Master 2 project / PhD proposition 2019-2020

Laboratory : **Dpt « Physique et Ingénierie pour le Vivant »**
Centre Interdisciplinaire de Nanoscience de Marseille (CINaM) – CNRS/AMU UMR 7325
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Cell nucleus mechanics and premature senescence

Cellular senescence is a normal process defined as the progressive decline of all functions, ending with cell cycle arrest. Accelerated cell senescence induces pathologies such as diabetes or cardiovascular disease typical of premature aging. In the most severe case (progeria), a pathway to senescence was related to disorganization of the lamina, a key component of the nuclear envelope (NE), which ensures the mechanical stability and rigidity of the nucleus (Fig. 1a). NE and associated proteins play a major role in cell response to various mechanical stimuli. It is today believed that alteration of such processes is critical in the occurrence of atherosclerosis and cardiovascular diseases.

This project aims at investigating the link between lamina mutations, alteration of cell mechanotransduction and severity of the disease from nuclear to multi-cellular scale. Firstly, we want to determine the viscoelastic properties of nuclei and cells affected by lamina mutations. Secondly, we aim to identify the effects of the mutations on the mechanotransductive response of cells to mechanical stimuli. Last but not least, our results will lead to a rheological model of the nucleus.

We will tackle these objectives by combining approaches from both physics and biology. Our collaborators will perform cell and molecular biology experiments for mutation study and gene expression investigation. In CINaM, we will use biophysical techniques (microfluidics (Fig. 1c), optical tweezers) to apply mechanical stresses on cells / extracted nuclei (Fig. 1b) and modeling to interpret the data. Together, these complementary approaches aim to propose an integrated model to better understand a pathway to premature senescence.

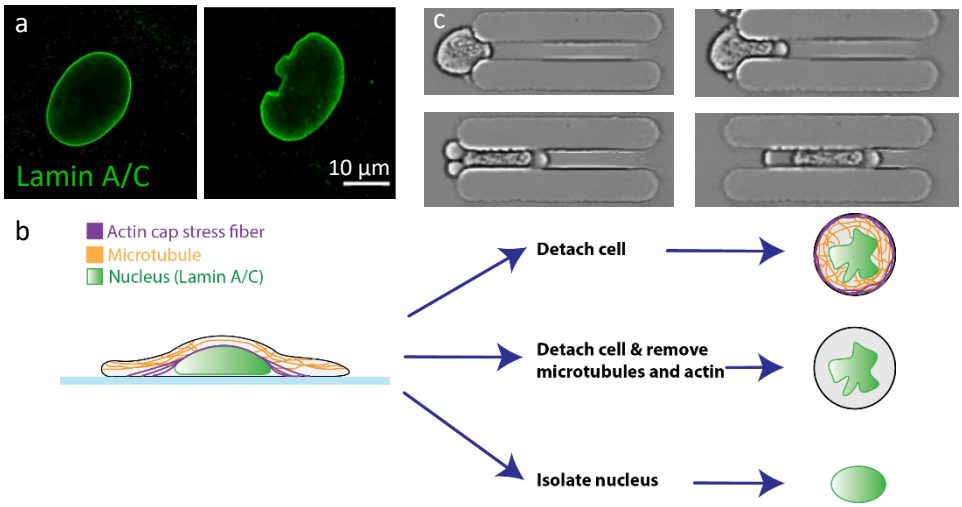

Figure 1. a- Cell nuclei of healthy (left) and Progeria-affected patients (right). **b-** Workflow used to explore the viscoelastics properties of single cells and nuclei: after harvesting and treatment (or not) cells and nuclei are injected inside a microfluidic device. **c-** Cell passing through a 6x6 µm constriction.

Keywords: nucleus mechanics, microfluidics, mechanotransduction, biochemistry, optical imaging, image analysis

Student profile: preferentially a physicist with interest towards biological questions, the subject is however flexible and can be adapted to fit specific interest and skills of the candidate