

# A fresh perspective into cancer cell development through the mechanics of cell architecture

How cells sense and respond to their environment is vitally important to their function within the complex tissues of an organism. Changes in the mechanical properties of cells and tissues, because of exposure to forces, have been linked to diseases such as cancer. This has brought about a new interdisciplinary field of study known as mechano-genetics to further understand the mechanisms involved. **Dr Francoise Argoul's** research looks into this, focusing on experimentally characterising the mechanical and genomic responses of cancer cells under external stress.

Over the past decade, the development of tools capable of mechanically probing cells and molecules in high-resolution detail has facilitated the study of how biochemical factors alter the mechanical properties of cells. This has provided Dr Francoise Argoul and her team at the Laboratory "Ondes et Matière d'Aquitaine" (LOMA), Bordeaux, France, with challenging new opportunities to probe the properties of cells. As such, she can now work towards answering some thus far neglected biological questions, informing our fundamental understanding of how changes can cause disease.

Understanding how the mechanical and biochemical properties of a cell influence, for example, the response of a cancer cell to treatment, may be the key to determining why some cancer cells become resistant to interventions. This new avenue of research therefore shows great potential in the development of much-needed novel therapeutics.

## MERGING MECHANICS AND GENETICS

Mechano-genetics is an interdisciplinary field that brings together elements of engineering, physics, genetics and cell biology to investigate the mechanical properties of

cells, how changes to these properties occur and how these relate to the genetics of the cell. Cell mechanics control cellular functions so, for a healthy cell, it is crucial that these parameters are maintained. Alterations to cell mechanics are increasingly being discovered to be implicated in a range of human diseases. Therefore, understanding the role of mechanical alterations in relation to cell transformation processes will help establish how malignant cells differ from healthy ones.

Historically, technological limitations in imaging potential have hindered the amount of progress made in uncovering these complex cellular properties. However, in recent years, great advances have been made to develop tools that provide a richer understanding of these factors and how they relate to genetics. This has allowed researchers to take a fresh look at diseases such as cancer and gain a new level of fundamental understanding as to which factors are involved in the invasion of cancerous cells into tissues.

## NOVEL TECHNOLOGY TACKLES LONG UNANSWERED QUESTIONS

Dr Argoul and her team have contributed a novel set-up of high resolution microscopy to further progress, which they have termed a 'Bioplasmoscope'. This new device combines

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a high-resolution microscope (with or without surface plasmon resonance amplification) and a nano-indentation head (scanning force spectroscopy).

Prior to this, techniques capable of accurately imaging in real time living cells in liquid media, up to nanoscales, had eluded researchers, providing a key issue for gaining deeper insights in molecular biology. Existing

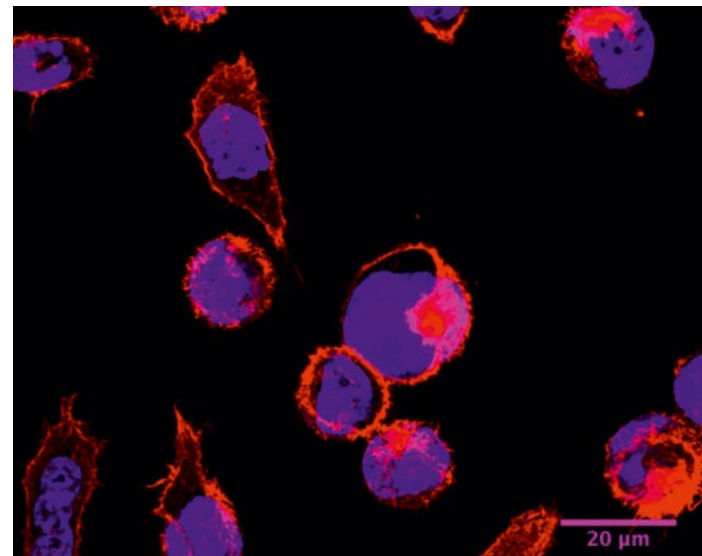
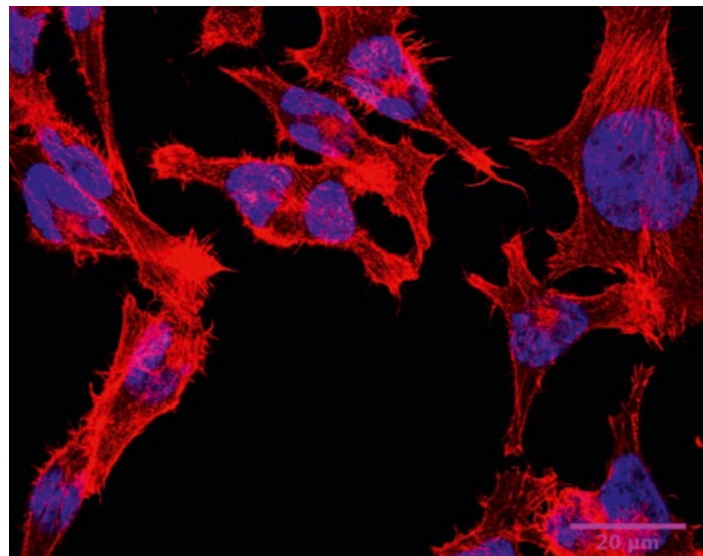
approaches were invasive and often required the use of fluorescence probes as labels, which consequently can suffer from unreliable photo-stability and can alter the molecular structure of biological complexes. Not only that, but the range of scales that could be attained using fluorescence microscopy techniques, and the molecular components that could be imaged together, was also limited.

Dr Argoul's Bioplasmoscope apparatus not only overcomes these problems but also offers the possibility to perform simultaneously optical and mechanical image reconstruction thanks to nanoindentation techniques ("acupuncture of cells") – a means of testing the hardness of small volumes of material – to probe the details of the architecture, the mechanics and the dynamics of living cells.

## STIFFENING LEUKAEMIA CELLS PROMOTES SURVIVAL

Dr Argoul and her team have utilised primary chronic myelogenous leukaemia (CML) hematopoietic stem cells as a model to measure the stress-to-strain response of cancer cells, to better understand the modifications that occur to their mechanical properties when they become cancerous. ►





Left: Normal hematopoietic cells. Right: The same hematopoietic cells after transfection by the CML oncogene. Photo courtesy of B Laperrousaz

During CML, bone marrow cell density increases, indicating that the physical properties of the hematopoietic stem cells may have changed. Dr Argoul obtained data from cells isolated in healthy and leukaemic bone marrows, and showed that there was a higher degree of stiffening occurring to the hematopoietic cancer cells, as well as more localised rupture events. This indicated that the cancer cells respond to physical force with a cascade of detectable brittle fracture events. These distinct brittle fractures as a response to stress could be used as a marker for how resilient cancer cells are to deformation. Not only that, but they could also be used as an indicator of cancer cell transformation in leukaemia. Dr Argoul's results also shine light on how leukaemia cells withstand the mechanical constraints posed by their environment, and how these characteristics promote their survival (i.e., how they can resist drug treatments).

#### MAINTENANCE OF ARCHITECTURE PROVES CRUCIAL FOR HEALTHY CELL FUNCTION

The support structure within cells is known as the cytoskeleton, a skeleton-like network

of structural fibres within cells, which consists of dynamically cross-linked biopolymer chains with varying structural properties. The networks are highly sensitive to physical stress, and have a high propensity for local structural failures; however, the cells also have repair mechanisms in place that can facilitate the recovery of their original architecture and their dynamical functions (motility, adhesion, mitosis, etc.). If damage to this is too frequent, or the force of a single event is too strong, the repair mechanisms can fail, and the cell can irreversibly lose its ability to regulate its homeostasis, resulting in cellular diseases such as cancer. It is this cytoskeletal disruption that Dr Argoul and her team have identified as one of the hallmarks of CML cancer cells. Hematopoietic stem cells, thanks to their multipotency, can generate a wide variety of blood cells. Unlike other immature blood cells, they can pass the bone marrow barrier to travel in the blood and migrate to other bone marrow niches and differentiate into specialised immune system cells (e.g. the thymus with T-cells). Through her research, Dr Argoul and her team have deduced that it is a change in the mechanical phenotype of some hematopoietic stem cells,

which could inhibit their migration out of the bone marrow and their division and increase their resistance to treatment.

#### NOVEL GENETIC PROFILING TO MAP DNA REPLICATION EVENTS

Alongside this research, Dr Argoul and her collaborators have also been investigating the genetic characteristics of CML cells, particularly related to their DNA structure. In partnership with the team of Dr Hyrien who developed cutting edge sequencing tools, they combined RNA (transcripts) and DNA (Okasaki fragments) sequencing from a large population of hematopoietic cancer cells and confirmed that the expression of genes interacting with the CML pathway was changed in the early stage of the synthetic phase (S-phase). More surprisingly, the DNA replication programme was found to be altered in the late S-phase, corresponding to gene deserts located in heterochromatin regions (epigenetics) at the nucleus periphery. Dr Argoul and her collaborators have raised the importance of the combination of different biomarkers (e.g., for transcription, replication and chromatin epigenetics) and multivariate analysis to better understand the temporal and spatial transformation of nuclear functions in CML.

Their methodology holds fantastic potential as an efficient tool for cancer diagnosis. Not only that, but its development could also provide more accurate patient prognoses and aid in personalising treatment. Following the success of her work, Dr Argoul now plans to extend the study to two other cancer types: Burkitt lymphoma and soft tissue sarcoma.

**Dr Argoul employs cutting-edge methodology to map DNA replication events to provide new insights into the spatio-temporal control of the process within cancerous cells**

## Q&A

#### How did you come to apply your understanding of biophysics to cancer cell biology?

I was initially trained as a chemical-physicist, and was interested in complex processes in nature, such as chaos, fractals, turbulence. In the late 1990s, I decided to move my interests to transdisciplinary questions such as how the mechanics of living systems impact their genetic functions. This type of question emerged progressively in my thoughts because I had been fascinated for more than two decades by the ancestral Chinese methods of acupuncture. Actually, I decided to train (during my weekends and vacations) as a Chinese traditional physician specialising in acupuncture and I completed the qualification for this in 2011. However, given that when you are not also trained for occidental medicine, this medicine is not recognised in France, it was difficult for me to initiate research projects in France on the physics of acupuncture. These years were a great challenge for me and I developed new skills and techniques (both in the laboratory and in my private life) to address very original questions at the frontier of physics, biology and medicine. The question of how physical concepts can help unravel unsolved issues of cancer cell transformation was key and I decided in 2010 to initiate a common project with a team at the Centre de Recherche en Cancérologie de Lyon, for which I immediately got a PhD student and an INSERM funding. I choose the CML because it seemed to me that this type of cancer could serve as a model for many other cancers, which was afterwards revealed to be true.

#### Since your development of the Bioplasmoscope, how is the technology being implemented in research?

The Bioplasmoscope is more a concept than a limited experimental set-up. The term plasmo can represent the plasmons known in optics, but also the plasma state of matter or the plasma from the blood, or more generally if we take the etymology of this term a form, a shape. This is why we chose this name. This technology is open in the sense that it evolves depending on the technical advances of opto-mechanics and nanosensing. The underlying idea is to

capture in real time and non-intrusively how living cells adapt or respond to mechanical stresses.

#### What questions would you like to tackle next in relation to the mechanical properties of cells?

The next question for which I am collaborating with a team from the Institute of Biochemistry and Cell Biology (Bordeaux) headed by Anne Devin is to study how the metabolic functions of living cells interact with the mechanical and dynamical functions of living cells. These dynamical functions rely on a permanent production of energy (ATP) to constantly remodel the cells, adapt their architecture, their motility, adhesion, division, ... It is of prime importance that this energy resource be delivered at the place (cell compartment) where it is needed each time. There is therefore a spatio-temporal interplay of the different networks involved in metabolic and mechanical functions to ensure that the cell can perform a specific function.

#### Are your findings regarding leukaemia cells being translated into a clinical context and how can this be achieved?

In collaboration with a team of doctors from the Bergonié Institute (a research centre for cancer in Bordeaux), we have started a new project that proposes a revisited blood smearing device to assist the diagnosis of blood diseases such as leukaemia and myelodysplasia.

#### How do you see your research progressing over the coming years?

I hope that our advances in the spatio-temporal control of DNA replication will disseminate the idea that we can no longer limit our sequencing methods to gene expression levels, but that other markers such as replication timing, replication fork polarity and chromatin structure are also fundamental to understand how cellular functions are impacted in cancer. Another aspect on which we are working now is to be able to perform this analysis at the single cell level, to understand better the variability of cancer cell transformations previously observed on cell populations.

## Detail

#### RESEARCH OBJECTIVES

Dr Argoul is a biophysicist who studies how the profile and mechanical properties of living cells change in the pathology of diseases such as cancer. To do this, she uses a number of novel, high-resolution techniques to identify and image cancerous cells.

#### FUNDING

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#### COLLABORATORS

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de Lyon **Key French Partners:**

**Lyon:** Centre de Recherche en Cancérologie de Lyon (F. Nicolini, V. Maguer-Satta, B. Laperrousaz), Institut des Nanotechnologies de Lyon (L. Berguiga) **Paris:** Institut

de Biologie de l'Ecole Normale Supérieure (O. Hyrien) **Bordeaux:** Institut de Biochimie et Génétique Cellulaire (A. Devin), Bergonié Institute (F. Chibon, G. Etienne) **Nantes:** University of Nantes (K. Rouger, L. Dubreuille).

#### BIO

Dr Françoise Argoul is a Director of Research of Centre National de la Recherche Scientifique at the Laboratoire Ondes et Matière d'Aquitaine where she manages a research programme devoted to the experimental characterisation of the mechanical and genomic response of cellular systems under an external stress.

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