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Intratumoral heterogeneity and the role of clonal cooperation in breast cancer

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INTRODUCTION: Breast cancer show a wide spectrum of genetic and epigenetic alterations, being the second most common cancer in the world and the most frequently diagnosed neoplasm in women and a leading cause of cancer death. One of the greatest issues in oncology concerns the intratumor heterogeneity, whereby the presence of clonal populations and their cooperation, which is currently postulated to be mediated by extracellular vesicles like exosomes, contributes to the overall malignancy and therapeutic resistance.

AIM: We are currently aiming at dissecting the molecular mechanisms underlying the cooperation between different clones within a tumour. Our main objectives are 1) to identify and characterize individual cell clones that confer an overall advantage to breast tumour growth and 2) to identify new secretable factors that confer tumorigenic advantages to the tumours, favouring invasive tumour growth.

METHODS AND RESULTS: We produced clonal cell lines from the MDA-MB-231 breast cancer cell line, using UbC-StarTrack system, allowing multiple clones to be color-tracked simultaneously. Characterization of these individual clonal lines *in vitro* revealed that there are striking differences in proliferation, cell metabolic activity, morphology among clones and slightly differences in migration. *In vivo*, all the individual clones are able to form tumors, but strikingly the growth rate differs among clones. In addition, injection of an equal mix of three different clones and the parental cell line, leads to the formation of tumors where some clones display a growth or survival advantage over others.

CONCLUSIONS: In summary, we were able to identify cell clones from the MDA-MB-231 cell line, and the results confirm heterogeneity is present even in stable cell lines. We are currently analyzing if this growth differences are mediated via secretable factors like exosomes which could ultimately serve as novel therapeutic targets for the treatment of breast cancer.