

**TP17:** Probing the role of bone marrow niche-derived SPARC (Secreted Protein Acidic Rich in Cysteine) in the metastatic behaviour of human breast cancer

### **Scientific staff**

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### **Project description**

This project is focused on the role of bone marrow niche-derived SPARC in breast-to-bone metastasis. Breast cancer, which accounts for approximately 10% of all diagnosed neoplasms, shows a particular high tropism for bones. Consequently, large autopsy series have demonstrated that bone metastases are present in 54-73% of breast cancer patients. To date, little is known about the influence of extra-cellular matrix proteins on the metastatic behavior of breast cancer. Here, we will investigate SPARC as an essential player of metastatic progression in bone, using in vivo PDX and state-of-the-art in vitro models. Hence, we hope to characterize molecular pathways underlying SPARC functions in the colonization of the bone by breast cancer cells and possibly identify novel therapeutic approaches to target tumor cells and/or stromal drivers of bone metastasis.

### **Expertise**

We have successfully generated several NSG SPARC knockout lines to study the role of niche-derived SPARC in human cancers (Tirado-Gonzalez et al., 2018). Likewise BLI imaging and bone clearing techniques for high resolution imaging by light sheet microscopy are well established in our lab, and allow precise monitoring of metastatic burden within the bone microenvironment. In addition, we recently developed a fully humanized bioengineered 3D bone marrow niche model, which will be used for ex-vivo experimentation. To comprehensively dissect the molecular mechanisms underlying SPARC function in bone metastasis, RNA sequencing and CRISPR/Cas in vivo screening will be performed.

### **Project-related publications**

Tirado-Gonzalez I, Czlonka E, Nevmerzhitskaya A, Soetopo D, Bergonzani E, Mahmoud A, Contreras A, Jeremias I, Platzbecker U, Bourquin JP, Klotz U, Van der Hoeven F, and Medyouf H (2018) CRISPR/Cas9 edited NSG mice as PDX models of human leukemia to address the role of niche-derived SPARC *Leukemia* 32: 1049-105

Guttlein LN, Benedetti LG, Fresno C, Spallanzani RG, Mansilla SF, Rotondaro C, Raffo Iraolagoitia XL, Salvatierra E, Bravo AI, Fernandez EA, Gottifredi V, Zwirner NW, Llera AS, Podhajcer OL (2017) Predictive Outcomes for HER2-enriched Cancer Using Growth and Metastasis Signatures Driven By SPARC. *Mol Cancer Res* 15: 304-316

Sharma S, Xing F, Liu Y, Wu K, Said N, Pochampally R, Shiozawa Y, Lin HK, Balaji KC, Watabe K (2016) Secreted Protein Acidic and Rich in Cysteine (SPARC) Mediates Metastatic Dormancy of Prostate Cancer in Bone. *J Biol Chem* 291: 19351-63

### **Further information:**

<http://www.georg-speyer-haus.de/en/research/research-groups/medyouf/research.html>  
<http://www.georg-speyer-haus.de/en/research/research-groups/sevenich/research.html>