



Postdoctoral fellowship



FOCAL ADHESION NANOSENSORS

The objective of the project is to engineer novel intracellular force nanosensors with the capacity to resolve forces at the piconewton (pN) level in living cells and to elucidate the mechanosensing mechanism within focal adhesion.

Cells interact with their environment (extracellular matrix) through self-assembling molecular nanoplateforms called focal adhesions (FA). These nanoplateforms allow cells to anchor and connect to cytoskeleton that, when contracted, allow cells to migrate. **Alterations of strength adhesion and cell adhesion mechanics play a role in the development of different pathologies.** For instance, in the context of cancer metastasis, it has been demonstrated that the cells crossing the endothelial barrier into blood vessels, reorganize their FA to regulate the rate of migration. ¹ **Fully understanding the mechanosensing could provide a better understanding of the disease.** To facilitate this, there is a **need of development of sensitive tools to resolve complex molecular interactions and forces occurring within FA at a single molecule (SM) level.** In this project we propose an **innovative strategy to measure forces at molecular level.** We will focus on the example of talin, huge mechanosensing factory within FA, able to sense mechanical strain exerted by the cytoskeleton. This protein was selected for the study due to its complex structure, which made it impossible to resolve its mechanosensing behavior using any available techniques such as Atomic Force Microscopy (AFM), magnetic tweezers or talin tension sensors (TS). ² The sequence of stretching events in different regions of the talin is the aspect of greatest difficulty in this field. This complexity arises from the intertwining of mechanical and biochemical responses.

More specifically, we will **develop FRET (Förster Resonance Energy Transfer) QD (Quantum Dot)-based nanosensors directed against two talin regions.** FRET is based on non-radiative energy transfer from excited donor molecules to acceptor molecules in their ground state. FRET is a technique widely used in biophysics as a nanoscale tool for biosensing and binding measurements. **FRET Nanosensors will be composed of a pair of fluorescent emitters: QD donor and dye acceptor.** QDs were chosen for their exceptional photophysical properties, including **photostability for long-term observations and brightness for single-molecule imaging.** In order for the sensor to fulfil the function of a **tension sensor, an elastic DNA tether** will be inserted between the donor and the acceptor. To investigate mechanosensing processes at the focal adhesion unit level and in real-time, we will **combine FRET with TIRFM (Total Internal Reflection Fluorescence Microscopy)** at SM level. Nanosensors will be first applied on **biomimetic systems** reconstituting adhesion unit (made of lipidic membranes and purified focal adhesion proteins). Finally, intracellular force measurement will be realized on **nontumorigenic versus metastatic cell lines.**

The project will mobilise ground-breaking imaging techniques such as :

- Single molecule fluorescence microscopy
- Förster resonance energy transfer (FRET)
- Total Internal Reflection Fluorescence Microscopy (TIRFM)



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In vitro and in cell experiments:

- In vitro biomimetic systems (Giant Unilamellar Vesicles, Supported Lipid Bilayers)
- Cell culture

Required candidate profile:

We are therefore looking for a **highly motivated, inquisitive** candidate who wishes to work in an interdisciplinary environment at the interface between biophysics and biochemistry. The candidate may hold a degree in biology, physics or biophysics and demonstrate a strong aptitude for experimental work. The **ability to work independently on the project is required**, as is the ability to work as part of a team.

Experience of working with DNA probes, biodetection, fluorescence microscopy, in vitro systems or expertise in protein purification would be a great asset.

The financial support for this postdoctoral fellowship is provided by an ANR grant. The successful candidate will be employed by CEA on a salary starting at 3,404 euros gross, depending on experience. The contract is for a period of 12 months, with the possibility of a further 12-month extension.

To apply please contact:

Marcelina CARDOSO DOS SANTOS : marcelina.cardoso-dos-santos@i2bc.paris-saclay.fr,