The 'ProtMechanics-Live' project, led by Dr. Jorge Alegre, awarded ERC Consolidator funding in the ERC-2020-COG call

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'ProtMechanics-Live' is based on unique expertise in protein mechanics and engineering, biophysics, biochemistry and cardiovascular biology and will allow to investigate protein mechanics for the first time in its functionally relevant physiological context

The project "ProtMechanics-Live: Uncovering Protein Mechanics in Physiology and Disease", directed by Dr. Jorge Alegre, from the National Center for Cardiovascular Research (CNIC) has been selected in the ERC-2020-CoG call of the European Commission. The project will receive 2 million euros for the next 5 years.

The ERC supports pioneering projects that promise to revolutionize health and society. **The ERC's touchstone for project funding is research excellence**. The 2 CNIC projects have been selected within the ERC Consolidator Grant program, which supports young investigators with an established record of leadership but who are still consolidating their research group. The ERC is the first Europe-wide organization to fund basic research projects on the sole basis of a researcher's scientific excellence and the innovative strength of her or his ideas, independently of nationality or research field.

The CNIC Molecular Mechanics of the Cardiovascular System group, led by Dr Jorge Alegre, investigates the fundamental influence of protein mechanics on heart form and function. "P**rotMechanics-Live builds on our unique experience in protein mechanics and engineering, biophysics, biochemistry, and cardiovascular biology and will for the first time permit investigation of protein mechanics in a functionally relevant physiological context**," said Dr Alegre.

While it is no secret that cells and living organisms in general respond to changes in their environment, in the past relatively little attention has been devoted to understanding how living beings respond to the mechanical forces they are continuously exposed to. "This relationship between cells and the mechanical forces acting upon them is immensely important and can explain multiple disease processes, including cancer metastasis, atherosclerosis, and cardiomyopathies currently lacking a defined underlying molecular mechanism," explained Dr Alegre.

Indirect approaches have indicated an important role for protein mechanics in these processes. However, the mechanisms involved remain elusive, largely due to the absence of methods to modulate protein mechanics in living systems.

The ProtMechanics-Live project aims to "overcome these technical barriers to scientific progress by establishing the manipulation of proteins in living cells and animals as a new research field," said Dr Alegre.

Advances over the past decades have produced new technologies that permit the study of the mechanical behavior of proteins that determines the ability of cells to sense and generate force. These techniques have enabled the characterization of the mechanical properties of individual proteins in isolation. **While this has transformed understanding of the relationship between force and biological molecules, these pioneering methods are limited to the study of simplified systems in the laboratory that do not reflect the real situation in living cells and organisms**. ProtMechanics-Live will translate this analysis to proteins' natural environment, the living cell, thus generating knowledge about how protein mechanics integrates with other systems essential for life. This approach has been impossible until now.

In the ERC evaluation report on ProtMechanics-Live, the international panel of experts emphasized that they were impressed by the quality of the proposal, which was considered to be highly original.

This innovative project has three goals. "To overcome the limitations of current methods," commented Dr Alegre, "we will first generate genetic loss- and gain-of-function models based on protein engineering to manipulate mechanical function. We will apply these new tools to the giant

protein titin, an important node for the generation and detection of force in cardiomyocytes that is implicated in several cardiovascular disorders."

"Once we have generated these tools, we will use them to define how perturbations in titin mechanics affect the function of healthy and diseased cardiomyocytes," Dr Alegre continued. **The third project goal is for these studies to "shed light on the contribution of titin mechanics to the initiation and progression of cardiomyopathies**, both those with a genetic cause and those arising after an event such as a myocardial infarction."

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