Tunneling nanotubes (TNTs) within the leukemia microenvironment; influence of metabolic remodeling and implications for therapy.

The interactions between cancer cells and their microenvironment are crucial for the biology of cancer, including leukemias. Cell-cell communication within the leukemia microenvironment provides a suitable niche and conditions for cancer cell growth and survival. It has been already demonstrated that the stromal component of leukemia microenvironment provides protective signaling. Thus, the microenvironment plays a crucial role in disease development and progression as well as resistance to treatment and disease relapse. Several mechanisms are involved in the leukemia-microenvironment crosstalk, such as cytokine/receptor interactions, direct cell contact, material exchange and microparticle-mediated cell communication. Recently, tunneling nanotubes (TNTs) have been considered as a new way of direct cell-cell contact and communication, mediating transfer of different cargos between two distant cells. Strong evidence suggest their critical role in the regulation of cell-cell crosstalk and signaling within the cellular networks

The general objective of the proposed studies is to elucidate novel regulators and functions of TNTs formed between stromal and leukemic cells, as a mechanism supporting adaptation, survival and therapy resistance of leukemia cells. As tunneling nanotubes have been discovered relatively recently, the mechanisms involved in regulation of their formation, structure and functions are still not clear. During initial studies we discovered that tunneling nanotubes are formed between leukemia and stromal cells, and that their formation depends on the cell type and metabolic conditions. Moreover we found that transfer of specific sets of molecules from stromal to leukemia cells results in increased resistance to anti-leukemic treatment.

During realization of this project we will verify the hypothesis that specific sets of cargos are transferred *via* TNTs between stromal and leukemic cells, and that its composition plays an important role in regulation of cell functions and response to therapy. Moreover, we propose that remodeling of microenvironmental metabolic conditions can be a major regulator of TNTs formation and activity. This could play a crucial role in leukemia progression and relapse by supporting adaptation of cancer cells and development of therapy resistance**.**

Altogether we expect to provide new data about the novel TNTs-mediated intercellular communication between leukemia and stroma cells, together with their role and mechanism of regulation. Taking into account that TNTs are proposed as a very potent therapeutic target not only for cancer treatment, but also other diseases, our studies may have therapeutical implications, making our hypothesis more attractive and placing our studies in both basic and translational research fields.