DOCTORAL CANDIDATE:

DEGREE:	Philosophiae Doctor
FACULTY:	Faculty of Mathematics and Natural Sciences
DEPARTMENT:	Department of Biosciences
AREA OF EXPERTISE:	Breast cancer
SUPERVISORS:	Doctor Antoni Hurtado Rodriguez (Main Supervisor) Professor Odd Stokke Gabrielsen (Co-supervisor)
DATE OF DISPUTATION:	18th of December 2017
DISSERTATION TITLE:	*Investigating signalling and epigenetic factors influencing the functions of transcription factors in breast cancer*

Breast cancer is a disease characterized with uncontrolled proliferation of epithelial cells in human mammary gland. Different proteins influencing cell growth and death can affect the tumor progression. In this PhD thesis, Shixiong Wang tried to understand how cellular factors, such as cell signaling and epigenetic marks, regulate transcription in breast cancer.

Breast cancer is the most common type of tumor in female worldwide, and is also the leading cause of death caused by cancer among women. The majority (70%) of breast cancers are positive of estrogen receptor α (ER), which is the main driver of tumor growth. ER is a transcription factor, which can bind its ligand estrogen. Upon ligand binding, ER will interact with chromatin and regulate gene transcription that will stimulate cell proliferation and inhibit cell death. In clinical, endocrine therapy targeting ER is the main treatment for ER positive breast cancer, however the resistance to endocrine therapy is common. Recent studies have shown that the function of ER is dependent of a type of transcription factors called pioneer transcription factor, such as FOXA1, GATA3, and PBX1. However, how pioneer transcription factors are regulated by other cellular factors in breast cancer, especially in the context of endocrine resistance still need to be elucidated.

In this PhD thesis, the main aim is to understand how cell signaling and epigenetic factors influence the function of pioneer transcription factors in breast cancer, in particular FOXA1. The work in this thesis has shown that the HER2/3 signaling, which contributes to endocrine resistance, inhibits the acetylation of FOXA1. FOXA1 with less acetylation level has a higher affinity to chromatin, and can also activate some genes favoring cell growth to overcome endocrine treatment. Moreover, by chemical screening we have identified a list of cell signaling pathway/proteins that could potentially regulate FOXA1 activity. In addition, in a study characterizing the correlation between epigenetic marks and gene expression in breast cancer patients, we have identified two epigenetic signatures reflecting intra- and inter-tumor heterogeneity of breast cancer.

These findings suggest in addition to ER, targeting other factors in breast cancer might be an alternative medication, and moreover epigenetic marks could also be used as a tumor signature with prognostic significance.