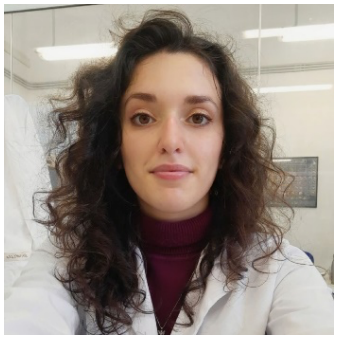
ROLE OF TRANSPORT PHENOMENA IN CANCER GROWTH AND INVASION



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Curriculum: Ingegneria Chimica

Cancer is a disease that arises from malfunctioning biological cells and it is still the second leading cause of death in advanced countries (29 percent of all deaths) after cardiovascular disease. In fact, in 2019 more than 17 million new cases of cancer and more than 9 million deaths were estimated worldwide. The development of an in vitro model to describe how different factors can change the response of the tumor is crucial to improve treatments and create strategies to provide patients a better life expectation.

In a tumor, the diseased cells proliferate uncontrollably and disrupt the organization of tissue. Its invasiveness, which can be induced by external chemical (chemotaxis) or mechanical stimuli, also involves the likelihood to migrate to other parts of the body via a process called metastasis. Metastasis is the predominant cause of death in cancer, so the cancer cells must be detected at the earliest possible stage before it metastasizes.

The aim of this work is to investigate the effect of (bio-) chemical and mechanical stimuli, using 3D spheroids as a model of not-vascularized tumor. Spheroids are a tightly bound cellular aggregate that tends to form when cells are maintained under nonadherent conditions. Studying tumor invasiveness in a quantitative way in a 3D environment able to mimic in-vivo conditions (also defined as ex-vivo), would allow better preclinical evaluation of anticancer drug candidates, compared to classical 2D in-vitro, in-silico, and animal models. The final goal of this research is the experimental validation of the tumor diffusional instability theory[1; 2; 3] and the development of in vitro model to describe the physiological condition of cancer growth and invasion.

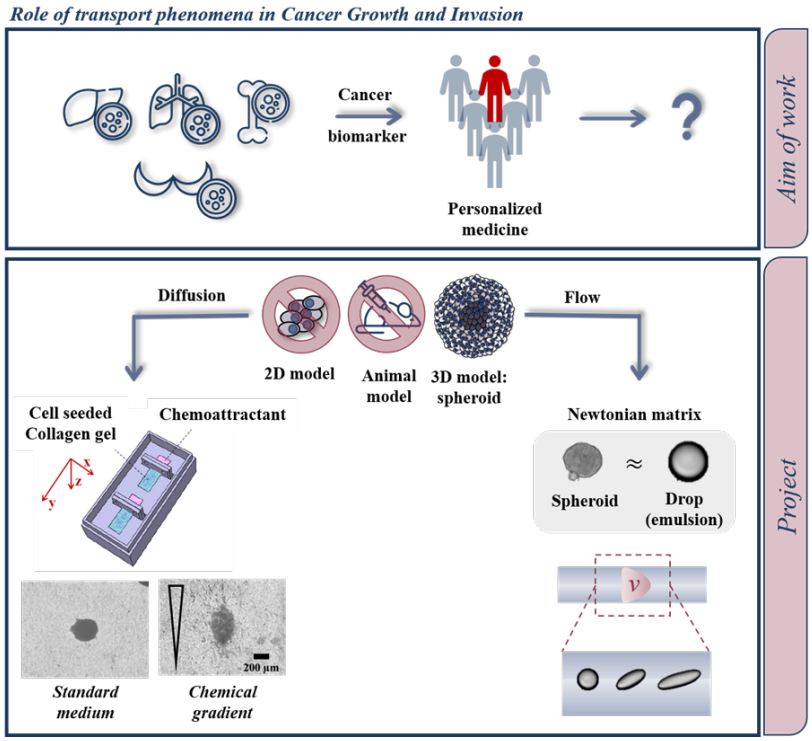
To quantify the morphological response of tumor to concentration gradients as function of time, we used a tumor invasion assay in 3-D collagen gels, based on a reusable direct visualization chamber in which a chemoattractant gradient is generated by diffusion through a porous membrane. A similar assay has already been used for the analysis of single cells motility[4; 5].

To quantify the influence of external mechanical stimuli on tumor, we apply a shear flow to the spheroids, using a “micro”- fluidic device. The spheroids were suspended in a fluid, formulated by adding polyvinylpyrrolidone (PVP) to standard culture medium, to increase the viscosity of the fluid and, consequently, to minimize spheroids sedimentation and to increase stress. Therefore, the morphology of tumor spheroids under external stress can be analyzed in analogy with a multiphase fluid, such as an emulsion[6]. In fact, in this experimental model, the tumor spheroids can be assimilated to a drop suspended in an immiscible fluid. In emulsions, interfacial stresses impose a spherical form to the drops. Similarly, cell-cell interactions maintain spheroids compact, while external stimuli can induce aggregates to lose compactness, deform and increase surface/volume ratio.

Summarizing, this research project is focused on the development and validation of innovative methodologies to measure the role of external (bio-) chemical and mechanical stimuli on the capacity of tumor to invade the surrounding healthy tissue. The assay will be based on a chemical engineering approach, focusing on the role of transport phenomena on cancer growth and invasion. To fully understand the behavior of a tumor, the project has been structured in 4 steps:

1. Wound healing assay[5; 7; 8]: to analyses cell motility for different cell lines using a 2D model;
2. Spheroid formation[9; 10]: transition from 2D to 3D model, in order to integrate all the key parameters that are missing in the two-dimensional models, necessary to better mimic the behavior of a tumor;
3. Chemotaxis assay[4, 15]: analysis of the morphological response of tumor spheroids to an external chemical stimulus, using a technique already used in the past for the analysis invasiveness of single tumoral cells;
4. Mechanical assay[11; 12; 13; 14]: analysis of the morphological response of the tumor spheroids to a mechanical stimulus (shear flow) in analogy with multiphase fluids.

Understanding these mechanisms can allow to develop models applicable to the prediction and design of the response of a tumor to targeted therapeutic treatments (personalized medicine).



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AERC 2021 (Annual European Rheology Conference 2021) online, April 13-15, 2021, poster – winner of the Best Scientific Poster Award;
ICR 2020 (18th International Congress on Rheology), 14-17 December 2020, Rio de Janeiro – Brazil (online), oral presentation;
II Meeting «Development of delivery systems for experimental clinical biochemistry and therapy», 2019, Trieste, oral presentation.

Rosalia Ferraro, PhD student XXXV cycle, May 2021