

**Specialty area: Pre-Clinical MR of Cancer**

**Speaker Name: Michal Neeman [michal.neeman@weizmann.ac.il](mailto:michal.neeman@weizmann.ac.il)**

**Highlights**

- The tumor should be viewed as a heterogeneous organ
- Tumors include multiple non cancer stroma cells
- Tumors interact with their microenvironment: oxygen, pH, interstitial pressure
- Tumor dormancy, prevalence and significance

**Title: Tumor Physiology**

**Target audience:** MR researchers and clinicians who are interested in understanding the biological mechanisms that affect tumor progression, and their impact on MR readouts of tumors.

**Objectives:** The learners will be able to appreciate the complexity of cancer and the importance of imaging in advancing our understanding of cancer progression

**The tumor as a heterogeneous organ:**

Although cancer is believed to arise from spontaneous somatic mutation resulting in its uncontrolled proliferation and evasion of the immune system, over the last years it has become clear that such malignant transformation, although necessary, is not sufficient to induce cancer progression. A growing tumor activates a range of developmental pathways found in physiological organogenesis. Thus, by the time detected, tumors show a host of interactions with their surrounding which are selected due to their role in facilitating cancer progression. A tumor of no more than a few millimeters will have already induced a significant change in its extracellular matrix, and it will attract blood vessels and a range of non-cancer stroma cells including macrophages and fibroblasts.

**The tumor microenvironment**

In contrast with the progression of normal organs in which the cells maintain tight control and well-regulated communication to achieve a well-structured tissue architecture, tumor progression is driven by deranged uncontrolled proliferation of the cancer cells. Thus cancer cells proliferate to the point of starvation, resulting in formation of hypoxic areas and shift to glycolytic metabolism with elevated extracellular pH. Such a metabolic shift, results in activation of inflammatory and angiogenic wound healing responses. In contrast to most organs in which metabolic homeostasis is maintained by balanced supply to the cellular demands, cancers typically show large spatial (and temporal) variations in nutrient and oxygen availability and hence also in cell proliferation and death. Such large spatial variability provides the required rich landscape in which genetic instability, cellular adaptation and selection can lead to further evolution of tumor heterogeneity.

**Tumor stroma cells**

Although the transformed cancer cell has attracted most of the attention of the research community, and has been the primary target for therapy, some tumors show a considerable contribution (sometimes more than half) of non cancer cells. Tumors attract macrophages and T-cells, which are 'educated' by the tumor microenvironment to become tolerant for the tumor cells. Tumors also contain a large contribution of fibroblasts, which can either come from the tumor surrounding or be recruited systemically. These cells too are 'educated' to become reactive myofibroblasts, which contribute to the mechanical stiffness of tumors. These cells deposit extracellular matrix and secrete growth factors that along with factors secreted by macrophages contribute to induction of angiogenesis and lymphangiogenesis. Finally, endothelial cells are recruited by tumors to form new blood vessels, which are highly leaky, tortuous and chaotic due to the elevated secretion of VEGF in the hypoxic tumor microenvironment. These leaky vessels result in elevated interstitial pressure, and a change of the extracellular matrix from the quiescent one to the activated fibrin rich provisional matrix.

**Tumor dormancy:**

Although of no immediate clinical significance and invisible to most screening and diagnostic tools, it is widely accepted that tumor dormancy is prevalent. The critical switches which induce tumor progression may well be related to complicated network of tumor stroma interactions. Revealing these interactions offers hope for novel strategies for preventive therapy through maintenance of tumor dormancy.