

## **Epigenetics in prostate cancer: from prognostication to tailored therapy**

Suzan Stelloo<sup>1\*</sup>, Ekaterina Nevedomskaya<sup>1,2\*</sup>, Karianne Schuurman<sup>1</sup>, Lodewyk FA Wessels<sup>2</sup>, Rui Henrique<sup>3</sup>, Carmen Jerónimo<sup>3</sup>, Henk van der Poel<sup>4</sup>, Andries M Bergman<sup>5</sup> and **Wilbert Zwart<sup>1</sup>**.

Divisions of Molecular Pathology<sup>1</sup>, Molecular Carcinogenesis<sup>2</sup>, Urology<sup>4</sup> and Medical Oncology<sup>5</sup>, the Netherlands Cancer Institute, Amsterdam, the Netherlands

<sup>3</sup>Department of Pathology, Portuguese Oncology Institute, Porto, Portugal

### **Background:**

The androgen receptor (AR) plays a pivotal role in prostate cancer development, progression and hormone therapy resistant disease. AR requires a permissive epigenetic state at distinct chromatin regions to facilitate gene expression programs. The vast majority of AR chromatin binding sites are found at active enhancer regions, hallmarked by histone modification H3K27Ac and devoid of repressive marks including H3K27me3. Previously we identified a distinct set of AR chromatin binding sites that enabled patient stratification on outcome, yielding a novel gene expression-based biomarker that functions synergistically with standard clinicopathological features (1).

### **Methods:**

In search for novel biomarkers for prostate cancer prognostication and to validate our original findings in a larger cohort, we performed chromatin immunoprecipitation followed by massive parallel sequencing (ChIP-seq) on AR in 100 primary prostate cancers, along with histone modifications H3K4me3, H3K27me3 and H3K27Ac, gene expression and copy number profiles. Furthermore, this approach was implemented two phase II clinical trials on response to Enzalutamide: one in the neoadjuvant setting and one in the metastatic setting.

### **Results:**

We successfully development and refined our ChIP-seq protocols to reliably detect AR chromatin binding along with a number of epigenetic histone modifications in 18G core needle biopsies. For surgical resections, AR and H3K27Ac ChIP-seq was successful in practically all samples tested. Our original prognostic AR chromatin binding classifier (1) that was developed on a low number of samples, was successfully validated on the 100 tumor samples, illustrating robustness of ChIP-seq based biomarkers.

### **Conclusions:**

Epigenetic profiling in core needle biopsies and surgical resections of prostate cancers is feasible and yields relevant data on patient prognostication. Current developments are aimed to bioinformatically mine and integrate our multidimensional Omics datasets. The integrative analysis of these large datasets will provide information on I) distinct profiles of AR and histone modifications that may bear prognostic potential, and II) the potential existence of distinct epigenetic subtypes in prostate cancer. Ultimately, we aim to further understand epigenetic regulation in prostate cancer along with its clinical implications on a genome-wide scale.

### **Conflict of Interest:**

Part of this work was funded by a research grant from Astellas pharma.

### **Funding Acknowledgements:**

Movember Foundation, Dutch Cancer Society, Astellas pharma, Netherlands Cancer Institute

1. Stelloo S, Nevedomkaya E, et al. Androgen receptor profiling predicts prostate cancer outcome. *EMBO molecular medicine*, 2015