

# Proposition de thèse avec financement

**Ecole doctorale Sciences de la Matière**

**Titre : Investigation of the mechanical forces and cell cycle control in Multicellular Tumor Spheroids using engineered microdevices**

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**Project:** Mechanoreciprocity adapts and maintains tension exerted by the cells on their microenvironment and is responsible for the maintenance and the homeostasis of a given tissue. Mechanoreciprocity is impaired in developing tumor and loss of tensional homeostasis is a hallmark of the cancer disease. Tumor growth results in a stiffness progressive increase that generates tension and forces responsible for local and regional impact on the surrounding tissue and organ. Tumor cells induce stiffness of the extracellular matrix, which in turn results in compression and tension forces that generate mechanical constraint opposed to tumor growth<sup>1</sup>. Mechanical properties of the microenvironment are transmitted through cell-extracellular matrix and cell-cell interactions to cytoskeleton through the activation of intracellular signaling pathways, thereby influencing cell behavior<sup>2</sup>.

An essential aspect of the maintenance of tissue homeostasis is the control of cell growth by intra- and extra-cellular cues. Such an accurate coupling relies on the activation of signaling pathways cascades impinging on the heart of the cell proliferation machinery, the cell cycle. It is therefore very likely that molecular mechanisms of cell cycle control are targeted by mechanical cues. Indeed, some aspects of this connection and this central role have been reported in the seminal work of Klein et al. and Thery et al.<sup>3,4</sup>. However these studies were performed in 2D cell culture models that do not take into account the cell heterogeneity and the intercellular interactions that are observed in the 3D context of the tumor.

MultiCellular Tumor Spheroids (MCTS) is a 3D model that recapitulates the microenvironment, cellular heterogeneity and cell-cell interactions found in tumors<sup>5</sup>.

The objective of this project is to characterize in 3D MCTS the link between the environmental mechanical properties and cell cycle control. Our goal is to assess the effects of substrate stiffness, mimicked by specifically designed polymer microdevices, on cancer cell behavior cultured as MCTS in order to elucidate cross-talk between cell cycle control and contractility, and more broadly, to generate a more accurate model for studying cancer development.

This project specifically aims at:

1. Designing and fabricating in a clean room environment, polymer microdevices mimicking mechanical properties of microenvironment and usable as force sensors
2. Characterizing and measuring tensional forces exerted by growing MCTS
3. Determining the consequence of mechanical constraints on polarity and growth of MCTS

This interdisciplinary research project associates two groups with complementary expertise in cancer biology and bionanotechnologies. B. Ducommun's group aims at investigating tumor cell proliferation in an integrated context using these original 3D multicellular models, giving much attention to the systemic study of the biology of cell cycle control and cell fate. C. Vieu's team is involved in the development of micro and nanotechnologies for life sciences.

Les compétences requises pour la réalisation de ce projet couvrent les champs des sciences physiques et de l'ingénierie, de la biologie cellulaire et de l'imagerie. Le ou la candidat(e) devra faire preuve avant tout d'une grande motivation pour un sujet de science expérimentale fortement interdisciplinaire. Les parcours de physiciens et/ou de biologistes seront considérés, une pré-expérience sur un sujet interdisciplinaire croisant physique, micro/nanotechnologies et biologie sera un atout.

**Contact:** Envoyer CV et lettre de motivation à : [cvieu@laas.fr](mailto:cvieu@laas.fr) et [bernard.ducommun@itav-recherche.fr](mailto:bernard.ducommun@itav-recherche.fr)

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<sup>1</sup> Yu, H et al. Trends Cell Biol, 21, 47-46 (2011)

<sup>2</sup> Mammoto, A et al. Current opinion in cell biology, 21, 864-870 (2009)

<sup>3</sup> Klein, EA et al., Curr Biol, 19, 1511-1518 (2009)

<sup>4</sup> Thery, M et al., Nat Cell Biol, 7, 947-953 (2005)

<sup>5</sup> Sutherland, RM, Science, 240, 177-184 (1988)