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DATE OF DISPUTATION:	18 November, 2016

DISSERTATION TITLE: *Functional interactions between key signaling pathways in prostate cancer cells - Androgens, the UPR and STAMP1*

Prostate cancer (PCa) represents a major health issue for men worldwide where 1 in 7 men develop the disease during their lifetime. Norway is one of the countries with highest incidence and mortality from PCa in the world with around 5000 new cases diagnosed annually. The male sex hormone androgens (such as testosterone) play a pivotal role in PCa progression, and therapies aimed to suppress androgen levels in the circulation often result in tumor shrinkage. However, most tumors grow again in the castration-resistant PCa (CRPC) form, for which no curative treatment is available today and mean life expectancy at this stage is approximately 18 months.

Endoplasmic reticulum (ER) is a key organelle in the cell that orchestrates the synthesis, production, and sorting of proteins as well as important functions in calcium and redox homeostasis. Perturbation of ER function, such as accumulation of unfolded/misfolded proteins, can cause ER stress and induce the unfolded protein response (UPR), an attempt by the cell to restore order again by for example shutting down new protein synthesis and increasing protein folding capacity in the ER. Previous work has indicated that different arms of the UPR can have differential roles in disease states, including cancer.

In the first part of this thesis, we found that androgens, through binding to the androgen receptor, divergently regulate the UPR signaling. The ‘proliferative’ arm of the UPR mediated by IRE1 was essential for PCa cell growth in culture and in murine xenograft models. Targeting this pathway genetically or using different small molecule compounds significantly impaired PCa cell growth in vitro and in vivo, including in CRPC Models.

The second part of this thesis focused on the six transmembrane protein of the prostate, STAMP1, originally cloned in our laboratory, the exact function of which is not known. By

genetic manipulation of STAMP1 expression, we found that STAMP1 is required for PCa growth in all models we have tested in vitro and in vivo. Studying the molecular mechanisms of STAMP1 action showed that it is important for the maintenance of AR and mTOR signaling, two of the most commonly altered cellular signaling pathways in PCa pathology.

Taken together, we have identified key components of molecular mechanisms of PCa with a focus on interactions between key signaling pathways. This knowledge enabled us to successfully target PCa in preclinical models which may be the basis for clinical studies.