DTCs in Ovarian Cancer

Although ovarian cancer (**OC**) has a characteristic property of rapid cancer progression along with formation of ascites and metastasis within the peritoneal cavity, the presence of hematogenous tumor cell dissemination is also a common phenomenon in OC. **DTCs** are detected in **20%** to **60%** of cases **before** the onset of **platinum-based chemotherapy**, depending on the method used, and were significantly associated with a **reduced PFS** and **OS** (**Figure 1**; **Fehm, Kasimir-Bauer et al., 2013;** Romero-Laorden et al., 2014; Cui et al., 2015).

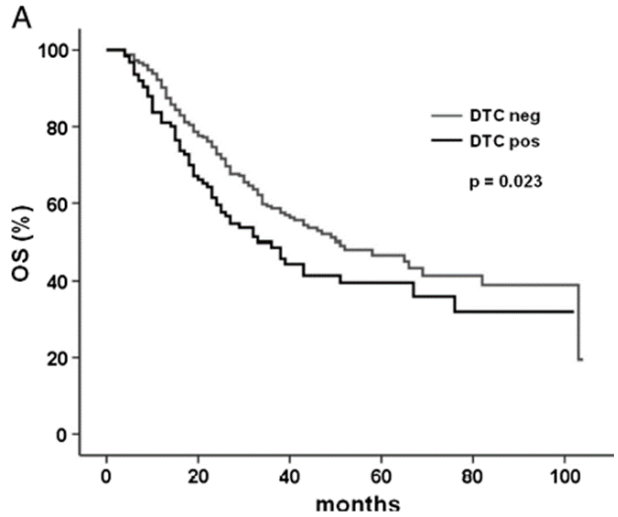

Figure 1: Prognostic significance of DTCs. Pooled analysis of 495 primary ovarian cancer patients (***Fehm, Kasimir-Bauer et al., 2013***).

We further demonstrated that **DTCs**, still present **after chemotherapy**, were **EpCAM-positive**, **non-apoptotic** and their **marked increase** was associated with a significantly **reduced PFS** (**Figure 2; Wimberger et al., 2007**). Interestingly, also in the context of current immunotherapeutic approaches, an additive EpCAM-specific **immunotherapy** in a palliative setting resulted in a reduction or **elimination of DTCs** as well as circulating tumor cells (**CTCs**) **(Wimberger et al., 2009)**.

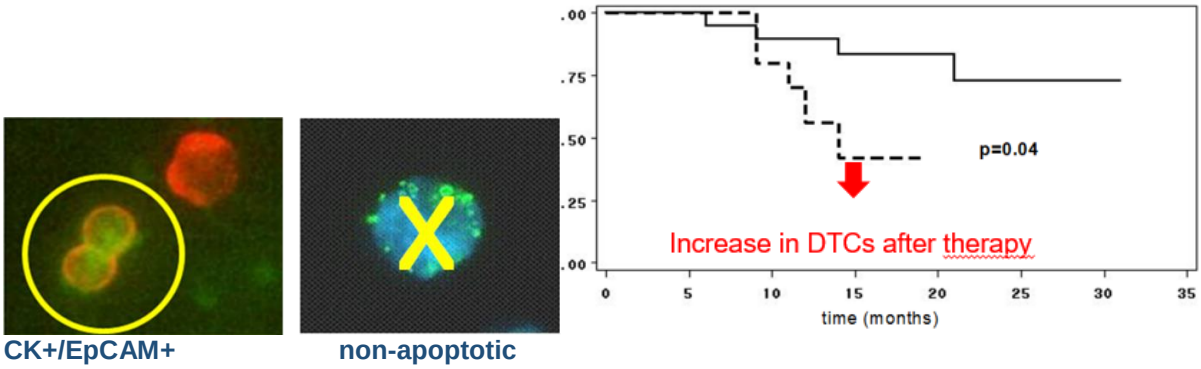

Figure 2: Characteristics and prognostic relevance of DTCs in ovarian cancer (***Wimberger et al., 2007***)**.**

In the following years, we were able to show that the **negative prognostic impact of DTCs** was related to their persistence after platinum-based chemotherapy and to a **stem cell character** (**Figure 3; Chebouti et al., 2016**). DTCs, present and persistent after therapy, also expressed the stem cell markers **Lin-28** and/or **SOX-2** and were even present **before the onset of therapy** which explained the significantly **shorter PFS** of patients who changed from being DTC-negative before to DTC-positive after therapy. Besides the detection of

CKpos/SOX-2pos (LIN-28pos) DTCs, we also identified **CKneg/SOX-2pos (LIN-28pos) cells** in all patients and assumed that these DTCs might be related to tumor cells that had undergone phenotypic changes, known mesenchymal transition (**EMT**) **(Chebouti et al., 2016)**. In this context, *in vitro* and mouse model studies revealed a role of chemotherapy-induced Jagged1 (a driver of cancer progression) in osteoblasts in promoting chemoresistance of bone metastasis which was confirmed in a collaborative project, where we demonstrated a significant increase of Jagged1 staining on osteoblasts of our patients` bone marrow samples after therapy **(Zheng et al., 2017)**.

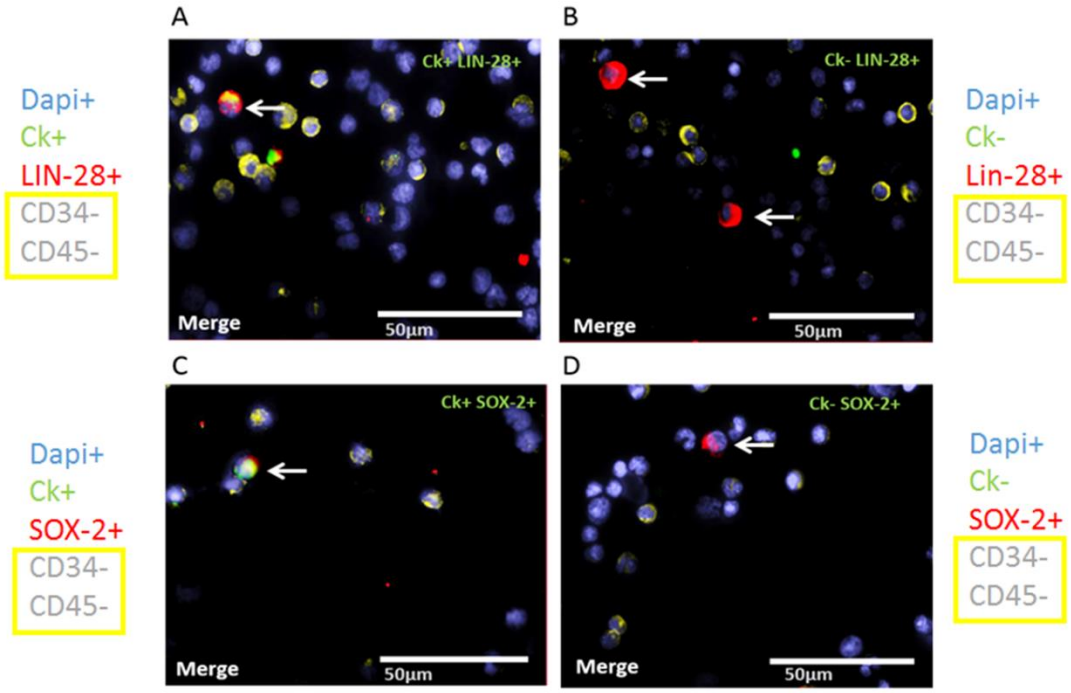

Figure 3: Representative four-fold immunofluorescence staining for DTCs with stem cell character. CKpos/LIN-28pos cells (A), CKneg/LIN28pos cell. (B), CKpos/SOX2pos cells (C) and CKneg/SOX2pos cell. (D), all CD45neg and CD34neg, magnification at 63× (***Chebouti et al., 2016***).

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