# Project 2

## Development of a microfluidic cancer cell sorter based on deformability

Acute myeloid leukemia (AML) develops in the bone marrow, notably from stem cells that transform into leukemic cells, which proliferate and lead to a decline in the production of normal hematopoietic cells. Despite the efforts of basic research and the use of intensive chemotherapies, the survival rate in AML remains around 20%. The rapid clonal expansion of leukemic cells in the bone marrow leads to changes in the physical properties of the marrow niche, and in the space dedicated to each cell population. In turn, the intrinsic rigidity of leukemia cells can be affected by the niche *via* a reciprocal mechanical response, becoming a potential factor in the development of treatment resistance. Indeed, our previous work seems to establish a connection between the ability of AML cells to resist treatment and their deformability. Using the so-called pressure drop measurement, we have shown that treatment-resistant cells tend to be more deformable than treatment-sensitive ones. In order to decipher the mechanisms underlying the resistance phenomenon, it is important to be able to isolate these cells and characterize their biomolecular signature and associated functions.

The main objective of this study is to develop a new microfluidic tool for isolating cells according to their deformability properties based on the pressure drop measurement. However, a first obstacle identified in this project is associated with the cell size/deformability coupling inherent in all micro-fluidic approaches in the literature to isolate cells according to deformability. Indeed, the few exam-ples in the literature that propose microsystems sorting cells on a deformability criterion are impacted by the coupling as they exploit the flow of cells through slots, constrictions or other geometric reduc-tions. Therefore, they will indiscriminately isolate a cell small enough to squeeze through - whatever its rigidity - as well as one deformable enough to pass through the restrictions. To take account of the variability in cell size within the sample, we propose to use a first microfluidic function based on the deterministic lateral displacement (DLD) to perform first a size-based sorting. This simple, proven technique can isolate subpopulations of reduced dispersion; the sub-population centered on the average cell size - and therefore the most abundant one - will be retained and then sorted according to rigidity in the second microfluidic function. Knowing the average size and limited dispersion of this sub-population will enable us to adapt the dimensions of the second function and therefore to take into account the variability in size between samples from different donors.

In the second function, we aim to associate the pressure drop measurement to assess cell stiffness and dielectrophoresis (DEP) to redirect cells of interest. When a cell whose deformability will be detected below a threshold value, it will be deviated towards the appropriate reservoir. A second crucial issue identified is the variability of the rigidity threshold applied for sorting. Indeed, depending on the patient, the presence or absence of resistant cells will have an impact on the variability of the sample in terms of rigidity.
To consider this, we propose to use the first few hundred cells passing through the chip to define the rigidity threshold in the detection section (corresponding to the pressure drop), without activating the sorting module. This allows “hyper-deformable” cells to be distinguished from other cells in a patient-specific way. Based on this statistics, the sorting threshold is set and the following cells are separated into two sub-populations, the “hyper-deformable” vs. the rest of the population.

Following the development of the device and its fine-tuning on model objects (beads of hydrogels of physiological rigidity), the sorter will then be validated on commercial AML cells both resistant and sensitive to therapeutic treatment, as well as on primary samples (patient cells). Finally, in order to better understand the origin of the resistance to treatment, we propose to study the biomolecular profile of these “hyper-deformable” cells. Among other parameters, we will look at the expression levels of certain mechano-transducers, adhesion properties and the expression of surface markers through our collaboration with Sylvain Lefort from Cancer Research Center of Lyon (UMR CNRS 5286).

In addition to proposing rigidity as a criterion for cell sorters to distinguish between flexible and rigid subpopulations within the AML cell population, this project will enable two major advances. Such a microsystem, which allows high-throughput sorting of cells resistant or sensitive to therapeutic molecules, will be a powerful tool for i) accelerating basic research in this field, with faster access to statistics obtained on larger populations, and ii) exploring the possibility of transforming it into a clinical tool to aid therapeutic decision-making in the context of personalized medicine.

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Proposed collaboration within ArchiFun network (not mandatory at this stage):

Proposed list of secondments (not mandatory, but recommended if known already):

Main ArchiFun theme involved:

- ☐ Host-pathogen interactions;
- ☐ Mechanisms of bacterial resistance and cancer onsets;
- ☐ Neurodegenerative and autoimmune diseases;
- ☑ Translational research in prevalent diseases;
- ☐ Physiology and ecology;
- ☐ Neurosciences and cognition.