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

**Attacking Therapeutic Resistance in Aggressive Brain Tumors**

- Glioblastoma (GBM) is a particularly aggressive and therapeutically resistant tumor of the brain. Even with maximal surgical resection followed by high doses of radiation and chemotherapy, 5-year survival remains around 5%.
- Tumor cells that survive radiation can become even more invasive and aggressive, compromising the effectiveness of treatment.
- The Fisher laboratory recently showed that MDA-9/Syntenin has an important role in GBM invasion and its expression increases with tumor grade and correlates with shorter survival times and poorer response to radiotherapy.
- Genetic knockdown of MDA-9/Syntenin sensitizes GBM cells to radiation, reducing post-radiation invasion gains.
- An effective, novel approach to specifically target MDA-9/Syntenin with a first-generation small molecule dramatically reduces invasion and combines with radiation to prolong survival in a mouse model of GBM.

**Boosting the Effect of Radiotherapy in GBM Through Targeted Drug Design**

Glioblastoma is an aggressive brain tumor and only incremental advances in treatment have been made in recent years. Despite the use of maximal interventions including surgery, chemotherapy, and radiation, median survival is only about 15 months. Our group previously showed that MDA-9/Syntenin, a highly conserved double-PDZ domain-containing scaffolding protein, is robustly expressed in human-derived GBM cell lines and patient samples and plays an important role in GBM invasion and angiogenesis. Through a successful collaboration with Dr. Maurizio Pellecchia's team from the Sanford-Burnham-Prebys Medical Discovery Institute, we now report that a
small molecule (PDZ1i) specifically targets the deleterious effects of MDA-9/Syntenin by binding its PDZ1 domain.

MDA-9/Syntenin acts to facilitate protein-protein interactions in a number of crucial oncogenic pathways, including Src, FAK, and EGFR. In particular, EGFR can be overexpressed or mutated in GBM. We demonstrate that MDA-9/Syntenin interacts with normal and mutant EGFR, and that inhibiting that interaction using PDZ1i can interrupt EGFR signaling. Radiation is a staple of GBM treatment, although even high doses cannot eradicate these tumors. Tumor cells that survive become more invasive and resistant to treatment. PDZ1i combines with radiation to synergistically kill GBM cells while reducing post-radiation invasion. This discovery of a first-generation small molecule directed against MDA-9/Syntenin is an advance in targeted therapy for GBM. Further iterations of this design are under investigation in other tumors and could augment a variety of cancer therapies.

This investigation was a fruitful collaboration between the laboratories and colleagues of Paul B. Fisher, MPh, PhD, Maurizio Pellecchia, PhD and Webster K. Cavenee, PhD. Timothy P. Kegelman, an MD/PhD student in Dr. Fisher’s laboratory at VCU, and Swadesh K. Das, PhD, an Assistant Professor at VCU and Member of the VIMM, are co-first authors of this paper, and performed much of the biological and animal work. The chemistry 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 type of collaboration between biologists and chemists that can lead to important advances in targeted cancer therapy. This research was supported by NIH/NCI Grant R01 CA168517 to Drs. Pellecchia and Fisher, an NCI Cancer Center Support Grant to 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. The study was published in PNAS on Dec 23rd, 2016.
Figure legend: Top, PDZ1i treatment combined with radiation in an in vivo model of GBM. (A) U1242-luc cells were injected intracranially into nude mice. After 7 d, mice were randomized to four groups, and mice receiving therapy were treated on days 11 to 14 as pictured. (B) Kaplan–Meier survival curves for each treatment group. Median survival is listed. (C) Brain tissue was isolated and sectioned, and H&E staining is shown. [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-mediated invasion gain. Upon radiation, EGFR is activated by developing a complex with MDA-9 through direct physical interaction. Src and EphA2, two potential downstream proteins are phosphorylated by this complex which further activate the NF-κB pathway responsible for enhancing the expression and conversion of active MMP-2, a hallmark for invasiveness.

Publications:


About the Investigators: Paul B. Fisher, MPh, PhD, is Professor and Chair of Human and Molecular Genetics (HMG), Director of the VCU Institute of Molecular Medicine (VIMM) and Thelma Newmeyer Corman Chair in Cancer Research in the VCU Massey Cancer Center (MCC), Virginia Commonwealth University, School of Medicine, Richmond, VA. Maurizio Pellecchia, PhD, is Adjunct Professor at the SBPDI and Professor of Biomedical Sciences and Director of the Center for Molecular and Translational Medicine, Daniel Hays Endowed Chair in Cancer Research, University of California Riverside, School of Medicine, Riverside, CA. Webster K. Cavenee, PhD, Director of Strategic Alliances in Central Nervous System Cancers, Ludwig Institute for Cancer Research, Distinguished Professor UCSD, University of California, San Diego, CA. Timothy P. Kegelman is a VCU MD/PhD student. Sarmistha Talukdar, PhD and Bin Hu, PhD are both postdoctoral research scientists in HMG. Swadesh
K. Das, PhD and Luni Emdad, MBBS, PhD are both Assistant Professors in HMG and Members of the VIMM. Devanand Sarkar is an Associate Professor in HMG, Associate Scientific Director of Therapeutics in the VIMM, and a Harrison Foundation Distinguished Professor in Cancer Research in the VCU MCC. Dr. Jason M. Beckta is a graduate of VCU’s MD/PhD program and now a resident physician at Yale University. Dr. Kristoffer Valerie is a Professor in the Department of Radiation Oncology at VCU. Frank B. Furnari, PhD, is a Member of the Ludwig Institute, as well as Professor of Pathology 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 SBPD and UCR.