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Resistance of s-SHIP positive tumor cells in the MMTV-Wnt1 mice model of breast cancer

Joséphine Louvieux, Xuefen Le Bourhis, Roland P Bourette

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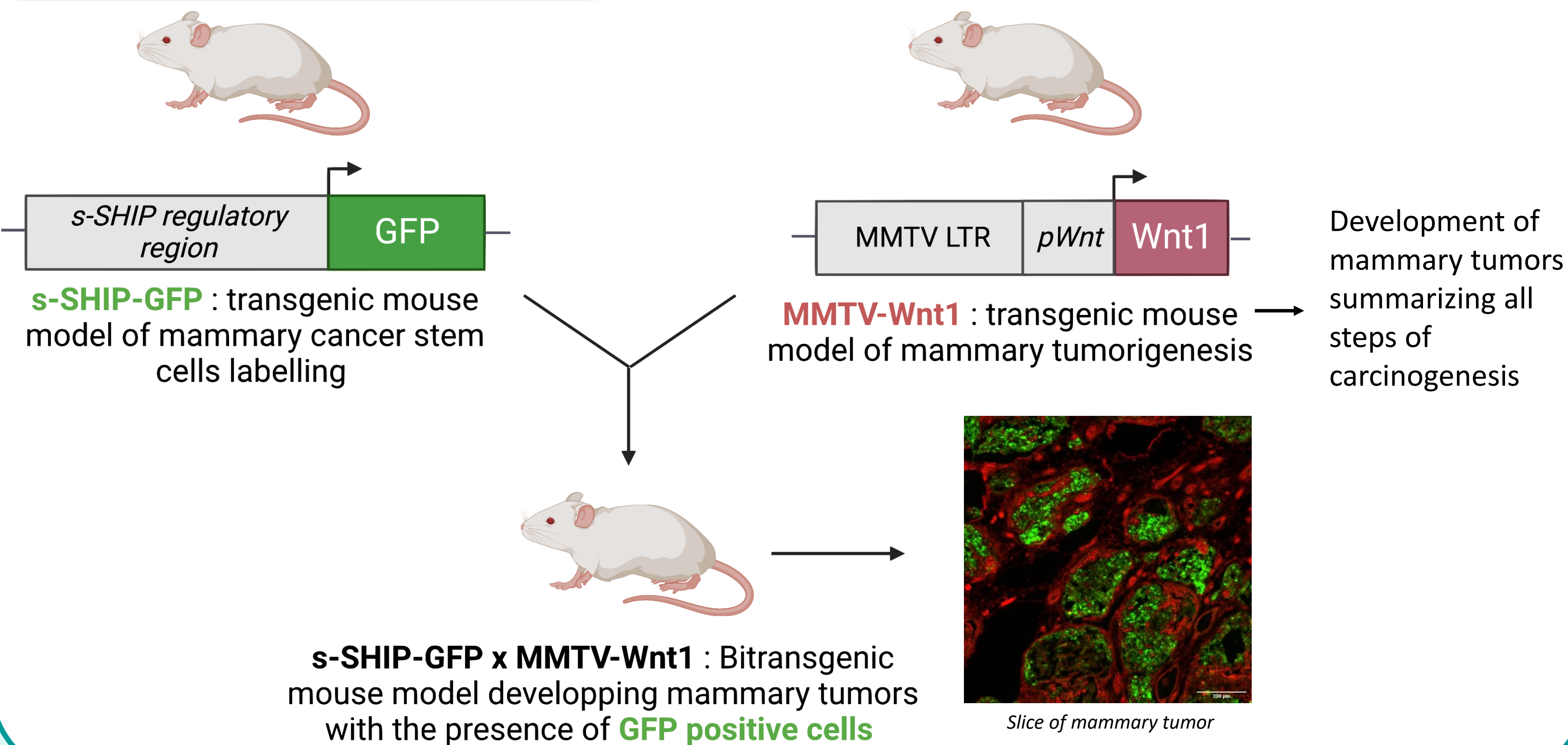
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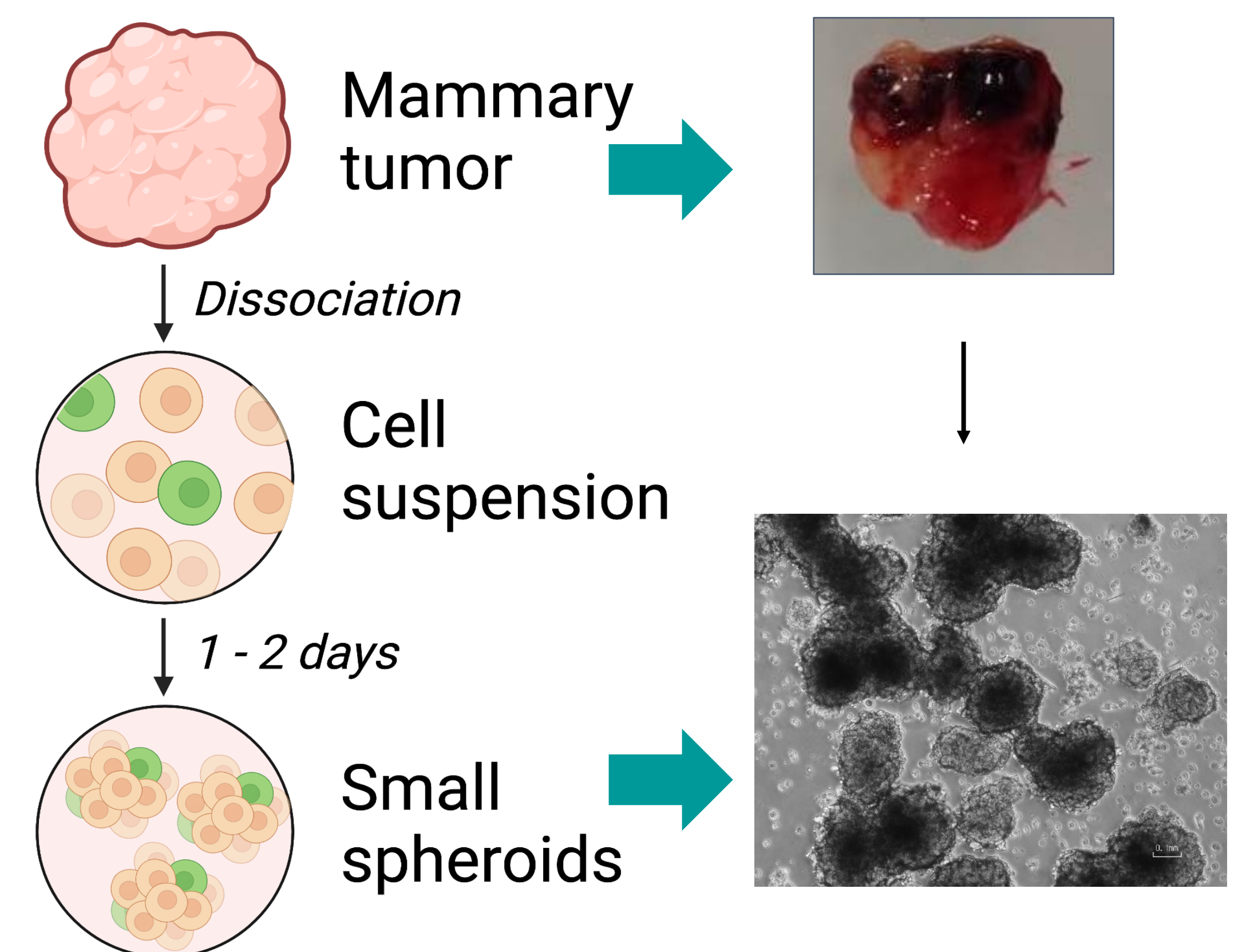
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Abstract : Triple Negative Breast Cancer (TNBC) is the most lethal subtype of breast cancer. Despite the successes of emerging targeted therapies, relapse, recurrence and therapy failure rates in TNBC significantly outpace other subtypes of breast cancer. Mounting evidence suggests accumulation of therapy resistant Cancer Stem Cell (CSC) populations within TNBCs contributes to poor clinical outcomes. In order to investigate the nature of these resistant CSC, two transgenic mice models are combined to study these CSC : (i) the **s-SHIP-GFP mice** express green fluorescent protein (GFP) from the s-SHIP promoter. By using these mice, we have previously shown that s-SHIP/GFP is a marker of both normal and cancer stem cells of the mammary gland. (ii) The **MMTV-Wnt1 mice** is a well-studied mouse model of multistep mammary tumorigenesis. We have generated **bitransgenic mice** by crossing these two models and obtained mammary tumors containing a subset of s-SHIP/GFP expressing cells. **3D cell cultures** were established to investigate the drug resistance of these tumor cells. We obtained heterogeneous **spheroids** that reproduce **tumor heterogeneity** with stromal, basal, and luminal cells, including a subset of s-SHIP/GFP positive cells. As a first approach, we investigated the effect of paclitaxel, a drug widely used in the treatment of breast cancer. We demonstrated that treatment with paclitaxel significantly increased the percentage of s-SHIP/GFP+ tumor cells suggesting that s-SHIP/GFP cells were more **resistant to drugs**. We want now to investigate resistance to other drugs and perform the transcriptomic analysis of these s-SHIP/GFP positive resistant cells to understand the underlying molecular mechanisms.

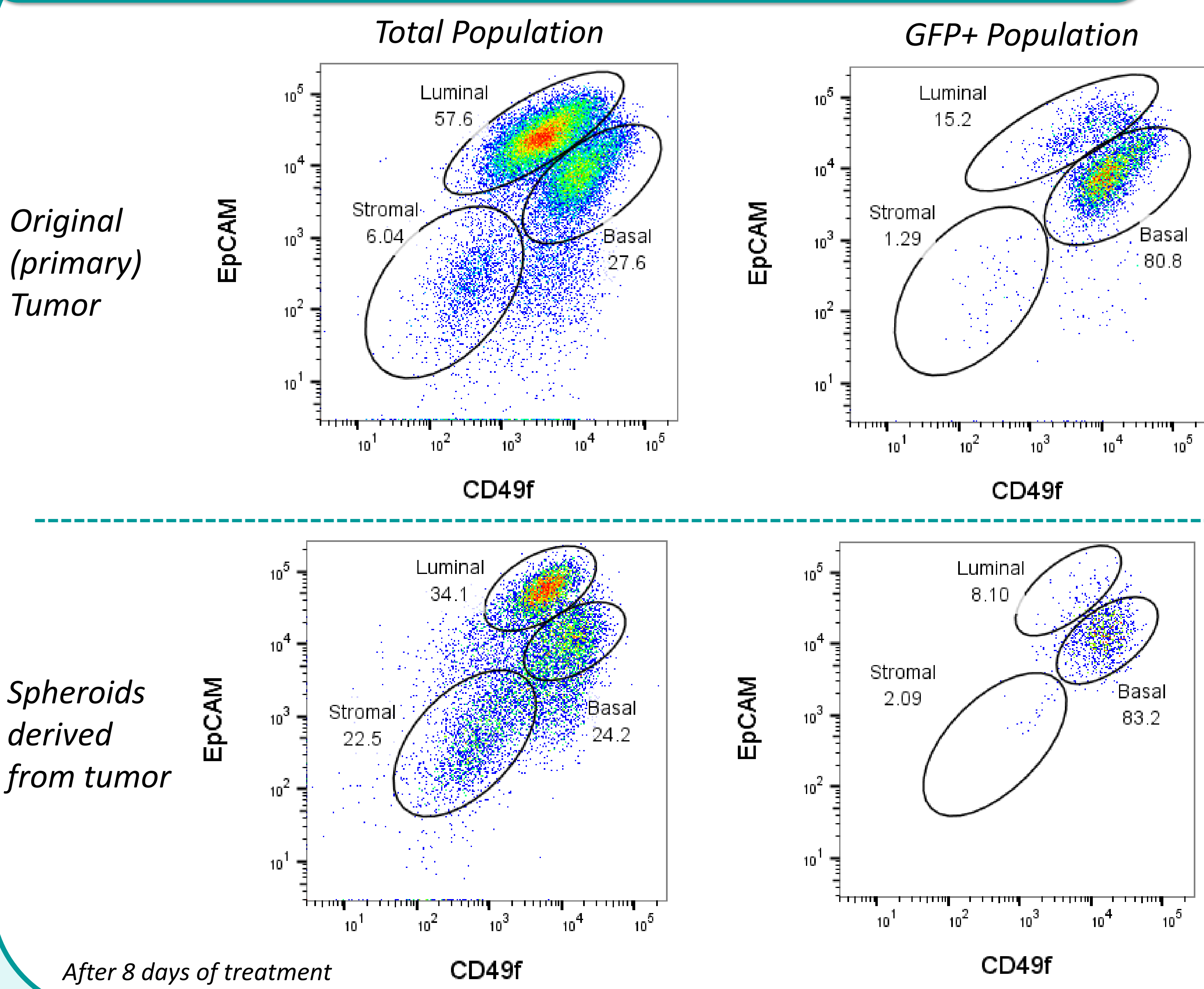
Bitransgenic mice model



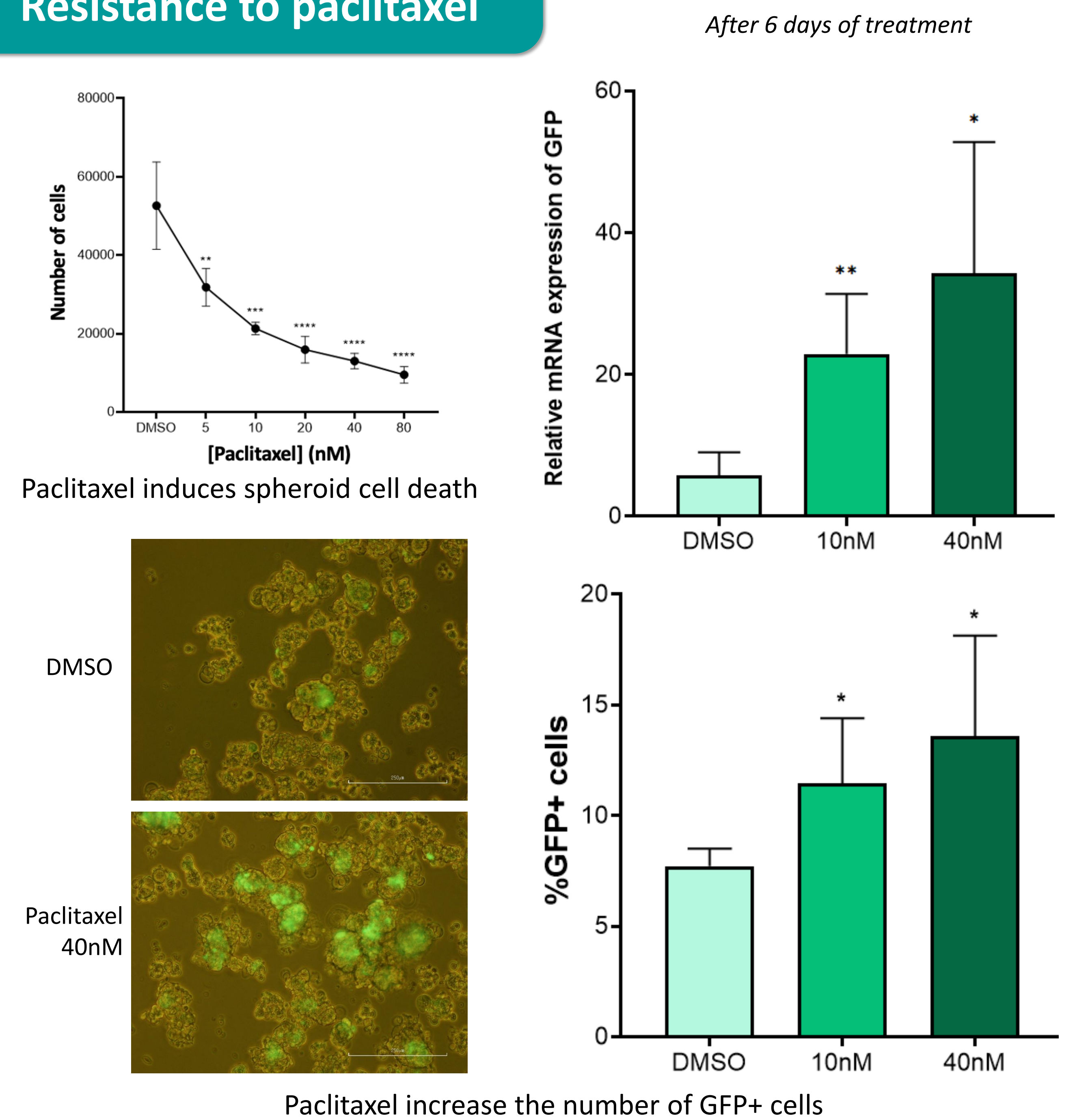
3D culture system



Analysis of cell compartments in tumor vs. spheroids



Resistance to paclitaxel



Conclusion on spheroids

Spheroids culture is a good model with the maintain of tumor **heterogeneity** :

- Basal and luminal epithelial cells
- Stromal compartment
- Presence of GFP positive cells in the same cell compartment

Resistant tumor cell population was enriched in s-SHIP/GFP positive cells

Suggesting an higher **resistance to chemotherapy** of s-SHIP/GFP positive cells

Perspectives

- More studies are necessary to fully characterize the different spheroids cell populations – Immune cells ?
- Confirm the drug resistance property with other chemotherapy – Combination Doxorubicine / Paclitaxel
- **RNA sequencing** to analyse the transcriptomic profile of s-SHIP/GFP+ resistant cells