BONE MARROW NICHE, A DRUG FREE SANCTUARY FOR CANCER STEM CELLS

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Survival of patients with hematological malignancies and cancer in general depends on our ability to eliminate the last bastion of malignant cells, the so called “minimal residual disease”. Inspired by Sir Paget’s “soil and seed” hypothesis, it is now clear that there is a constant feedback between the cancer cells and their surrounding microenvironment. This “molecular conversation” reinforces a protective niche that can support cancer cells and needs to be overcome in order to eliminate minimal residual disease and improve cure rates in our patients. Studying the role of bone marrow mesenchymal microenvironment, we have discovered that normal hematopoietic stem cells are intrinsically programmed to undergo differentiation and form blood with subsequent exhaustion. It is the bone marrow niche that controls stem cell behavior to match physiological needs and maintain stem cells for the life span of the organism. During these studies, we have uncovered that bone marrow mesenchymal cells express drug detoxifying enzyme at levels comparable to hepatocytes. More so, these mesenchymal cells are able to metabolize chemotherapy and create true “drug-free sanctuaries” in the bone marrow. The biochemical barrier generated by the bone marrow mesenchymal cells is in many ways similar to the better known “blood-brain barrier” and should be by-passed in order to eliminate resting cancer stem cells. Our more recent data bring to light how the malignant cells promote their survival by re-enforcing this barrier. Tools to by-pass this protective mechanism have been developed in our laboratory and are in phase II clinical trials at John Hopkins and soon to be tested at Fundeni Clinical Institute.