

## **Development of small molecule inhibitors targeting the N-terminal domain of human androgen receptor**

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### **Background**

The failure to help CRPC patients has created an urgent need to explore new treatments with non-conventional mechanisms of drug action. Although other signalling pathways and co-factors influence PCa progression, the androgen receptor (AR) remains as the master regulator of tumor promoting genes, representing the most credential target in both PCa and CRPC. The search for new small molecule inhibitors that target alternative pocket sites and surface exposed regions of the AR has intensified in recent years.

### **Methods**

It has become clear that androgen deprivation and other currently used hormone therapies have inherent limitations, partly due to recent discoveries pertaining to AR splice variants, such as AR-V7 lacking a ligand-binding domain (LBD), that are implicated in the reactivation of AR signalling in CRPC. Thus, small molecules targeting critical and V7-relevant regulatory regions such as the AR-N-terminal Domain (AR NTD) are expected to have completely different mechanisms of action compared to conventional anti-androgens and are less likely to cause cross resistance.

### **Results**

Based on a compounds screen conducted in our laboratory, a potential AR NTD inhibitor, termed VPC - 2055, with a novel chemical scaffold was discovered. This chemical was found to inhibit the full-length AR and the truncated AR isoforms at low micromolar concentrations through possible covalent binding to unspecified amino-acids in the AR NTD region. Furthermore, VPC-2055 could inhibit the growth of AR- and ARV7- driven PCa cells, without any effect on AR-negative PC3 cells. VPC-2055 also demonstrated complete AR selectivity with no detected inhibition of closely related ER, PR and GR transcription factors. Using methods of computer-aided drug discovery we further designed a series of VPC-2055 analogues which demonstrated much improved AR NTD inhibition. Two of such compounds, VPC-220010 and VPC-20062 demonstrated favourable drug-like properties and laid a foundation for pre-clinical optimization of novel front-line CRPC therapy.

### **Conclusions**

Potent and selective small molecule inhibitors of the AR NTD have been developed. We anticipate that these drug candidates will bypass known resistance mechanism in CRPC including mutations in the LBD and the expression of LBD-truncated splice variants. It is also projected that our continuous efforts to improve the potency and stability of the compounds will lead to successful pre-clinical studies and, eventually, human clinical trials.

### **Conflict of Interest**

No conflicts to declare

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