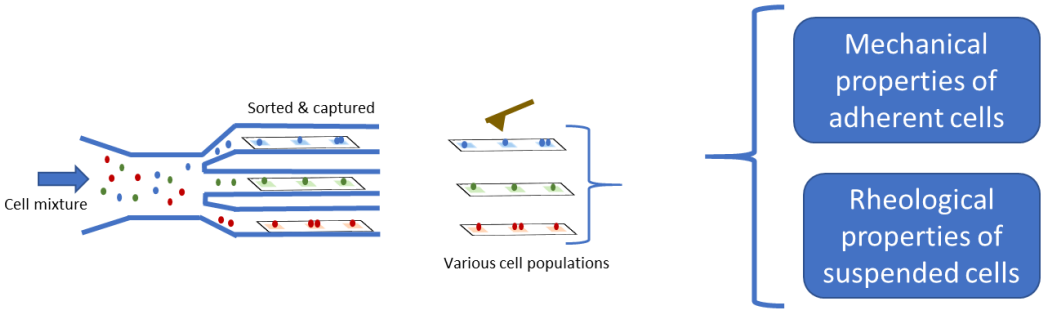
IFJPAN – NTNU

Biomechanical heterogeneity of cancer cells as a parameter for high throughput detectability

Despite large progress in cancer research leading to the identification of various key molecules and processes, cancer is still a leading cause of death worldwide. Most of cancer-related deaths are associated with the metastases that develop during years after primary tumor diagnosis. A huge number of mutations, accumulated over this time, leads to a large heterogeneity present in the structure, properties, and functioning of cells and affected organs. A serious consequence is that mechanisms discovered for one type of cancer may not necessarily be valid for others. Knowledge gathered so far shows that the deformability of single cells can be directly linked with pathological changes. Thus, the biomechanical properties are potential non-labeled fingerprints of various diseases. A large degree of cancer cell heterogeneity in solid tumors (containing populations of cells with similar or nearly similar deformability) limits the identification of a specific population of cells forming metastasis. One of the obstacles is a lack of reliable, high-throughput devices that qualitatively and reliably can detect mechanically altered cells in biological samples characterized by a large degree of heterogeneity. **The idea of our project is to combine the microfluidic approach with atomic force microscopy (AFM) to enhance the identification of mechanically altered cells.**



The objectives to be achieved are:

Objective 1. To develop and investigate a novel generation of the microfluidic devices combined with microarrays approach and with surfaces of biomimetic hydrogels to select a particular cell population.

Objective 2. To understand the mechanisms of viscoelastic changes in cells flowing through microfluidic channels by using model substances of various rheological properties.

Objective 3. To determine mechanical/rheological properties of cells used further to define criteria for effective recognition of altered cells.

Objective 4. To demonstrate that the level of biomechanical detectability in cancer cells characterized by a large and small deformability difference.

Altered deformability of cancer cells, being the manifestation of cancer-related changes, can be used to discriminate between healthy and cancerous states. The use of microfluidic devices will be used to sort cells floating through the channels. Their mechanical/rheological properties will be quantified using model substances of various rheological properties. Furthermore, cells will be captured on modified microarray surfaces and measured by AFM. We expect that already reported data limiting the quantification of cellular

deformability to the comparison of healthy and pathologically altered cells, will be overcome by understanding the mechanical/rheological properties of floating cells. Therefore, two groups of cancer cells will be studied, those with a much larger and much smaller deformability difference. Although AFM-based elasticity measurements have already demonstrated larger deformability of cancerous cells, it should be noted here that their mechanical properties are determined at the steady-state conditions, for a flat, nicely spread cells. In microfluidics, floating cells are round, therefore, it is essential to understand the relation between mechanical properties of adherent cells and cells in suspension. This is essential for enhancing the identification of cells by microfluidic devices.

The proposed project aims to identify these cancerous cells that possess the study of both the invasive and mechanical properties of the cells and to link these properties with the cell sorting efficiency. This will be possible only through the development of a novel microfluidic-based cell sorter combined with microarray approach used to identify a specific population of cells. Mechanical properties of suspended cells will be determined based on model substances. Mechanical properties will be quantified by the measurements with atomic force microscopy (AFM) working in classical force spectroscopy and microrheology modes. A microfluidic device used to sort cells and to place them on microarrays opens the way for the characterization of the mechanical properties of a high number of cells over prolonged periods.

The novelty of the proposed project concerns a few aspects. First of all, it is a development of the microfluidic device, which is capable to differentiate/separate specific cancer cell populations in suspension composed of cells characterized by small deformability differences. In parallel, the relation between the mechanical properties of suspended and adherent cells will be elaborated. It is assumed that larger deformability of adherent cancerous cells translates directly into their mechanical properties in suspension. So far, there is no direct proof showing to what extent initially larger cellular deformability is preserved in floating cancer cells. Therefore, it is interesting to compare microfluidic-based results with the AFM. This, simultaneously, demonstrate the applicability of the latter technique as a reference. Translate the obtained results into cancer research and evaluation its usefulness for cancer diagnosis.