PhD thesis subject :

Breast cancer (BC) is now the most common cancer in European women. Among all different BC subtypes, some of them overexpress the human epidermal growth factor receptor 2 (HER2, ErbB2). Until a few years ago, these patients had unfavorable outcome but the overall survival radically improved thanks to anti-HER2 antibody-based treatments such as trastuzumab (Herceptin®) or the more sophisticated antibody-drug conjugate (ADC) [1] ado-trastuzumab emtansine (T-DM1, Kadcyla®). However, HER2-positive BCs, which can gain benefit from these new targeted therapies, concern only 1 out of 5 patients. Some BC tumors can become resistant, while others are heterogeneous and contain cells naturally expressing a (very) low level or lack of expression of HER2, like **triple negative breast cancer (TNBC), against which both Herceptin® and Kadcyla® are inefficient**. TNBC represents 20% of BCs and is characterized by the absence of estrogen (ER) and progesterone (PR) receptors and HER2 gene amplification. TNBC has a high mortality rate because of its aggressive behavior associated with a strong metastatic potential and a usual resistance to standard therapeutic strategies. Neither single standard chemotherapy nor **FDA-approved antibody-based therapy** are available to treat patients with relapse/refractory metastatic TNBC (mTNBC). Interestingly, recent researches highlighted an overexpression of an **undisclosed target** in mTNBCs and other BCs. This **target** is overexpressed in many solid cancers, increasing cancer growth, tumor aggressiveness, metastasis occurrence, and poor prognosis.

In this context, the aim of our project is to develop original homogeneous ADCs [2] and scFv-drug conjugates (SDCs) [3] to offer new chemotherapeutic strategies in the management of TNBCs and other BCs. Proprietary, original and optimized antibodies will be developed. The PhD student will develop new chemical linkers to control the hydrophobicity of the linker-drug moieties and their site-specific bioconjugation onto a proprietary mAb and its scFv counterpart. The corresponding ADCs and SDCs will be evaluated *in vitro* on TNBC cell lines or HER2-positive cells resistant to Herceptin® and Kadcyla®, and then *in vivo* in various breast cancer mouse models.

[1] Joubert *et al*. Towards antibody-drug conjugates and prodrug strategies with extracellular stimuli-responsive drug delivery in the tumor microenvironment for cancer therapy. *Eur J Med Chem.* **2017**, 142, 393. doi: 10.1016/j.ejmech.2017.08.049.
[2] Bryden *et al.* Impact of cathepsin B-sensitive triggers and hydrophilic linkers on in vitro efficacy of novel site-specific antibody-drug conjugates. *Org Biomol Chem.* **2018**, 16, 1882. doi: 10.1039/c7ob02780j.
[3] Aubrey *et al.* Site-Specific Conjugation of Auristatins onto Engineered scFv Using Second Generation Maleimide to Target HER2-positive Breast Cancer in Vitro. *Bioconjug Chem.* **2018**, 29, 3516. doi: 10.1021/acs.bioconjchem.8b00668.