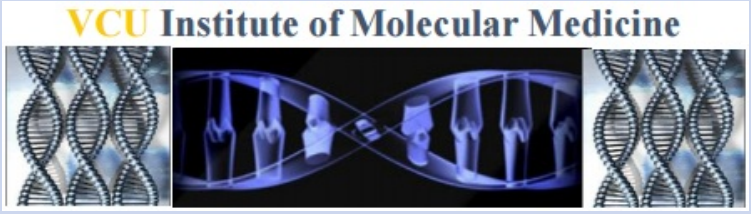
Issue No. 4, February 2017

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.



Promoting protectiveantitumor immunity for cancer eradication

- Management of localizedprostate cancer (PC) through surgical, radiation and chemotherapeuticapproaches can be successful, but metastatic prostate cancer remainsessentially incurable because no effectiveand safe treatment modality is available.
- Melanomadifferentiation associated gene-5 (MDA-5), a type I interferon (IFN)-induciblegene, was originally cloned in human melanoma. Thisstudy indicates that MDA-5 can induce a direct tumoricidal or type IIFN-promoting effect in PC cells.
- Thisis the first demonstration of antitumor immunity induced by targeting the viral-sensingMDA-5 signaling pathway in prostate tumors. Therapeutic activation of MDA-5 at thetumor site is exploited to mobilize systemic innate and adaptive antitumorimmune responses to eradicate metastatic PC.
- This MDA-5-targeting immunotherapy can be used either alone orin combination with other approaches to treat PC and other malignancies.

Counteracting the immunosuppressive tumor microenvironment (TME)and restoring immune effector cell functions remains a major challenge forsuccessful cancer immunotherapy. In a study recently published in the journalof Cancer Research*, investigators in the VCU Institute of Molecular Medicine(VIMM) developed a novel strategy targeting the TME, which results indestruction of PC cells and concurrent induction of an antitumor immuneresponse.

Melanoma differentiation associated gene-5 (MDA-5) was initiallyidentified and cloned by Dr. Paul B. Fisher as a type I interferon(IFN)-inducible gene in human melanoma. Subsequent studies showed that MDA-5represents a major innate immune receptor critically required for sensing viralpathogens and initiating an anti-viral host response involving production oftype

I IFNs. Dr. Fisher and his colleagues previously reported that forcedexpression of the MDA-5 gene kills cancer cells without harming normal cells.In this study involving a collaboration between Dr. Xiang-Yang (Shawn) Wang'slaboratory and Dr. Fisher, the investigators provide new insights into thebiological impact of MDA-5 activation in cancer cells by defining thestructural domains that confer a direct tumoricidal or type I IFN-promotingeffect, which advances the understanding of the selective pro-apoptoticactivity of MDA-5 in cancer cells, and not normal cells. A striking finding ofthis work is that intra-tumoral delivery of MDA-5 using an adenovirus results inregression of pre-established PCs and development of long-term protectiveantitumor immunity in immune competent mouse models. The mechanistic studiesshowed that this superior antitumor efficacy is primarily due to the activationof tumor-reactive cytotoxic T lymphocytes and/or natural killer cells, which isdependent on the type I IFN pathway in the TME. These findings underscore a previouslyunappreciated role of the MDA5-mediated viral sensing pathway in the inductionof antitumor immunity, offering a new opportunity for therapeutic targeting ofthe immunosuppressive TME to restore systemic antitumor immunity for cancereradication and prevention of relapse. Although this research was conducted inprostate cancer mouse models, it is believed that these data may have broadimplications in the treatment of other malignancies and metastatic diseases.These promising preclinical results provide a strong scientific rationale tosupport potential translation of MDA-5-based immunotherapy. This study was supportedin part by NIH grants CA175033, CA154708 (X.-Y. Wang), Department of DefenseW81XWH-11-0480/0481, W81XWH-13-0409/0455 (P.B. Fisher and X.-Y. Wang), theNational Foundation for Cancer Research (P.B. Fisher).

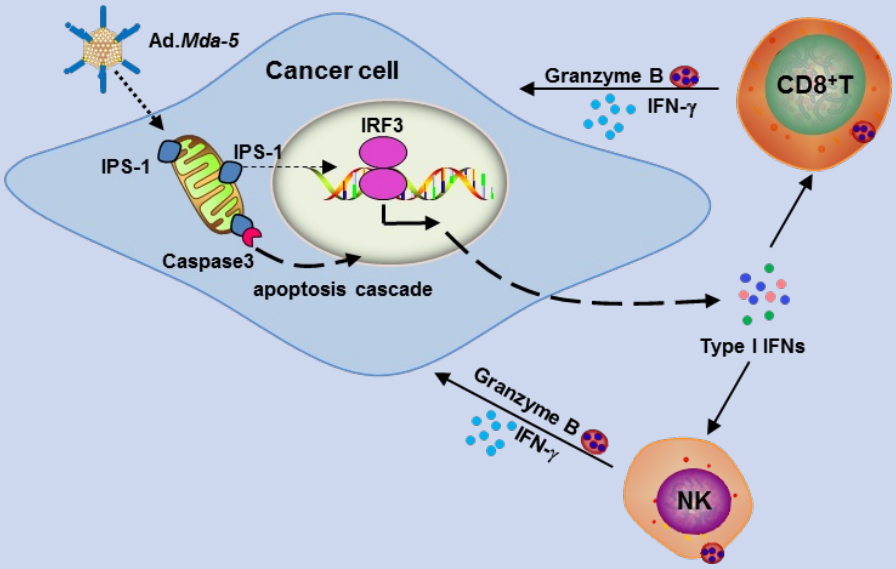


Figure legend: Targetingthe MDA-5–IPS-1 pathway in tumors to potentiate protective antitumor immunity.Overexpression of MDA-5, a sensor for viral dsRNA, in cancer cells triggersactivation of IRF-3 and caspase-3 in an IPS-1–dependent manner. The interactionbetween MDA-5 and its downstream adapter protein IPS-1 results in theproduction of type I IFNs and concomitant cancer cell death. The type I IFNspromote the activation and effector functions of NK cells and/or CTLs.Collaborative action of tumor-reactive innate and adaptive immune cells leadsto effective tumor eradication. [Yu et al, Cancer Res. 2016 April 15, PMCID:PMC4873369].*

Publications:

*Yu X, Wang H, Li X, Guo C, YuanF, **Fisher PB**, **Wang XY**. Activation of the MDA-5-IPS-1Viral Sensing Pathway Induces Cancer Cell Death and Type I IFN-DependentAntitumor Immunity. CancerRes. 2016 Apr 15;76(8):2166-76. PMCID:PMC4873369

Tormo D, Checińska A, Alonso-Curbelo D, Pérez-Guijarro E,Cañón E, Riveiro-Falkenbach E, Calvo TG, Larribere L, Megías D, Mulero F, PirisMA, Dash R, Barral PM, Rodríguez-Peralto JL, Ortiz-Romero P, Tüting T, **Fisher PB**, Soengas MS. Targeted activation of innate immunity for therapeuticinduction of autophagy and apoptosis in melanoma cells. Cancer Cell. 2009 Aug 4;16(2):103-14.PMCID: PMC2851205.

Kang DC, Gopalkrishnan RV, Wu Q, Jankowsky E, Pyle AM, **Fisher PB**. mda-5: An

interferon-inducible putative RNAhelicase with double-stranded RNA-dependent ATPase activity and melanomagrowth-suppressive properties.Proc Natl Acad Sci U S A. 2002 Jan 22;99(2):637-42. PMCID: PMC4873369.

About the Investigators: Xiang-Yang Wang, PhD, isProfessor of Human and Molecular Genetics (HMG), Associate Scientific Directorof Immunology of the VCU Institute of Molecular Medicine (VIMM) and MaryAnderson Harrison Distinguished Professor in Cancer Research in the VCU MasseyCancer Center (MCC), Virginia Commonwealth University, School of Medicine,Richmond, VA. 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. Xiaofei Yu, PhD was an Instructor in HMG. Other researchers from Dr.Wang's Laboratory, including Hongxia Wang, PhD, Xia Li, PhD, Fang Yuan, MS, andChunqing Guo, PhD, also contributed to the study.
