# Seminar series FOR2127 – Selection and adaptation during metastatic cancer progression

**Thursday, 29 Seprember 2016**
**Biopark I, Hörsaal**
**14.00 h**


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**Early cancer cell dissemination, dormancy and the paradigm of metastasis**

The major challenge faced by physicians is the prevention and treatment of metastasis, the main reason for cancer related deaths. Our understanding of metastasis has lagged behind that of primary tumor biology and we are far behind grasping its complexities. Progress has been hampered by the research paradigm itself, which states that metastasis is an extremely late event in micro-evolutionary and temporal scales. The prevailing idea is that metastases are aggressive tumor cells linearly derived from detectable primary tumors. Clinical observations and experimental work has however reshaped the paradigm of metastasis by showing that cancer cells can disseminate at very early times in cancer evolution and give rise to metastasis. Our study revealed that during stages when only non-invasive lesions are detected, a subpopulation of of HER2+ early cancer cells that may go undetected by conventional pathology, are intermingled with non-invasive cells and are highly efficient in systemically disseminating from early primary lesions. These early disseminated cancer cells or eDCCs we define as having a $HER2^{+}$/P-$ATF2^{lo}$/E-$cadherin^{lo}$ signature, which was found also in a subset of cells in human HER2+ DCIS samples. Further, the eDCC precursors underwent a Wnt-driven program that resembles an epithelium to mesenchyme transition (EMT). We used mouse genetics to determine what components of this EMT-like response were p38- and/or HER2-dependent. In addition, we used high resolution intra-vital imaging to visualize how these eDCC precursors invade the local stroma, intravasate and circulate to target organs. This led us to determine that the interplay between HER2, Wnt and p38 signaling is responsible for regulating anoikis resistance, invasion and dissemination during a time when such events had never been observed. Surprisingly, eDCCs can still initiate metastasis albeit after variable dormancy periods. Importantly, this HER2-driven deregulation of branching morphogenesis appears to endow early cancer cells with powerful disseminating and metastasis initiating capacity.

## Selected reading:


Sosa MS, Parikh F, Maia AG, Estrada Y, Bosch A, Bragado P, Ekpin E, George A, Zheng Y, Lam HM, Morrissey C, Chung CY, Farias EF, Bernstein E, Aguirre-Ghiso JA. NR2F1 controls tumour cell dormancy via SOX9- and RARβ-driven quiescence programmes. Nat Commun. 2015 Jan 30;6:6170. doi: 10.1038/ncomms7170. PubMed PMID: 25636082; PubMed Central PMCID: PMC4313575.

Bragado P, Estrada Y, Parikh F, Krause S, Capobianco C, Farina HG, Schewe DM, Aguirre-Ghiso JA. TGF-β2 dictates disseminated tumour cell fate in target organs through TGF-β-RIII and p38α/β signalling. Nat Cell Biol. 2013 Nov;15(11):1351-61. doi: 10.1038/ncb2861. Epub 2013 Oct 27. PubMed PMID: 24161934; PubMed Central PMCID: PMC4006312.