Engineered Bone for Probing Organotypic Growth and Therapy Response of Prostate Cancer Tumoroids *in vitro*

Claudia Paindelli[1,2], Nora Navone[1], Christopher J Logothetis[1], Peter Friedl[1,2,3] and **Eleonora Dondossola[1]**

[1] David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Radboud University Nijmegen, Nijmegen, The Netherlands; [3] Cancer Genomics Centre (CGC.nl), 3584 Utrecht, The Netherlands

Background: Despite recent advances in prostate cancer (PCa) treatment, the outcome of metastatic disease remains frequently fatal and the underlying biology poorly understood. Thus, the development of clinically relevant *in vitro* models to monitor PCa biology in organotypic bone-like environment is critical to uncover mechanisms of therapy resistance and identify more effective treatments.
Methods: To establish a bone-mimetic culture, we combined the following components: (i) bioactive osteoblasts depositing bone-like calcified extracellular matrix, (ii) complex 3D surface geometries, (iii) multicellular tumor application as spheroids/organoids; and (iv) applicability for live-cell microscopy to monitor the development of lesions over time.
Results: Calcified polycaprolactone (PCL) scaffolds were functionalized with human mesenchymal stem cells (hMSCs) differentiated to osteoblasts, to generate a 3D niche-like calcified environment. PCa spheroids (PC3; C4-2B; patient-derived xenografts, PDXs) were "onplanted" and their growth and invasion longitudinally monitored by advanced microscopy up to months. Bone mimetic cultures proved suitable for investigating the therapy response to docetaxel, a first-line drug for advanced PCa, and Radium 223, a radio-isotope with bone seeking properties recently approved for metastatic PCa patients. The bone mimetic culture further revealed differential resistance mechanisms depending on the presence of osteoblasts.
Conclusions: As a result, we generated mechanistic, three-dimensional and time-resolved insights into positioning and function of established cell models and PDX cultures, their adjacent environment, and stroma-induced resistance to therapy response.

Conflict of interests: None

Funding Acknowledgments: Eleonora Dondossola is supported by PCF (2016 Young Investigator Award), The Rolanette and Berdon Lawrence Bone Disease Program of Texas (The Bone Research Award 2017), Sage Bionetworks (Interdisciplinary Approaches to Cancer Metastasis 2017) and The University of Texas MD Anderson Cancer Center Spore Prostate Cancer (2018).