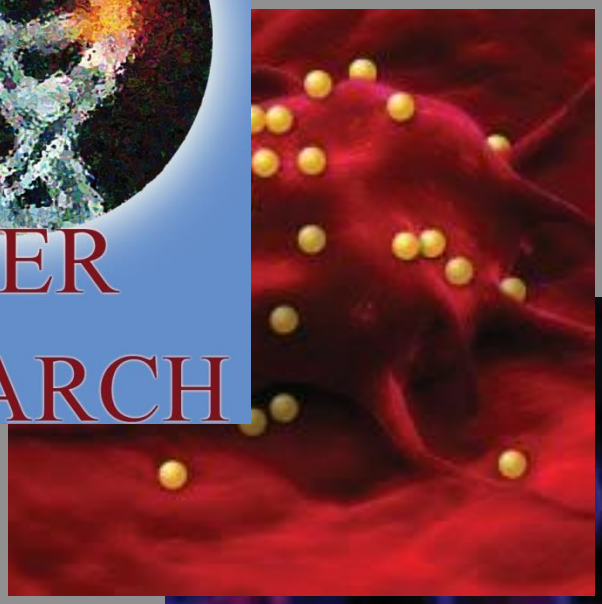
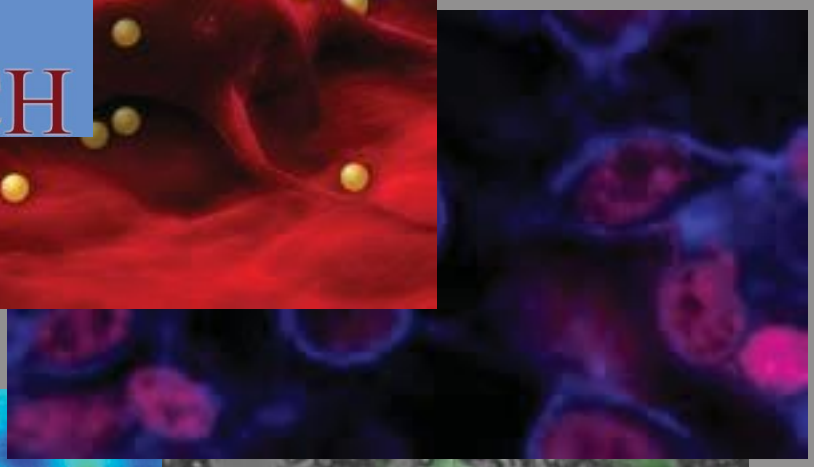
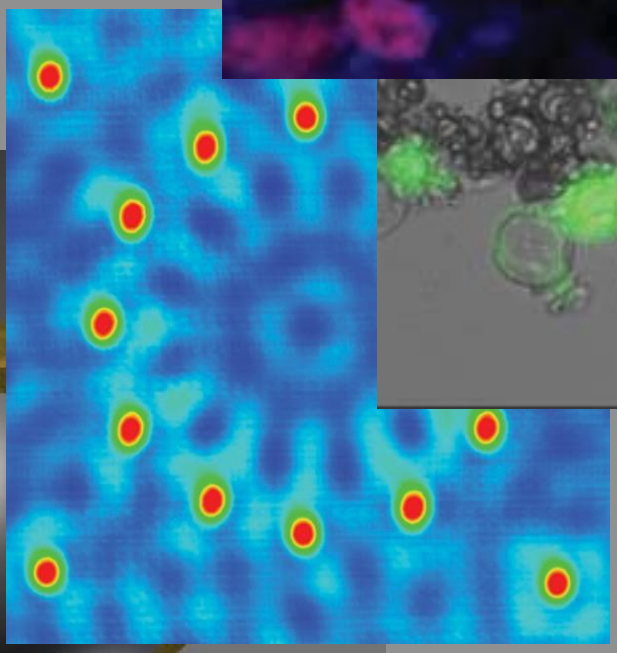
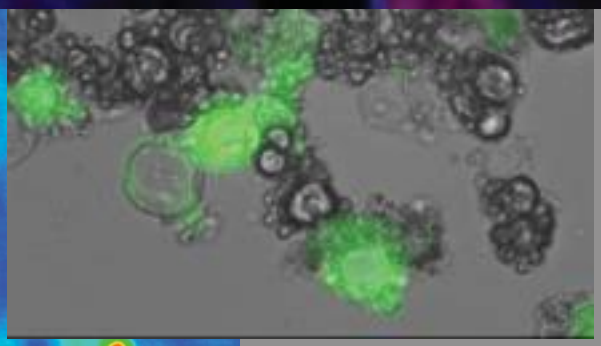
Capital Region Cancer Research

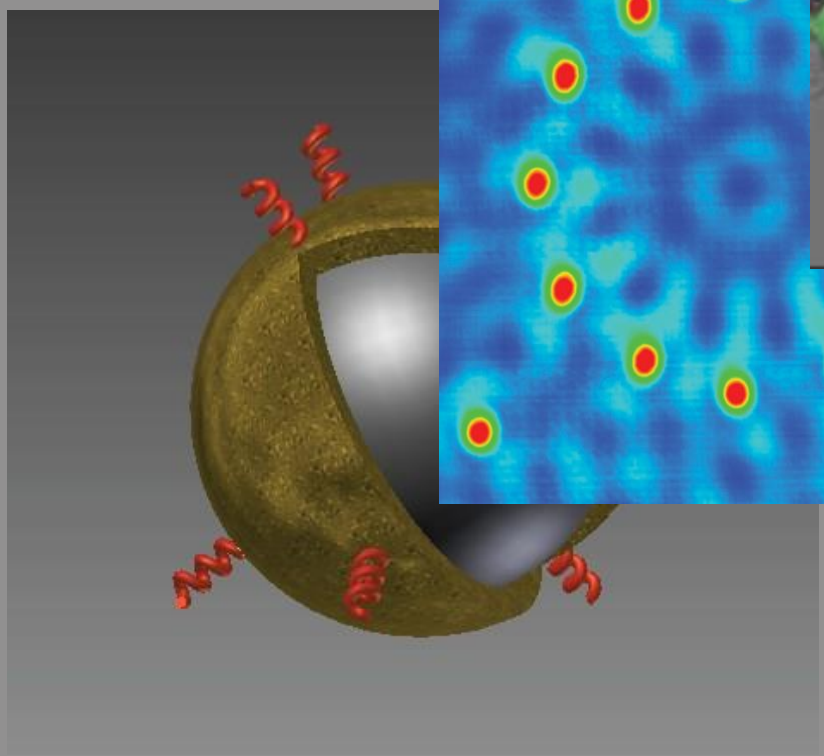
New Frontiers Symposium 2021: Precision Medicine in Cancer Treatment and Prevention











June 11, 2021

June 11, 2021; 9:00 AM – 2:30 PM

ZOOM hosted by Albany College of Pharmacy/PRI
Albany, New York

PROGRAM ORGANIZING COMMITTEE

Dr. Dana Crawford, Chair, *Albany Medical College*

Dr. Shaker Mousa, *Albany College of Pharmacy and Health Sciences/PRI*

Dr. Janet Paluh, *SUNY Polytechnic Institute*

Dr. Ramune Reliene, *University at Albany*

Dr. Tom Begley, *UAlbany and RNA Institute*

Dr. Erasmus Schneider, *Wadsworth Center*

Dr. Dong Joo (Ellen) Cheon, *Albany Medical College*

Dr. David Isaacson, *Rensselaer Polytechnic Institute*

Dr. Deborah McGuinness, *Rensselaer Polytechnic Institute*

CONFERENCE COORDINATORS

Ellyn Ford, *Bioconnex, Center for Economic Growth*

Danielle Cowin, *Albany College of Pharmacy and Health Sciences/ Pharmaceutical Research Institute (PRI)*

Raneela Khan, *Albany College of Pharmacy and Health Sciences*

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The CRCR is an inter-institutional organization that was created in the New York Capital district region in the summer of 2006. The purpose of the group is to promote cancer research interactions among different Albany area facilities and personnel. Member organizations include Wadsworth Center, SUNY-Albany, Albany Medical Center (AMC), Rensselaer Polytechnic Institute (RPI), SUNY Polytechnic Institute, Albany College of Pharmacy and Health Sciences/Pharmaceutical Research Institute (ACPHS/PRI), Stratton VA Medical Center, General Electric Global Research (GE), Taconic Biosciences, and New York Oncology Hematology (NYOH)

PROGRAM SCHEDULE

9:00 **Dana Crawford, PhD** (Albany Medical College), **Chair, Capital Region Cancer Research** (CRCR) Introductory remarks on behalf of the CRCR group

9:05 **SESSION 1 – BASIC STUDIES, CHALLENGES AND INNOVATION**
Chair: **Dong-Joo (Ellen) Cheon, PhD** (Albany Medical College)

- **9:05** **HY Lin, PhD** (Taipei Medical University) "Dual targeting theranostics in cancers"
- **9:30** **Henri Tiedge, PhD** (SUNY Downstate) "Neuronal BC RNAs: dysregulation in breast cancer"
- **9:55** **Kideok Jin, PhD** (Albany College of Pharmacy and Health Sciences) "Cytokine-directed therapy for breast cancer in crosstalk of stromal components"
- **10:20** **Alena Rudkouskaya, PhD** (Albany Medical College) "Multiscale quantification of drug target engagement in breast cancer models using Fluorescent Lifetime FRET imaging"
- **10:45** **C Allison Stewart, PhD (**MD Anderson Cancer Center) "Resistance contains multitudes: increasing transcriptional diversity following small cell lung cancer treatment"
- **11:10** **Noureldien Darwish, MD, PhD Post-Doc** (ACPHS/PRI) **"**Novel Thyrointegrin αvβ3 antagonist for the effective management of acute myeloid leukemia (AML)"

11:20 **COMMUNITY ORGANIZATIONS (To Life!, American Cancer Society, The Leukemia & Lymphoma Society, The Komen Foundation): Presentation by Mara Ginsberg** (Founder and President Emeritus of To Life!, Scientific Advisory Council chair, and breast cancer survivor) on "What research means to breast cancer patients and survivors" followed by each group and Q and A

11:50 **BREAK**

12:20 **SESSION 2 – PATIENT-BASED CANCER STUDIES**
Chair: **David Isaacson, PhD** (Rensselaer Polytechnic Institute)

- **12:20** **Jung-Min Lee, MD** (National Cancer Institute) "Women's cancers: evolution of management in the era of precision medicine"
- **12:50** **Laura Martello-Rooney, PhD** (SUNY Downstate) "GI Cancer Research Models and Studies to Enhance Precision Medicine for African American Patients"
- **1:15** **Makenzi Evangelist, MD** (New York Oncology Hematology) "The MYLUNG consortium: Understanding molecular testing barriers to improve care for lung cancer patients"
- **1:45** **Ge Wang, PhD (**Rensselaer Polytechnic Institute) "Artificial Intelligence (AI) for precision medicine"
- **2:10** **Rakshitha Miskin, Graduate Student** (Albany Medical College) "Integrin α3β1 promotes invasive and metastatic properties of breast cancer cells through induction of BRN-2"
- **2:20** **Closing Remarks (Dr. Janet Paluh,** SUNY Polytechnic Institute)

ABSTRACTS

Dual Targeting Theranostics in Cancers

Tsai-Mu Cheng Cheng, Dana R. Crawford, Paul J. Davis, Shaker A Mousa, Hung-Yun Lin.
Taipei Medical University Taipei, Taiwan, Albany Medical College, and Albany College of Pharmacy, Albany, NY, USA

Recently, nanotechnologies have been used in the biomedical field for detection, and therapeutic purposes. CEACAM6 and integrin αvβ3, two cell surface targets present on cancer cells. Integrin αvβ3 also expresses on highly growing endothelial cells. They participate in the signaling transduction pathway essential for proliferation and metastasis in cancer cells. Crosstalks among integrin, CEACAM6 and other signal transduction pathways play vital roles in modulating cancer proliferation. Blockage CEACAM6 signals by antibodies show a promising target in cancer therapies. We contracture nano-anti-CEACAM6 antibodies targeting cancer cell surface CEACAM6. On the other hand, 3,3',5,5'-tetraiodothyroacetic acid (**tetrac)** completes with thyroid hormone to bind to integrin related to integrin αvβ3 to suppress cancer proliferation. Nano-particulate derivative of tetrac (NDAT) derivatives demonstrate effective anti-proliferation in different types of cancers. We present the potentiation of nano-anti-CEACAM6 antibody payload NDAT against late-stage cancers.

Neuronal BC RNAs: dysregulation in breast cancer

Henri Tiedge

SUNY Downstate Health Sciences University

In brain, local protein synthesis at the synapse is a key requisite for neuronal function and plasticity. Brain-Cytoplasmic RNAs (BC RNAs) control this mechanism as they regulate translation of locally available mRNAs in an input-specific and activity-dependent manner. Expression of BC RNAs is typically restricted to neurons, with two notable exceptions: germ cells and certain types of malignant tumor cells. Invasive breast cancer cells express high levels of human BC200 RNA while fibroadenoma cells, in contrast, express only background levels.

We have recently reported that in invasive breast cancer patients, BC200 RNA is detectable in circulating tumor cells. Expression levels are high at diagnosis but decrease non-uniformly with treatment. In addition, recent data indicate that BC200 RNA regulates translation of tumor suppressor gene products. The combined evidence raises the possibility that BC200 RNA plays a role in breast cancer tumorigenesis, and that its expression may be of diagnostic-prognostic utility.

Multiscale Quantification of Drug -Target Engagement in Breast Cancer Models Using Fluorescent Lifetime FRET Imaging

Alena Rudkouskaya[a], Jason Smith[b], Cassidy Roberge[b], David Corr[b], Xavier Intes[b] and Margarida Barroso[a]

[a]*Department of Cellular and Molecular Physiology, Albany Medical College, Albany, NY*

[b]*Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, NY*

The ability to non-invasively monitor and quantify the target engagement in preclinical studies of oncologic drug delivery remains a great challenge. Fluorescent Lifetime FRET (FLI-FRET) imaging offers a unique approach to detect fluorescently labeled ligands or antibody binding to dimeric receptors followed by their uptake into cancer cells in vitro and in vivo. By using multiscale breast cancer models (2D, 3D aggregates and bioprinted microcapsules, and tumor xenografts) we successfully validated this method of quantification of target engagement by measuring FRET between donor- and acceptor-labeled probes bound to the dimerized and/or oligomerized receptors, based on the reduction of donor fluorophore lifetime. This approach is especially relevant for imaging live animals as it provides the ability to discriminate unbound probe from the internalized in cancer cells non-invasively and longitudinally. So far, we demonstrated the efficacy of FLI-FRET for direct and robust measurement of target engagement in tumors using NIR-labeled probes against HER2, important breast cancer oncogene, and transferrin receptor, a commonly used cancer target. By leveraging the dark quencher IRdye QC-1 we multiplex drug delivery and metabolic monitoring of tumors by simultaneous imaging of transferrin-AF700 and IRDye 800CW 2-DG. This approach is well positioned to dramatically transform the field of targeted drug delivery.

NOVEL THYROINTEGRIN αvβ3 ANTAGONIST FOR THE EFFECTIVE MANAGEMENT OF ACUTE MYELOID LEUKEMIA (AML)

Noureldien H. E. Darwish, Bruce Hay, Gennadi V. Glinsky, Shaker A. Mousa

The Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, Rensselaer, NY; and NanoPharmaceuticals LLC, Rensselaer, NY

AML is one of the most aggressive malignant hematological disorders on worldwide basis. More than 19,000 new cases are estimated in the United States in 2020 (1.1% of all new cancer cases). The estimated death rate from AML is 11,180 that represent 56% of the new cases (1.8% of all cancer death), with an overall 5-year survival rate of 27.4%. New broad spectrum effective and safe treatment options are urgently needed for the different types of AML. Our study reports the discovery of a novel anticancer agent that is a thyrointegrin αvβ3 antagonist, named fb-PMT. fb-PMT effectively suppresses the malignant growth of human acute myeloid leukemia (AML) after successful engraftment in transgenic NSG-S xenograft mouse models of either established human AML cell line or primary AML cells. Daily treatment with fb-PMT (1-10 mg/kg body weight) subcutaneously (s.c.) for 3-4 weeks was associated with marked regression of leukemogenesis and extended survival in both models. The efficiency of the fb-PMT therapy was verified using IVIS imaging, flowcytometry and histopathological examination to monitor the engraftment of leukemic daily doses exhibited significant reduction ($P<0.0001$) of leukemic cell burden of 74% and >95%, respectively. All fb-PMT-treated mice in the 10 mg/kg treatment arm successfully maintained remission after discontinuing the daily treatment. Comprehensive fb-PMT safety assessments demonstrated excellent safety and tolerability at multiple folds above the anticipated human therapeutic doses. Lastly, our genome-wide microarray screens demonstrated that fb-PMT works through the molecular interference mechanism with multiple signaling pathways contributing to growth and survival of leukemic cells such as MYC, HIF1A, TFAP2C, TWIST1; SNAI. Also, fb-PMT-induced other gene expression signatures of transcriptional pathway's activation include RB1; IRF9; MAML1; RAP1A; and GATA4 pathways which contribute to the fb-PMT anticancer activity. Collectively, preclinical findings of fb-PMT warrant its clinical investigation for the effective and safe management of AML.

Women's cancers: evolution of management in the era of precision medicine

Jung-Min Lee, MD

Investigator, NIH Lasker Clinical Research Scholar

Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, USA

Over the last two decades, discoveries related to the breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*) have significantly advanced our understanding and management of hereditary breast and ovarian cancers. The concept of synthetic lethality, which arises when cells become vulnerable to a combination of deficiencies in DNA damage response, has driven the expanding roles of poly (adenosine diphosphate (ADP)-ribose) polymerase inhibitors (PARPis) in BRCA-associated cancers. Moreover, successful introduction of PARPis has led to a new paradigm in women's malignancies, in particular, ovarian cancer treatment and maintenance therapy.

PARP inhibition causes DNA damage via catalytic inhibition of PARP enzyme and trapping of DNA-PARP complexes, resulting in synthetic lethality in cells deficient in homologous recombination repair. Emerging data suggest the efficacy of PARPi may be associated with immunomodulation. High levels of IFNγ increases the cytotoxic effect of PARPi in BRCA-deficient ovarian or breast cancer preclinical models. PARPi also upregulates PD-L1 expression through a variety of mechanisms in ovarian, breast and lung cancer preclinical studies. Further, increased DNA damage by PARPi activates the STING pathway, resulting in systemic antitumor immunity. Broken DNA fragments enter the cytoplasm and bind to cyclic GMP-AMP synthase (cGAS), leading to upregulation of the cGAS-STING pathway. The PARPi olaparib promotes accumulation of cytosolic DNA fragments and STING pathway activation in both BRCA1-deficient and BRCA-proficient ovarian cancer cell line and mouse models. Hence, addition of PARPi may complement the clinical activity of immune checkpoint blockade by creating more immunogenic micromilieu. As such, early clinical activity has been observed in subsets of breast and ovarian cancer patients.

Current research is now focused on further elucidating the roles of PARPis in immune milieu as well as tumor microenvironment, investigating other key processes and proteins and linking aberrant DNA repair with carcinogenesis and angiogenesis for the novel combination approaches.

MYLUNG: MOLECULARLY INFORMED LUNG CANCER TREATMENT IN A COMMUNITY CANCER NETWORK: A PRAGMATIC REAL-WORLD EVIDENCE PROGRAM.

Author: Makenzi Evangelist, MD

Affiliation: New York Oncology Hematology, US Oncology Research

Recent improvements in lung cancer mortality can be ascribed to the discovery of molecular drivers and utilization of drugs targeting these alterations. Despite national organizations endorsing comprehensive biomarker testing for patients with NSCLC, obstacles to routine testing and their use in driving therapeutic decisions remain. Engaging community practices within the US Oncology Network (USON), we initiated a real-world evidence program aimed to pragmatically identify and overcome barriers to timely and appropriate comprehensive biomarker testing in a large community-based diverse population of lung cancer patients. Over the next 5 years, the program will evaluate testing workflows and algorithms, provider acceptance and use of biomarker testing results, and appropriate adoption of new treatments as they become approved for these patients. The program is comprised of three principal and integrated components. Protocol 1 is a retrospective cohort study evaluating biomarker testing practices, results, and initial treatment over a 2-year period ending in October 31, 2020. Protocol 2 is a prospective, non-interventional study which will enroll approximately 1000 patients with histologically or cytologically documented early, locally advanced, or advanced stage non-small cell lung cancer patients who are eligible for active systemic therapy across 10 community practices in the USON. Protocol 2 will evaluate the current and evolving testing practices of newly diagnosed lung cancer patients. Protocol 3 is a platform of prospective interventional trials, engaging 20-30 resource and geographically diverse practices in USON, which will enroll approximately 7500 patients. Index Protocol 2 practices will serve as their own controls for subsequent interventional trials in Protocol 3.

Artificial Intelligence (AI) for precision medicine

Ge Wang, PhD, Rensselaer Polytechnic Institute, Troy, NY

Over the past several years, artificial intelligence (AI) has become a paradigm shift featured by deep learning and data sciences. AI-based medical imaging is a new frontier of research and has great potential for clinical translation. AI, especially deep learning, is well known for its successes in computer vision and image analysis, which deal with existing images, improve them, and produce features (from images to features). Since 2016, deep learning techniques are actively developed for clinical tomography. Tomographic reconstruction produces images of multi-dimensional structures from externally measured data in the form of various transforms (features to images). In this presentation, we provide some key elements of the general background, highlight our recent results on deep medical imaging, and discuss issues to be addressed in this applied AI field for precision medicine.

INTEGRIN α3β1 PROMOTES INVASIVE AND METASTATIC PROPERTIES OF BREAST CANCER CELLS THROUGH INDUCTION OF THE BRN-2 TRANSCRIPTION FACTOR

Rakshitha Pandulal Miskin [1], Janine S A Warren [2], Abibatou Ndoye [3], Lei Wu [3], John M Lamar [2], C Michael DiPersio [2 3]

[1]Department of Regenerative & Cancer Cell Biology, Albany Medical College, Albany, NY 12208, USA.

[2]Department of Molecular & Cellular Physiology, Albany Medical College, Albany, NY 12208, USA.

[3]Department of Surgery, Albany Medical College, Albany, NY 12208, USA.

In the current study, we demonstrate that integrin α3β1 promotes invasive and metastatic traits of triple-negative breast cancer (TNBC) cells through induction of the transcription factor, Brain-2 (Brn-2). We show that RNAi-mediated suppression of α3β1 in MDA-MB-231 cells caused reduced expression of Brn-2 mRNA and protein and reduced activity of the *BRN2* gene promoter. In addition, RNAi-targeting of Brn-2 in MDA-MB-231 cells decreased invasion in vitro and lung colonization in vivo, and exogenous Brn-2 expression partially restored invasion to cells in which α3β1 was suppressed. RNAi-mediated suppression of α3β1 decreased phospho-Akt levels in MDA-MB-231 cells, and treatment of α3β1 expressing cells with a pharmacological Akt inhibitor (MK-2206) reduced both Brn-2 expression and cell invasion, indicating that α3β1-Akt signaling contributes to Brn-2 induction. Analysis of RNA sequencing data from patients with invasive breast carcinoma revealed that patients with high *BRN2* expression have poor survival. Moreover, patients with basal-like breast cancer expressing high α3β1 are likely to express high *BRN2*, which is consistent with our experimental findings that α3β1 induces Brn-2 in TNBC cells. Together, our study demonstrates a pro-invasive/pro-metastatic role for Brn-2 in breast cancer cells and identifies a role for integrin α3β1 in regulating Brn-2 expression, thereby revealing a novel mechanism of integrin-dependent breast cancer cell invasion.

Novel Thyrointegrin αvβ3 Antagonist in the effective treatment of Glioblastoma Multiforme

Kavitha Godugu, Thangirala Sudha, Bruce Hay, *Mehdi Rajabi,* Shaker A. Mousa

The Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, and NanoPharmaceuticals LLC, Rensselaer, NY

Background: The proliferative and the pro-angiogenesis actions mediated by L-thyroxine, pro-inflammatory, and all known growth factors in glioblastoma multiforme (GBM) are initiated at cell surface thyrointegrin αvβ3 receptors for thyroid hormone on the extracellular domain of αvβ3 integrin. Thyrointegrin αvβ3 receptors are over-expressed on cancer and rapidly dividing blood vessel cells, but quiescent on normal cells. A macromolecule **P**olyethylene Glycol conjugated **bi**-**T**ri**A**zole **T**etraiodothyroacetic acid (**P-bi-TAT**) and fluorobenzyl conjugated to monodisperse PEG via mono-Triazole TAT (**fb-PMT**) act with high affinity (Ki 0.2-0.3 nM) and specificity for the thyrointegrin αvβ3 receptors without any significant nuclear translocation versus the non-polymer-conjugated **TAT**.

Methods: In the present studies, U87 glioma cell line and primary human GBMs were implanted orthotopically or subcutaneously (SC) into nude mice and treated daily for up to 21 days with P-bi-TAT or fb-PMT at different doses. Additionally, preclinical Pharmacokinetic and Safety assessment was carried out in multiple species.

Results: Pharmacokinetic profiles revealed Once a day dosing and Safety assessment studies demonstrated high safety and tolerability at 100-fold over the anticipated human equivalent dose upon repeated dosing. Fluorescence labeled P-bi-TAT or fb-PMT administered SC demonstrated high and comparable biodistribution to GBM tumor in the brain versus peripherally implanted tumor. P-bi-TAT or fb-PMT administered once daily for 21 days SC at 1.0-10 mg/kg resulted in a dose-dependent suppression of GBM tumor growth and viability monitored with IVIS imaging ($p < 0.001$). Histopathological analysis of tumors revealed > 95% loss of the vascularity of treated tumors ($p < 0.001$) along with extensive cellular necrosis and apoptosis, without intratumoral hemorrhage. GBM tumors had a 97% volume loss and maximal loss of GBM cell viability during the 22 days off-treatment period ($p < 0.001$). Additionally, P-bi-TAT or fb-PMT demonstrated enhanced chemo and radio-response in various solid tumors. Genomic micro-array studies with human primary GBM revealed that multiple pathways relevant to the progression of GBM are modulated with fb-PMT treatment. Large scaleup production of GMP fb-PMT at >96-98% purity versus P-bi-TAT was more achievable that favor advancing fb-PMT is our lead clinical candidate in various solid tumors and hematological malignancies.

Conclusions: fb-PMT is a potent thyrointegrin αvβ3 antagonist that promote apoptosis, necrosis, and devascularization in GBM. Fb-PMT is a lead clinical candidate for the treatment of human GBM.