Therapy Optimization to Prevent Resistance in Prostate Cancer using Molecular Inflection Points and Clinical Nanocarriers

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Background: Personalized therapy based on patient stratification is critically needed in prostate cancer, ideally based on the innovative use of translational agents and new understanding of disease mechanisms. Considering the molecular crosstalk between the androgen receptor and PI3K pathway, we hypothesized that nanocarriers that can simultaneously deliver combination therapy to the prostatic lesion can effectively suppress tumor growth, averting recurrence and side effects.

Methods: To test our hypothesis, we used the clinical iron oxide nanoparticle Ferumoxytol, which is used in the clinic for the treatment of anemia. We also developed iron-free nanoparticles, which consisted solely of the glucose-based polysaccharide Dextran that is utilized in the pharmaceutical and food industries. These nanocarriers were characterized through spectroscopic techniques and dynamic light scattering, as well as extensive drug release and pharmacokinetic studies. Cytotoxicity and tumor regression studies were performed with various prostate cancer cell lines.

Results: First, in order to trace the nanoparticles *in vivo*, we achieved stable retention of the positron emitter 89-zirconium and the MRI contrast agent gadolinium, without the need of a chelator. Animal studies revealed that apart from PET imaging, the ^{89}Zr-nanobeacons could guided the surgical resection of sentinel lymph nodes, utilizing their inherent Cerenkov luminescence. Through weak electrostatic interactions, the unmodified nanoparticles carried combinations of chemotherapeutics for the simultaneous inhibition of oncogenic pathways, resulting in enhanced tumor regression. We also achieved active targeting of the nanocarries, by facilitating their association with the prostate-specific membrane antigen, which is found in >90% of prostatic lesions and correlates to disease stage. The nanoparticles allowed visualization of the tumors through magnetic resonance imaging and fluorescence molecular tomography. Since many solid tumors, including prostate cancer, frequently develop resistance to targeted chemotherapies, we delivered a novel cytotoxic peptide with a unique mechanism of action that affects key oncogenic clients, achieving tumor regression without any adverse effects or relapse.

Conclusion: We foresee the use of these systems in patient-tailored treatment strategies in prostate cancer, improving survival and lowering treatment costs.

Conflict of Interest: C.K. and A.K. financial interests in SEVA Therapeutics.

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