# Intravital imaging of stem cell and cancer cell plasticity

Jacco van Rheenen

Hubrecht Institute-KNAW & University Medical Center Utrecht
Uppsalalaan 8, 3584CT, Utrecht, the Netherlands, fax: +31 (0)30 251 64 64, email: j.vanrheenen@hubrecht.eu

Although histological techniques have provided important information on epithelial stem cells and cancer, they draw static images of dynamic processes. To study dynamic processes, we have developed various imaging windows to image intestinal, liver and breast tissue, and visualize the behavior of individual cells at subcellular resolution for several weeks with two-photon intravital microscropy (IVM). In this talk I will discuss how we have used these techniques to study the identity and behavior of (cancer) stem cells during pubertal mammary morphogenesis and tumor growth, and to study the plasticity of tumor heterogeneity.

Our IVM experiments illustrate that cellular properties and fate of (cancer) stem cells are highly dynamic and change over time. For example, we show in healthy and tumorigenic tissues, that cells can acquire and lose stem cell properties, illustrating that stemness is a state as opposed to an intrinsic property of a cell. Moreover, our data implies that the behavior and even the identity of stem cells cannot be linked directly to a single molecular profile or specific markers, but must be defined functionally.

In the last part of the talk, I will discuss a project where we have studied the plasticity of tumor heterogeneity. An aspect that complicates tumor heterogeneity is that cells may exchange active biomolecules through the release and uptake of extracellular vesicles (EVs). Our data shows, in living mice, that malignant tumor cells, through transfer of EVs, enhance the migratory behavior and metastatic capacity of more benign cells. Taken together, these data exemplify that tumor heterogeneity and tumor microenvironment are far more complex than currently anticipated, which has profound consequences for our ideas on the mechanisms of tumor progression and for designing optimal treatment strategies.