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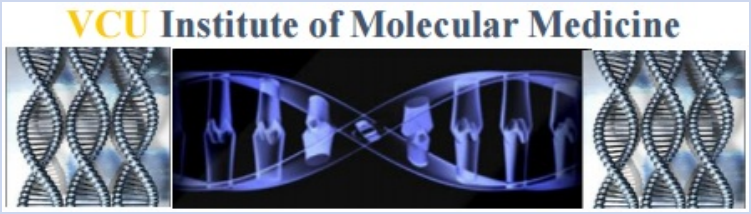
VCU VIRGINIA COMMONWEALTH UNIVERSITY

Institute of Molecular Medicine

VCU Institute ofMolecular Medicine (VIMM) NEWS & VIEWS

The VIMM, established in 2008 by Paul B. Fisher, M.Ph., Ph.D.,the Founding Director, is comprised of outstanding scientists/clinicians fromVCU School of Medicine focusing on important medical-related research incancer, neurodegeneration and infectious diseases. The purpose of this NEWS& VIEWS is to highlight the exciting research being performed by the VIMMmembers.



MolecularTargeted Immunotherapy for Eradication of Prostate Cancer

- Prostate cancer (PCa) is the leading cause of cancer deaths inmen in the United States despite advances in chemo-, radio- andhormonal-therapies.
- The absence of curative therapies for advanced or recurrentforms of PCa emphasizes the crucial need to develop innovative treatmentstrategies that are efficacious, with minimal toxicity, against systemicdisease.
- Inpre-clinical experiments, researchers at the VIMM have reported promisingresults in halting PCa recurrence using a unique combination of moleculartherapy, chemotherapy and immunotherapy.
- Thisinnovative research from the teams led by **Dr. Paul B. Fisher** and **Dr.Xiang-Yang Wang** is funded by the U.S. Department of Defense ProstateCancer Research Program (PCRP) and was recently highlighted on theCongressionally 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 prostatecancer (PCa) highlights the crucial need for development of new, innovativetreatment strategies. To address this need, the PCRP funded two separate **Synergisticldea Development awards, in FY10 and FY13**, to support collaborative effortsbetween 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 othertreatment modalities such as radiation therapy, chemotherapy, and targetedmolecular therapy.

Public and Technical Abstracts:

TargetingDanger-Sensing Pattern Recognition Receptors for Prostate Cancer Therapy

Molecular-TargetedAdoptive Immune Therapy for Eradication of Metastatic Prostate Cancer

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Melanoma differentiation associatedgene-7/Interleukin-24 (MDA-7/IL-24), a unique therapeutic cytokine discoveredin Dr. Fisher's laboratory, holds promise for cancer therapy due to itsmultiple antitumor properties demonstrated in nearly all cancers, includingPCa. This agent directly kills cancer cells through induction of apoptosis ortoxic autophagy, promotion of cancer cell killing by activating the immunesystem, and inhibition of blood vessel formation that supports cancer growth.Under their PCRP-funded work, the Fisher and Wang laboratories created cancerterminator viruses (CTV) that selectively replicate and produce MDA-7/IL-24 intumor cells resulting in direct killing of cancer cells and stimulation of theimmune system without harming normal cells. To further augment therapeuticefficacy, the CTV was combined with a small molecule inhibitor of Mcl-1, acritical protein mediating cancer cell growth and survival, resulting in enhancedcancer specific killing by the CTV.

In vivo applications of this combinatorial scheme in animal models of PCa werefacilitated 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 therapeuticproteins or chemotherapeutic agents, directly to the prostate gland and itssurrounding vasculature in a surreptitious manner by incorporating viruses inmicrobubbles that are subsequently disrupted using targeted ultrasound. Thesenew reagents and innovative combinatorial cancer-killing and immune-modulatingstrategies are now primed for clinical applications for the therapy of advancedprostate cancer. The team is currently working on moving this therapy into theclinic with the hopes of improving treatment options for patients withmetastatic PCa.

Combinatorial effect ofa CTV and a Mcl-1 inhibitor (BI-97D6) in eradicating CaP:
CTV was mixed with targetedmicrobubbles (MB) and injected intravenously followed by delivery to theprostate region by the UTMD approach. Following release and subsequentinfection of the CaP cells, CTV selectively replicates in CaP cells resultingin production of mda-7/IL-24. MDA-7/IL-24 can promote mitochondrial intrinsicapoptosis as well as extrinsic apoptosis, together with ER stress or toxicautophagy in prostate tumors (primary site of infection). BI-97D6, whichdisplays some antitumor activity in CaP as a single agent, synergisticallyco-operates with CTV in inducing cancer-specific apoptosis. BI-97D6 alsostabilized mda-7/IL-24 mRNA further enhancing the production of MDA-7/IL-24protein, which acts as a cytokine on adjacent uninfected CaP cells or tumorslocated distantly (lung, bone metastasis) via receptor dimerization and signaltransduction culminating in cancer-specific apoptosis. It can also activateanti-angiogenesis effects and antitumor-immune

responses further amplifying theantitumor effects of MDA-7/IL-24, thereby culminating in eradicating theprimary CaP as well as any metastasis to distant sites in the body.

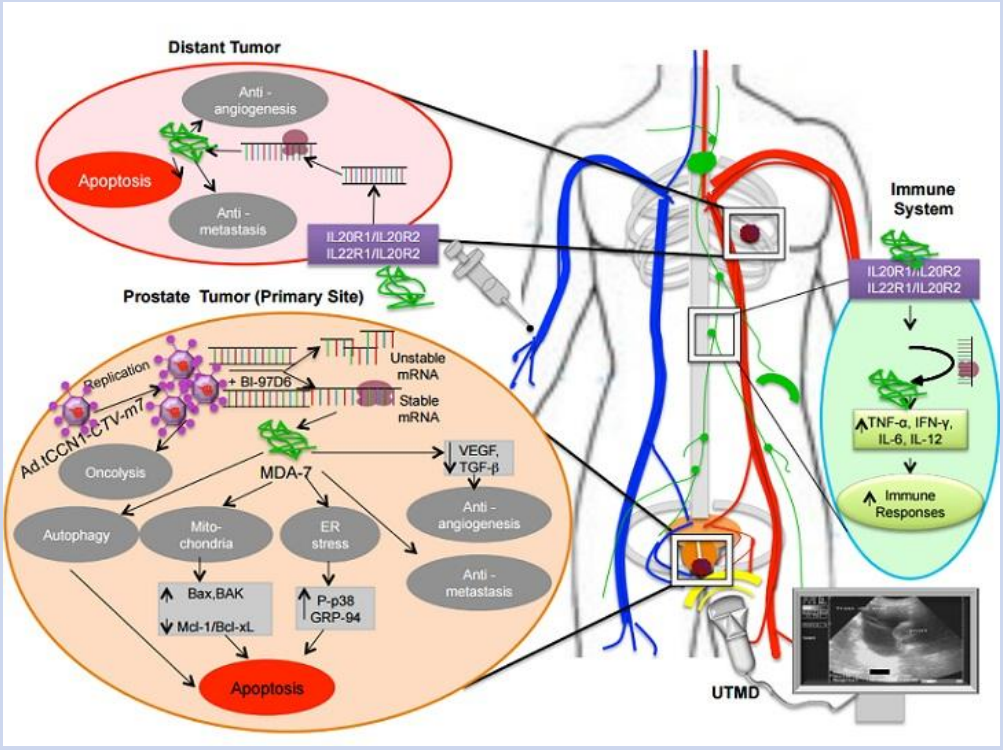

Figure: Ad.tCCN1-*CTV-m7* and BI-97D6 eradicates prostatecancer (CaP): Ad.tCCN1-*CTV-m7* (a type 5 adenovirus with atruncated CCN1 promoter driving replication and producing mda-7/IL-24, a CancerTerminator Virus) was mixed with targeted microbubbles (MB) specific for bindingwith prostate tumor vasculature which overexpresses VCAM-1, and injected i.v.followed by targeted delivery in the prostate region by the ultrasound targetedmicrobubble destruction (UTMD) approach. Following infection, Ad.tCCN1-CTV-m7selectively replicates in CaP cells producing mda-7/IL-24, which on translationproduced 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 ofinfection). BI-97D6 synergistically co-operated with Ad.tCCN1-*CTV-m7* in inducing cancer-specific apoptosis.BI-97D6 also stabilized *mda*-7/IL-24mRNA further enhancing the activity of *mda*-7/IL-24.The secreted MDA-7/IL-24 acts on adjacent uninfected CaP cells or tumor cells locateddistantly (lung, bone metastasis) via receptor dimerization and signal transductionculminating in cancer-specific apoptosis. It can also activateanti-tumor-immune responses in further enhancing the antitumor effect ofMDA-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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Sarkar S,Quinn BA, Shen XN, Dash R, Das SK, Emdad L, Klibanov AL, Wang XY, Pellecchia M,Sarkar D, Fisher PB. 2015. Therapy of prostate cancer using a novel cancerterminator virus and a small molecule BH-3 mimetic. Oncotarget. 6(13):10712-27. PMCID:PMC4484414.

Menezes ME, Bhatia S, Bhoopathi P, Das SK, Emdad L,Dasgupta S, Dent P, Wang XY, Sarkar D, Fisher PB. 2014. MDA-7/IL-24: multifunctionalcancer killing cytokine. Adv Exp Med

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About the Investigators: Paul B. Fisher, MPh, PhD, is Professor and Chair of Human andMolecular Genetics (HMG), Director of the VCU Institute of Molecular Medicine(VIMM) and Thelma Newmeyer Corman Chair in Cancer Research in the VCU MasseyCancer Center (MCC), Virginia Commonwealth University, School of Medicine,Richmond, VA. Xiang-Yang Wang, PhD is aProfessor in HMG, Mary Anderson Harrison Distinguished Professor ofCancer Research in the VCU MCC and Associate Scientific Director of Immunology and InfectiousDiseases of the VIMM. Siddik Sarkar, PhD and Anjan K. Pradhan, PhD are both postdoctoralresearch scientists in HMG. Swadesh K. Das, PhD and Luni Emdad, MBBS, PhD are both AssistantProfessors in HMG and Members of the VIMM. Devanand Sarkar is an AssociateProfessor in HMG, Associate Scientific Director of Therapeutics in the VIMM,and a Harrison FoundationDistinguished Professor in Cancer Research in the VCU MCC. Maurizio Pellecchia, PhD, is Adjunct Professor at the Sanford-Burnham-PrebysDiscovery Institute (SBPDI) and Professor of Biomedical Sciences and Directorof the Center for Molecular and Translational Medicine, Daniel Hays EndowedChair in Cancer Research, University of California Riverside, School ofMedicine, Riverside, CA.
