multidisciplinary approach, integrating both theoretical and experimental methodologies along with rigorous behavioural analysis, to investigate the computational principles underlying perceptual decision-making.

Luís Moita (IGC)

Initiation of immune responses by surveillance of homeostasis perturbations

Luis Ferreira Moita's project "Initiation of immune responses by surveillance of homeostasis perturbations" aims to understand how physiologic perturbations caused by infections contribute to immune response initiation and regulation and was one of the xxx la Caixa Health Research awarded in 2023. With a total funding of 499,900.00 €, the project will start in September 2023 and run for the next three years.

Luís Moita, a doctor by training, leads the Innate Immunity and Inflammation Laboratory at the IGC since 2014, after 8 years leading a laboratory at the Instituto de Medicina Molecular Lobo Antunes, in Lisbon. He did his postdoc at the Whitehead Institute (MIT) and the Massachusetts General Hospital (Harvard Medical School) in Boston, United States of America, after completing his PhD at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. This award is significant to Luís Moita because "We do not understand well enough how immune responses are initiated and what role physiologic perturbations caused by infection have in that process. Without this knowledge, we cannot effectively develop a new generation of drugs to treat severe infections and inflammation".

Infection is a leading and growing global cause of morbidity and mortality. For example, sepsis - a severe generalised infection- affects nearly 50 million people yearly. More than 10 million die

of this condition alone. So far, most models of immune response initiation are based on the direct sensing of a foreign microorganism. This model has significant limitations and fails to account for many observations. The new project proposes that in addition to the direct identification of a microorganism that has the potential to cause infection, the organism also senses physiologic changes caused by the presence of microorganisms. The integration of both types of information will determine if and how an immune response is initiated and its quality. Substantial improvements in treating infection will require a much better understanding of how an immune response is initiated and how the organism responds to the aggression caused by a pathogen.

Maria Mota (iMM)

Understanding the enemy - *Plasmodium* - to fight malaria

Malaria is a devastating disease caused by the *Plasmodium* parasite. Despite a significant decrease in the incidence of the disease between 2000 and 2015, malaria remains a major concern for the World Health Organization, killing one child every minute. It is therefore very important to understand the parasite's life cycle to fight it better. After being bitten by an infected mosquito, the parasites travel to the host's liver, where they infect liver cells. During this phase of infection, the parasite multiplies exuberantly: each parasite inside a liver cell gives rise to tens of thousands of new parasites, which are then able to infect the blood and cause disease. It’s now known that the number of parasites formed in the liver is associated with the severity of the disease.

Curiously, the multiplication of parasites in the liver has unusual characteristics. Unlike our cells, parasites initially multiply by replicating basic units of their DNA which only later become individual parasites. The researchers have recently observed that this massive multiplication, and the particular characteristics of the division, leads to damage to the parasite's DNA. They now propose that this is a source of genetic variability. "In this project we want to explore the hypothesis that the accumulation of damage to the parasites' DNA generates a great variability and diversity of new parasites, giving them a greater chance of escaping our immune system and causing serious illness. It's as if the parasites in the liver divide and conquer!" explains Maria Mota.

The project now funded by the “la Caixa” Foundation will allow the multidisciplinary team led by researcher Maria Mota to explore the relationship between the exacerbated multiplication of parasites in the liver and the severity of the disease. "Understanding these basic mechanisms of parasite development and their interaction with the host will be an asset to open new doors in the fight against malaria," adds Maria Mota.

Bio: Maria Manuel Mota, biologist and master in immunology, obtained a PhD in Parasitology in 1998 from the University College London (UK). After a postdoc and teaching position at the York University Medical School (USA), Maria returned to Portugal in 2002 to lead a research group at the Instituto Gulbenkian de Ciência, in Oeiras. In 2005 she became a Professor at the Medical School of University of Lisbon and the leader of the Malaria Unit of the Instituto de Medicina Molecular João Lobo Antunes (iMM), where she is currently the Executive Director. Her research focuses on studying the interactions of *Plasmodium* parasites, causative agents of malaria, with the human hosts.

Maria has been recognized with several distinctions, including the election as a member of the European Molecular Biology Organization, several grants from the European Research Council, the EMBO Young Investigator Award and the Pessoa Prize.

Nowadays, Maria has a monthly column in the Portuguese newspaper Expresso, as a contribution to reach her dream of living in a knowledge-centred society.

Pedro Sousa-Victor (iMM)

The ageing immune system and metabolic diseases

While metabolic diseases and the associated cardiovascular complications have several causes, ageing stands out as a major risk factor. The most relevant preventive and therapeutical interventions often revolve around exercise, which improves skeletal muscle function, a key regulator of metabolism. However, ageing itself alters the response to exercise and limits the capacity of the current therapies.

As life-expectancy continues to increase, ageing-related diseases become major contributors to the increase in health costs. Designing new therapeutical interventions for these diseases is a crucial societal challenge. “In this project now funded by the “la Caixa” Foundation, we will study how immune ageing affects skeletal muscle health”, explains the project leader Pedro Sousa-Victor. By understanding the changes in the immune system in skeletal muscle during ageing, and how they affect metabolic health and the response of muscle to exercise, the researchers will contribute to the development and improvement of the current therapies for ageing associated metabolic diseases. “Our main aim is to develop new strategies to modulate the immune system in the elderly population, to improve metabolic health and response to exercise. Securing funding by the “la Caixa'' Foundation is a determinant step to achieve this aim”, adds Pedro Sousa-Victor.

Bio: Pedro Sousa-Victor is a Group Leader at the Instituto de Medicina Molecular João Lobo Antunes (iMM), in Lisbon, since 2019. He is interested in understanding the process of adult stem cell ageing and developing strategies of organ rejuvenation to improve health in the elderly. Pedro Sousa-Victor received his PhD from Pompeu Fabra University, Barcelona, in 2012, studying novel mechanisms of muscle stem cell ageing. During his postdoctoral career, at the Buck Institute in California, USA, Pedro Sousa-Victor expanded his work in ageing biology, focusing on systemic regulation of ageing and tissue repair. In 2019, Pedro Sousa-Victor returned to Portugal to start his own lab supported by a "la Caixa" Junior leader Fellowship and an EMBO Installation Grant.

Mariana G. Pinho, Co-PI (ITQB NOVA)

ChaoTROPIC Antimicrobial Hybrids for Bacterial Penetration - A new approach to facilitate the transport of antibiotics across the cell

Bacterial antibiotic resistance is becoming one of the greatest challenges for the future of human health. The increase in multi-resistant microorganisms, coupled with the lack of new antibiotics, is predicted to cause the death of ten million people per year by 2050.

One of the main challenges in developing new antibiotics is that many of the available molecules, although promising in their bactericidal capacity, are unable to cross the bacterial membrane. "Some bacteria, known as gram positive, have one membrane, while others, known as gram negative, have a second membrane, the outer membrane, which is a very efficient barrier. Many antibiotics are able to cross the first membrane, but not the second", explains Mariana G. Pinho, ITQB NOVA Principal Investigador. "This is one of the reasons why it is more difficult to develop new antibiotics against gram-negative bacteria, which are currently the main cause of deaths by antibiotic resistant infections", she says.

In this project, led by Javier Montenegro, from the University of Santiago de Compostela, and co-PI Mariana G. Pinho, two groups with perfect synergy in chemistry and microbiology will join forces to accomplish this high-risk-high gain objective. The researchers will use a new approach to face this challenge, relying on a recently discovered property of boron clusters that allows the transport of hydrophilic molecules across membranes while maintaining their stability and solubility. "Exploring this property will open the door to using boron clusters to transport molecules with antibiotic properties across the two bacterial membranes. This can be a valuable weapon in the fight against multiresistant bacteria", says Mariana G. Pinho.

Ultimately, the researchers hope to attach boron clusters to well-known antibiotic compounds that are efficient against gram-positive bacteria, but have limited outer membrane penetration, to treat bacterial infections caused by gram-negative bacteria. This research will not only allow the exploitation of a new range of repurposed antibiotics, but also give rise to an entirely new area of research for the fight against bacterial resistance.

Bio: Mariana Gomes de Pinho has a degree in Applied Chemistry from the NOVA School of Science and Technology (FCT NOVA). She began her research career studying mechanisms of antibiotic resistance in Hermínia de Lencastre's Laboratory, in ITQB NOVA. In 1997, she moved to the Rockefeller University, New York, where she did her PhD work on the same topic. In 2001 she moved to Oxford University, UK, for a postdoc studying the intracellular organisation of bacteria. She returned to Portugal and, in 2006, started her own research group, the Bacterial Cell Biology Laboratory, at ITQB NOVA. She is a member of the European Academy of Microbiology (EAM), the European Molecular Biology Organization (EMBO) and the Academia Europaea. Mariana Pinho has won three consecutive ERC grants: Starting (2012), Consolidator (2017) and Advanced (2023). She is also the proud mother of three daughters.

About the CaixaResearch Contest:

The “la Caixa” Foundation has allocated a total of €7.9 million for 11 projects hailing from Portugal. These initiatives are set to unfold over the forthcoming three years.

For this edition of the contest, 493 proposals were put forward, reflecting the contest's mission to spotlight and foster projects that embody scientific excellence, vast potential, and profound societal impact, spanning basic to clinical, translational, and pioneering research.

The CaixaResearch Contest collaborates closely with the Foundation for Science and Technology (FCT), the Portuguese public agency that supports science, technology and innovation, in all scientific domains. In this edition, FCT is funding 5 out of the 11 selected Portuguese projects, contributing €2.3 million.

The financial aid provided to the chosen projects is categorised into two brackets:

1. Up to €500,000 over a span of three years for projects presented by a singular research entity.
2. Up to €1,000,000 over three years for projects presented by consortia, comprising 2 to 5 research entities.

Since its inception in 2018, the La Caixa Foundation has dedicated €120.5 million to 171 innovative research projects with significant societal impact. Of these, 117 were spearheaded by Spanish teams and 54 by Portuguese research groups. This makes the La Caixa Foundation unique, as it is the sole contest that supports health research across both Spain and Portugal. A panel of international experts meticulously evaluates the proposals for each edition, conducting interviews with shortlisted candidates and selecting the most promising projects.

Contacts

Champalimaud Foundation
Afonso Vaz Pinto, JLMA - 969 658 256
Raul Araújo, JLMA - 927 414 665

Gulbenkian Science Institute
Ana Morais
Head of Institutional Communication
@: anamorais@igc.gulbenkian.pt
Contact: +351 965 249 488

Instituto de Medicina Molecular
Helena Ribeiro de Carvalho Pinheiro
Science Communication Officer
@: hpinheiro@medicina.ulisboa.pt

ITQB NOVA
Renata Ramalho
Head Of Communication
@: renata.ramalho@itqb.unl.pt
Contact: +351 965 007 727