Molecular Targeted Immunotherapy for Eradication of Prostate Cancer

- Prostate cancer (PCa) is the leading cause of cancer deaths in men in the United States despite advances in chemo-, radio- and hormonal-therapies.

- The absence of curative therapies for advanced or recurrent forms of PCa emphasizes the crucial need to develop innovative treatment strategies that are efficacious, with minimal toxicity, against systemic disease.

- In pre-clinical experiments, researchers at the VIMM have reported promising results in halting PCa recurrence using a unique combination of molecular therapy, chemotherapy and immunotherapy.

- This innovative research from the teams led by Dr. Paul B. Fisher and Dr. Xiang-Yang Wang is funded by the U.S. Department of Defense Prostate Cancer Research Program (PCRP) and was recently highlighted on the Congressionally Directed Medical Research Programs (CDMRP) website at http://cdmrp.army.mil/pcrp/research_highlights/16fisher-wang_highlight

The absence of curative treatments for advanced, metastatic prostate cancer (PCa) highlights the crucial need for development of new, innovative treatment strategies. To address this need, the PCRP funded two separate Synergistic Idea Development awards, in FY10 and FY13, to support collaborative efforts between the two research teams led by Dr. Paul B. Fisher and Dr. Xiang-Yang Wang at the VIMM. The synergy between these laboratories...
bringstogether experts in molecular, cellular, and immune biology to develop methodsto attack PCa on multiple fronts by combining immunotherapy with other treatment modalities such as radiation therapy, chemotherapy, and targeted molecular therapy.

Public and Technical Abstracts:

**Targeting Danger-Sensing Pattern Recognition Receptors for Prostate Cancer Therapy**

**Molecular-Targeted Adoptive Immune Therapy for Eradication of Metastatic Prostate Cancer**

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Melanoma differentiation associated gene-7/Interleukin-24 (MDA-7/IL-24), a unique therapeutic cytokine discovered in Dr. Fisher’s laboratory, holds promise for cancer therapy due to its multiple antitumor properties demonstrated in nearly all cancers, including PCa. This agent directly kills cancer cells through induction of apoptosis or toxic autophagy, promotion of cancer cell killing by activating the immune system, and inhibition of blood vessel formation that supports cancer growth. Under their PCRP-funded work, the Fisher and Wang laboratories created cancer terminator viruses (CTV) that selectively replicate and produce MDA-7/IL-24 in tumor cells resulting in direct killing of cancer cells and stimulation of the immune system without harming normal cells. To further augment therapeutic efficacy, the CTV was combined with a small molecule inhibitor of Mcl-1, a critical protein mediating cancer cell growth and survival, resulting in enhanced cancer specific killing by the CTV.

*In vivo* applications of this combinatorial scheme in animal models of PCa were facilitated by using an ingenious delivery approach being pioneered by Drs. Fisher and Wang that employs ultrasound-targeted microbubble destruction (UTMD). The UTMD method permits the delivery of the CTV, as well as therapeutic proteins or chemotherapeutic agents, directly to the prostate gland and its surrounding vasculature in a surreptitious manner by incorporating viruses in microbubbles that are subsequently disrupted using targeted ultrasound. These new reagents and innovative combinatorial cancer-killing and immune-modulating strategies are now primed for clinical applications for the therapy of advanced prostate cancer. The team is currently working on moving this therapy into the clinic with the hopes of improving treatment options for patients with metastatic PCa.

**Combination effect of a CTV and a Mcl-1 inhibitor (BI-97D6) in eradicating CaP:**

CTV was mixed with targeted microbubbles (MB) and injected intravenously followed by delivery to the prostate region by the UTMD approach. Following release and subsequent infection of the CaP cells, CTV selectively replicates in CaP cells resulting in production of mda-7/IL-24. MDA-7/IL-24 can promote mitochondrial intrinsic apoptosis as well as extrinsic apoptosis, together with ER stress or toxic autophagy in prostate tumors (primary site of infection). BI-97D6, which displays some antitumor activity in CaP as a single agent, synergistically co-operates with CTV in inducing cancer-specific apoptosis. BI-97D6 also stabilizes mda-7/IL-24 mRNA further enhancing the production of MDA-7/IL-24 protein, which acts as a cytokine on adjacent uninfected CaP cells or tumors located distantly (lung, bone metastasis) via receptor dimerization and signal transduction culminating in cancer-specific apoptosis. It can also activate anti-angiogenesis effects and antitumor-immune response.
responses further amplifying the antitumor effects of MDA-7/IL-24, thereby culminating in eradicating the primary CaP as well as any metastasis to distant sites in the body.

**Figure:** Ad.tCCN1-CTV-m7 and BI-97D6 eradicate prostate cancer (CaP): Ad.tCCN1-CTV-m7 (a type 5 adenovirus with a truncated CCN1 promoter driving replication and producing mda-7/IL-24, a Cancer Terminator Virus) was mixed with targeted microbubbles (MB) specific for binding with prostate tumor vasculature which overexpresses VCAM-1, and injected i.v. followed by targeted delivery in the prostate region by the ultrasound targeted microbubble destruction (UTMD) approach. Following infection, Ad.tCCN1-CTV-m7 selectively replicates in CaP cells producing mda-7/IL-24, which on translation produces secretory cytokine MDA-7/IL-24. MDA-7 induced apoptosis via Bcl-2-dependent (mitochondria), ER stress or toxic autophagy in prostate tumor (primary site of infection). BI-97D6 synergistically co-operated with Ad.tCCN1-CTV-m7 in inducing cancer-specific apoptosis. BI-97D6 also stabilized mda-7/IL-24 mRNA further enhancing the activity of mda-7/IL-24. The secreted MDA-7/IL-24 acts on adjacent uninfected CaP cells or tumor cells located distantly (lung, bone metastasis) via receptor dimerization and signal transduction culminating in cancer-specific apoptosis. It can also activate anti-tumor-immune responses in further enhancing the antitumor effect of MDA-7/IL-24, and thus eradicate both primary CaP and CaP metastases. [Sarkar Set al., Oncoimmunology, 5(3), e1078059. PMCID:PMC4839355]

**Publications:**


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