

## Development of a Novel Autophagy Inducing Multi-Kinase Inhibitor for the Treatment of Castration Resistant Prostate Cancer

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Inhibition of the androgen axis has revolutionized the treatment of metastatic castration resistant prostate cancer (mCRPC). However, mCRPC continues to be a leading cause of cancer-related deaths in men. Here, we characterized a Phase I-cleared multi-kinase inhibitor, ESK981, in prostate cancer pre-clinical models. ESK981 was markedly more potent *in vitro* than other kinase inhibitors, including cabozantinib and crizotinib, that have been evaluated clinically in prostate cancer. Surprisingly, we observed that ESK981 was a potent inducer of cellular vacuolization that was associated with an autophagic response. ESK981-induced autophagy could be blocked by either the depletion of the autophagy vesicle formation gene, *atg5*, or by autophagy inhibitors such as bafilomycin. ESK981 was further shown to induce autophagy in yeast, which is an evolutionarily conserved core cellular pathway. Moreover, ESK981 triggered prostate cancer cells to release chemokines such as CXCL10 into the cell secretome, thus suggesting that ESK981 may stimulate immune surveillance while exerting its tumor inhibitory effect. Together, ESK981 is a novel and potent autophagy-inducing multi-kinase inhibitor that effectively inhibits CRPC growth through the activation of the autophagic cascade.

### Conflict of Interest Statement

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