

# BRAV3 Project: Cardiac regenerative medicine

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## **Prof Felipe Prósper, Head of Department, and Dr Manuel Mazo, from the University of Navarra & Clínica Universidad de Navarra, shares his expertise in cardiovascular diseases, focusing on the work of the BRAV3 project, which includes research in cardiac regenerative medicine**

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Cardiovascular diseases (CVDs), that is, those affecting the heart and the blood vessels, account for almost half of deaths worldwide. Amongst them, cardiac ischemia, often termed myocardial infarction, is the leading single cause of death globally. The increase in population ageing, added to the normalisation of sedentary and unhealthy lifestyles, has turned this disease into a healthcare emergency. Patients who survive the acute insult are chained to lifelong medical oversight and multi-medication.

This also entails a huge humane and economic burden for usually strained healthcare systems. The main culprit is the almost lack of regenerative capacity of the human heart. When an artery that supplies blood to an organ is blocked, causing an ischemic event, the heart's contracting cells, called cardiomyocytes, start to die shortly afterwards.

As highly specialised cells, cardiomyocytes have one of the lowest rates of duplication in the organism, meaning that those lost will not be replaced. The heart then starts a preventive process by which the dead portion of the organ is replaced by a non-contractile scar. This, although life-saving in the early stages, will progressively deteriorate the patient's condition, often leading to heart failure.

At this stage, the pumping capacity of the heart can no longer meet physiological demands. Heart failure has an estimated survival rate of 50% in five years, and its only curative option is organ transplant, which is, in the best cases, a severely limited option.

### **Cardiac regenerative medicine**

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Rising with the turn of the century, cardiac regenerative medicine seeks to solve this conundrum by using the latest knowledge and technology. The initial enthusiasm raised by the possibility of applying adult stem cells to the task led to an explosion in clinical trials. However, results failed to achieve the sought regeneration: their effect was, when found, modest and caused by the secretion of beneficial molecules rather than by a direct contribution to producing new myocardium.

The early 2000s also saw the rise of two novel technologies posed to break this stalemate. On the one hand, cellular reprogramming delivered for the first time the possibility of generating the cardiac cells needed for therapy in a number sufficiently large as to repopulate the damaged tissue. These novel stem cells, termed induced pluripotent

stem cells or iPSCs, can be derived from the patient's own biological material, paving the way for an autologous and personalised therapy. On the other hand, the breakthrough of progressively more advanced additive manufacturing, such as 3D printing and bioprinting, now enables the fabrication in the lab of increasingly complex structures, including biological ones.

## **Human myocardium and more in the BRAV3 project**

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The H2020 project BRAV3 is an EU- funded initiative that aims to capitalise on state-of-the-art expertise in these areas and beyond to generate a large piece of human myocardium termed BioVAD, after the biological ventricular assist device. The idea is to mimic the architecture of the heart to the highest extent possible so that this novel engineered tissue can support a diseased heart contracting.

Professor Felipe Prósper leads the project from the University of Navarra in Pamplona, Spain. It involves collaboration with experts from Spain, Portugal, Germany, Belgium, the Netherlands, and Ireland, forming a highly interdisciplinary team that covers biofabrication, medical devices, translational cardiology, or stem cells, among other areas.

However, a critical piece of this jigsaw needed to be added to the project. When intending to fabricate something, it is crucial to have the design specifications for what is intended. And for the human heart, that information is very much missing! In consequence, the project has spent a significant amount of effort mapping the mechanical and electrical properties of the myocardium to the highest detail, especially how cardiomyocytes align in the tissue on a human-scale model in pigs.

This latter information is of particular interest. In the heart, contraction is efficient because cardiomyocytes are well-aligned with neighbouring cells, and this orientation is modulating through the thickness of the organ and in 3D, in such a complex manner that few attempts have been made to unravel this. But the team in BRAV3 has cracked it. By using powerful imaging technology, termed DTi-MRI, they have generated a 3D map of how cells are aligned in the 3D space of the heart and, importantly, how this changes when infarction hits.

## **Computational modelling in the BRAV3 project**

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Applying powerful computational modelling and fuelled by the gathered information, the project has optimised a design for the BioVAD. In fact, the novel computational models help BRAV3 to determine practical facts like how to transplant the BioVAD, how to orient it with respect to the damaged tissue, or how to interface it with respect to the residual working myocardium. And all these without performing the myriad animal experiments that would be needed, thus complying with the highest ethical standards.

Now, BRAV3's inspiration is to use these advanced computational tools to direct the design of the most therapeutic BioVAD possible and make it efficient and payable. BRAV3 has developed new upscaled and economically efficient methods to generate the large numbers (hundreds of millions to billions) of cells needed for a single BioVAD.

## Final thoughts on the BRAV3 project

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The project has also designed and fabricated the required devices to sustain the culture and function of this large bioartificial tissue. All these advances will soon be tested in a large animal model of myocardial infarction to determine not only the feasibility and efficacy of BioVADs as a therapy but also their safety, which is crucial before any potential in-patient application.

The beauty of this process is that it can be tailored to fit the individual's needs, as infarcts can differ in size, position and magnitude. The patient would undergo cardiac imaging to retrieve this information, which, by feeding it into the computational models, will determine the precise BioVAD to be 3D printed to treat his or her specific infarct in a fully personalised therapy.

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