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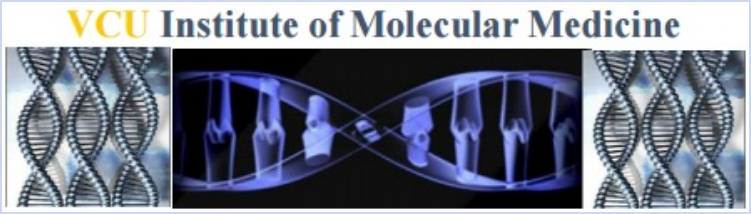
VCU VIRGINIA COMMONWEALTH UNIVERSITY

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.



Attacking Therapeutic Resistance in Aggressive Brain Tumors

- Glioblastoma (GBM) is a particularly aggressive andtherapeutically resistant tumor of the brain. Even with maximal surgicalresection followed by high doses of radiation and chemotherapy, 5-year survivalremains around 5%.
- Tumor cells that survive radiation can become even more invasiveand aggressive, compromising the effectiveness of treatment.
- The Fisher laboratory recently showed that MDA-9/Syntenin has animportant role in GBM invasion and its expression increases with tumor gradeand correlates with shorter survival times and poorer response to radiotherapy.
- Genetic knockdown of MDA-9/Syntenin sensitizes GBM cells toradiation, reducing post-radiation invasion gains.
- An effective, novelapproach to specifically target MDA-9/Syntenin with a first-generation smallmolecule dramatically reduces invasion and combines with radiation to prolongsurvival in a mouse model of GBM.

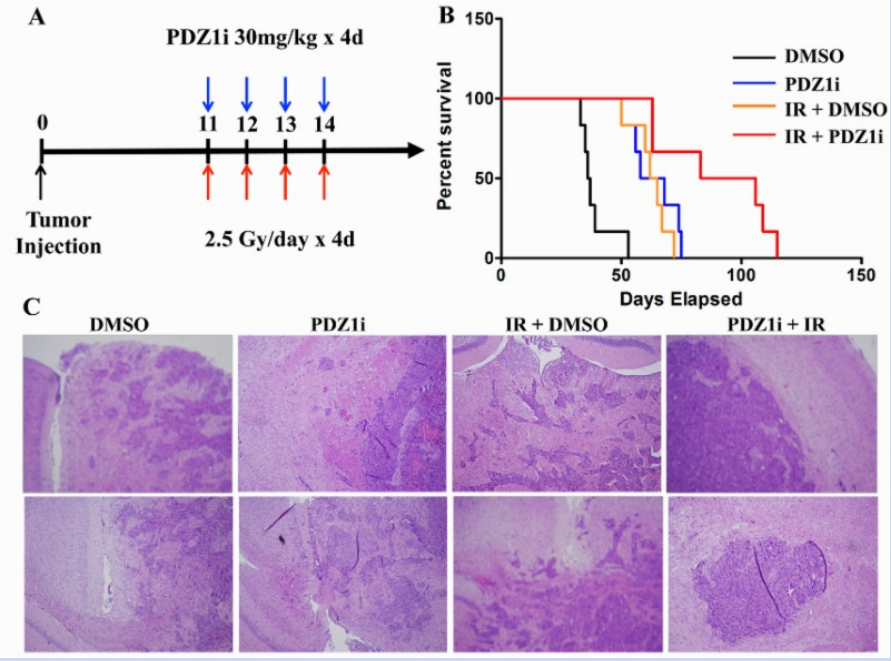
Boosting the Effect of Radiotherapy in GBM ThroughTargeted Drug Design

Glioblastoma is an aggressive brain tumor and onlyincremental advances in treatment have been made in recent years. Despite theuse of maximal interventions including surgery, chemotherapy, and radiation,median survival is only about 15 months. Our group previously showed thatMDA-9/Syntenin, a highly conserved double-PDZ domain-containing scaffoldingprotein, is robustly expressed in human-derived GBM cell lines and patientsamples and plays an important role in GBM invasion and angiogenesis. Through asuccessful collaboration with Dr. Maurizio Pellecchia's team from theSanford-Burnham-Prebys Medical Discovery Institute, we now report that a

smallmolecule (PDZ1i) specifically targets the deleterious effects of MDA-9/Syntenin by binding its PDZ1 domain.

MDA-9/Syntenin acts to facilitate protein-proteininteractions in a number of crucial oncogenic pathways, including Src, FAK, andEGFR. In particular, EGFR can be overexpressed or mutated in GBM. Wedemonstrate that MDA-9/Syntenin interacts with normal and mutant EGFR, and thatinhibiting that interaction using PDZ1i can interrupt EGFR signaling. Radiationis a staple of GBM treatment, although even high doses cannot eradicate thesetumors. Tumor cells that survive become more invasive and resistant totreatment. PDZ1i combines with radiation to synergistically kill GBM cellswhile reducing post-radiation invasion. This discovery of a first-generationsmall molecule directed against MDA-9/Syntenin is an advance in targetedtherapy for GBM. Further iterations of this design are under investigation inother tumors and could augment a variety of cancer therapies.

This investigation was a fruitful collaboration betweenthe laboratories and colleagues of Paul B. Fisher, MPh, PhD, MaurizioPellecchia, PhD and Webster K. Cavenee, PhD. Timothy P. Kegelman, an MD/PhDstudent in Dr. Fisher's laboratory at VCU, and Swadesh K. Das, PhD, an Assistant Professorat VCU and Member of the VIMM, are co-first authorsof this paper, and performed much of the biological and animal work. Thechemistry was performed predominantly by co-first author Bainan Wu, PhD in Dr.Pellecchia's group at the Sanford-Burnham-Prebys Discovery Institute (SBPDI)and University of California Riverside. This work demonstrates the vital typeof collaboration between biologists and chemists that can lead to importantadvances in targeted cancer therapy. This research was supported by NIH/NCI GrantR01 CA168517 to Drs. Pellecchia and Fisher, an NCI Cancer Center Support Grantto the VCU Massey Cancer Center (MCC) P30 CA016059 to Drs. Sarkar and Fisher,and National Foundation for Cancer Research awards to Drs. Cavenee and Fisher. Thestudy was published in PNAS on Dec 23rd, 2016*.



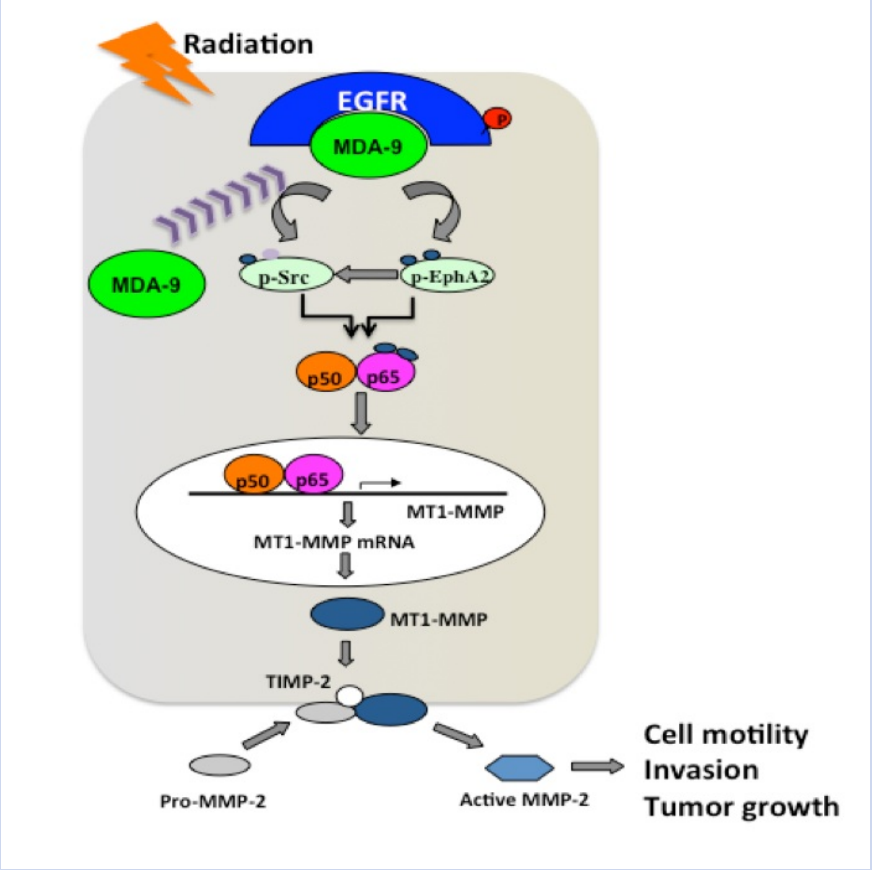


Figure legend: Top, PDZ1i treatment combinedwith radiation in an *in vivo* model of GBM. (A) U1242-luc cells wereinjected intracranially into nude mice. After 7 d, mice were randomized to fourgroups, and mice receiving therapy were treated on days 11 to 14 as pictured.(B) Kaplan–Meier survival curves for each treatment group. Median survival isas listed. (C) Brain tissue was isolated and sectioned, and H&E staining isshown. [Kegelman et al, Proc Natl Acad Sci U S A. 2016 Dec 23, DOI:10.1073/pnas.1616100114]. Bottom, Hypothetical model of MDA-9's role in radiation-mediatedinvasion gain. Upon radiation, EGFR is activated by developing a complex withMDA-9 through direct physical interaction. Src and EphA2, two potentialdownstream proteins are phosphorylated by this complex which further activatethe NF-κB pathway responsible for enhancing the expression and conversion ofactive MMP-2, a hallmark for invasiveness.

Publications:

*Kegelman TP, Wu B, Das SK,Talukdar S, Beckta JM, Hu B, Emdad L, Valerie K, Sarkar D, Furnari FB, CaveneeWK, Wei J, Purves A, De SK, Pellecchia M, Fisher PB. Inhibition of radiation-inducedglioblastoma invasion by genetic and pharmacological targeting ofMDA-9/Syntenin. ProcNatl Acad Sci U S A. 2016 Dec 23. pii: 201616100. DOI:10.1073/pnas.1616100114 PMID: 28011764.

Kegelman TP, Das SK, Hu B, Bacolod MD, Fuller CE, MenezesME, Emdad L, Dasgupta S, BaldwinAS, Bruce JN, Dent P, Pellecchia M, Sarkar D, Fisher PB. MDA-9/syntenin is a key regulator of glioma pathogenesis. Neuro Oncol. 2014 Jan;16(1):50-61. PMCID:PMC3870820.

About the Investigators: Paul B. Fisher, MPh, PhD,is Professor and Chair of Human and Molecular Genetics (HMG), Director of theVCU Institute of Molecular Medicine (VIMM) and Thelma Newmeyer Corman Chair inCancer Research in the VCU Massey Cancer Center (MCC), Virginia CommonwealthUniversity, School of Medicine, Richmond, VA. Maurizio Pellecchia, PhD, isAdjunct Professor at the SBPDI and Professor of Biomedical Sciences andDirector of the Center for Molecular and Translational Medicine, Daniel HaysEndowed Chair in Cancer Research, University of California Riverside, School ofMedicine, Riverside, CA. Webster K. Cavenee, PhD, Director of StrategicAlliances in Central Nervous System Cancers, Ludwig Institute for CancerResearch, Distinguished Professor UCSD, University of California, San Diego,CA. Timothy P. Kegelman is a VCU MD/PhDstudent. Sarmistha Talukdar, PhD and Bin Hu, 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. Dr. Jason M. Beckta is agraduate of VCU's MD/PhD program and now a resident physician at YaleUniversity. Dr. Kristoffer Valerie is a Professor in the Department ofRadiation Oncology at VCU. Frank B Furnari,PhD, is a Member of the Ludwig Institute, as well as Professor ofPathology at UCSD. Bainan Wu, PhD, Jun Wei, PhD, Angela Purves, and Surya K. De,PhD are research scientists working in the Pellecchia Laboratory at the SBPDland UCR.
