

CENTER: **Centro Nacional de Investigaciones Cardiovasculares "Carlos III" (CNIC)**

VACANCIES: **1**

CONTACT: **Jorge Alegre-Cebollada, PhD** (jalegre@cnic.es), group leader "Single-molecule Mechanobiochemistry Laboratory"

DESCRIPTION OF THE OFFER

Research line: "A novel framework to investigate mechanical alterations in proteins associated with hypertrophy cardiomyopathy"

The human heart is a formidable mechanical machine that pumps thousands of liters of blood every day. It is becoming increasingly evident that mutations in cardiac proteins with key mechanical roles, such as titin, cause different forms of heart disease. In our group, we are interested in mutations that lead to hypertrophy cardiomyopathy, a disease that affects 1 in 500 people and can lead to sudden cardiac death and heart failure. Using single-molecule Atomic Force Microscopy, we have found that mutations induce subtle mechanical alterations to the polypeptides. These changes are close the limit of the resolution that current AFM instrumentation can distinguish. This project will:

- i. Develop new theoretical analyses and Monte Carlo simulations to estimate significance of AFM results.
- ii. Implement new molecular biology strategies to increase the resolution of AFM experiments.

We seek a student with interest in multidisciplinary science (biology, physics, chemistry). Some programming knowledge is preferred. By the end of the formative period, the student will have become familiar with molecular biology techniques to produce and purify AFM-ready polyproteins, single-molecule AFM experiments and analysis, and programming in Igor.

Our group was established in 2014 at CNIC to examine the mechanical function of the heart from a molecular biophysics perspective. Our team is composed to 1 senior postdoc, 1 graduate technician and 2 PhD students, one of which is in charge of the hypertrophic cardiomyopathy project. For more information, please visit:

<https://www.cnic.es/en/investigacion/single-molecule-mechanobiochemistry>

References:

1. Alegre-Cebollada, J., Kosuri, P., Giganti, D., Eckels, E., Rivas-Pardo, J. A., Hamdani, N., Warren, C. M., Solaro, R. J., Linke, W. A. & Fernandez, J. M. S-glutathionylation of cryptic cysteines enhances titin elasticity by blocking protein folding. *Cell* 156, 1235-1246. (2014).

2. Popa, I., Kosuri, P., Alegre-Cebollada, J., Garcia-Manyes, S. & Fernandez, J. M. Force dependency of biochemical reactions measured by single-molecule force-clamp spectroscopy. *Nature Protocols* 8, 1261-1276. (2013).