

Faculty in Focus: Immunotherapy





CANCER **IMMUNOTHERAPY** AT UAB

Faculty in Focus

Dr. Schneider - Interview 4

Recent Graduates

5

Incoming Class Follow-up 6

Events

Accolades

10





UAB GBS CANCER BIOLOGY THEME

Theme directors:

Theresa Strong Ph.D.

Lalita Shevde-Samant Ph.D.

Program manager:

Patricia Matthews

Cancer Biology Theme News Editorial Board:

Lalita Shevde-Samant Ph.D.
Samuel Fehling
Joshua Fried
Abhishek Gangrade
Ann Hanna
Hawley Pruitt

Anh Tran

From the Directors

elcome to the Summer Edition of the Hallmark! In this issue, we focus on Cancer Immunotherapy at UAB. After years of painstaking research to better understand the interaction between tumors and the host immune system, the knowledge gained is now being applied to unleash a robust immune response against tumors. Immunotherapy approaches for cancer are starting to realize their promise, eliciting dramatic and lasting responses in some patients. The challenges now include better predicting how patients will respond so that therapy can be appropriately tailored, enhancing immunotherapy strategies to increase the number of patients whose tumors are amenable to such approaches, and scaling up to be able to treat more individuals. Drs. Lamb and Di Stasi are two UAB investigators working on these issues, and their research is discussed on page 3. We also highlight some of the exciting transitions in the Cancer Biology Theme. Several students have successfully completed their PhD (p5), our upper year students are making significant contributions through numerous presentations and publications (p 7-10), our first year students have all settled into their "lab homes" (p6), and Dr. David Schneider has assumed the position of Associate Dean for Graduate Biomedical Sciences (p4).

Finally, an added note from Theresa: Although it has been extremely rewarding to serve as Co-Director of the Cancer Biology Theme for the past five years, I will be stepping down at the end of the summer to focus on some new opportunities. It's truly been a pleasure collaborating with the GBS faculty, administrators and students to advance the work of the Cancer Biology Theme. The caliber of the research that is being generated by our graduate students reflects the hard work and dedication of all involved. As this issue of the Hallmark goes to press, the process for selection of a new Co-Director has just been completed and we are thrilled that Dr. Soory Varambally will become the new Co-Director. He brings expertise in cancer biology, genomics and bioinformatics, as well as a strong commitment to student success. I have tremendous confidence that the Cancer Biology Theme will continue to grow and thrive under the guidance of Drs. Lalita Shevde-Samant and Varambally.

Theresa Strong Ph.D. & Lalita Shevde-Samant Ph.D.

Visit our website: http://www.uab.edu/gbs/cancerbiology



FACULTY IN FOCUS

Cancer Immunotherapy at UAB

by Ann Hanna







Antonio Di Stasi, MD

In this issue, we focus on the field of immunotherapy, an area of cancer research extensively pursued in recent years. UAB houses several laboratories specializing in immunotherapy research including Dr. Lawrence Lamb and Dr. Antonio Di Stasi in the Hematology and Oncology Division in the Department of Medicine.

Dr. Lawrence Lamb is an immunologist invested in studying immunotherapy in cancer treatment. His work pioneered clinical trials describing gamma/delta T cells recovery post alpha/beta T cell depleted bone marrow transplant in patients and the association between disease-free survival, bone marrow transplantation in patients and gamma/delta T cell recovery. He also studied the CDR3 T cell receptor in leukemia patients. Dr. Lamb served as the Leadership Chair for the National Brain Tumor Society's Glioblastoma Research for three years. Dr. Lamb currently serves as the director for the UAB Cell Therapy Laboratory for the Bone Marrow Transplantation Program; he also hold appointments in several departments including the Department of Pathology and Department of Pediatrics. His research focuses on gamma/delta T cell association with high-grade gliomas and aims to target them therapeutically through biological modifications in order to treat glioma patients in the clinic. Dr. Lamb's research is funded by several agencies including the National Cancer Institute, National Institute of Neurological Disorders and Stroke, and Leukemia and Lymphoma Society.

Dr. Antonio Di Stasi earned his medical education in Italy, focusing on hematological malignancy management, particularly stem cell transplantation. He then moved to the United States to pursue postdoctoral training at Baylor College of Medicine investigating the clinical application of relapsed Hodgkin lymphoma treatment and suicide gene safety switch for graft-versus-host disease post lymphocyte infusion.

Dr. Di Stasi's current research interests involve the validation of pre-clinical adoptive T cell immunotherapy for hematologic malignancies, particularly the genetic modifications of T cells with artificial receptors designed to target tumor antigens as well as the inclusion of Caspase9 suicide gene to ensure the clinical safety of the lymphocyte infusions. Dr. Di Stasi's work has laid the foundation for several clinical studies including standardizing CD3 T cell dose for stem cell transplantation in patients. Dr. Di Stasi is also involved in clinical trials with Dr. Lawrence Lamb to assess the use of cyclophosphamide to prevent acute graft-versus-host disease post bone marrow transplantation and the combination of fludarabine and irradiation to ensure the success of stem cell transplants in patients with high-risk conditions.

GBS

Sit down with Dr. Schneider

Summarized Interview by Joshua Fried

Josh: When did you officially begin your new position?

Dr. Schneider: January 1st, 2016.

JF: What is your official title?

DS: Associate Dean for Graduate Biomedical Sciences.

JF: What was the selection / election process like? Who was involved?

DS: First there was a call for internal candidates. I submitted my CV along with an application. Then there was a narrowing process followed by a panel interview composed of professors from across campus, with Lori McMahon playing a critical role. Following the panel interview there were two remaining candidates, myself and Alicia Gross. We each had an all-day public interview, where anyone could come and ask us questions. Finally there was a public vote.

JF: What are your roles and responsibilities in your new position?

DS: To direct the GBS program, to support and improve the PhD program, to manage the program managers. Also I manage the budget, communicate with students, and support the growth of students. The managers do a good job of handling most day to day issues.

JF: How has what you've experienced so far compared to your expectations?

DS: Very similar. It is a lot of work. I have had heavy involvement with the role before so I came in well prepared.

JF: What are some of the changes that you have made or initiated?

DS: I have made some changes to the organization structure. For example the oversight committee has been removed. Also there is now a panel of the theme directors. Additionally there is now a comment box on the website for people to anonymously leave feedback for me. I also had a specific email address for people to email me feedback. I hold open forums with students and with chairs. I have provided the program chairs

with more of a voice in how the program is run.

JF: What are some changes that you would like to make in the future during your tenure?

DS: I would like to make communication between students, faculty and administrators more efficient. I have also proposed tuition changes, but that may be difficult to pass. We will be making a new and more modern and user friendly GBS website. First year poster changes are going to be removed and replaced with a GBS wide symposium where all students and faculty accepting students can present their work.

My vision for the future of my tenure is to have a slight culture change in the program. I would like to lessen the gap between students and faculty. I would like for students to become more independent and for faculty to provide guidance.

JF: Are there any changes you have wanted to make but were unable due to bureaucratic reasons?

DS: Not yet, I did want to create a new summer program but I backed out of that idea myself.

JF: What are your day to day duties in this position?

DS: Every day is different. Most of my duties are concerned with administration. I talk to students, faculty, and program managers. I am currently working on updating the student handbook. I also solve problems that the managers are not able to handle on their own. One thing I am working on is thinking of new ways to promote the GBS program.

JF: The Cancer Biology Theme will be appointing a new codirector soon, what is involved in that process?

DS: Students and faculty will be emailed asking them to nominate faculty. Nominated faculty will then be asked if they would like to apply. Many faculty actually turn down the nomination. Faculty that say yes then submit and statement of purpose and a CV. I then evaluate the applicants

with the other theme directors. Since there are usually two directors in each program I place a higher value on the input of the remaining director. So, in this instance Dr. Lalita Samant will have more say then the other directors.

JF: What are some of the projects that you are investigating in your lab?

DS: I have an ADDA funded project to discover inhibitors of ribosome biosynthesis. Cancer cells have a higher demand for new ribosomes so we think this inhibitor can be used across many different cancer types. We current have identified two chemical compounds that have demonstrated potent inhibition of ribosome biosynthesis. We are currently testing these compounds in breast and melanoma cancer cell lines.

We are also working on the discovery of yeast ribosome biosynthesis regulators, and defining the relationship between rDNA transcription and rRNA processing. Lastly, we are doing enzymology studies of RNA polymerase 1.

RECENT GRADUATES 5

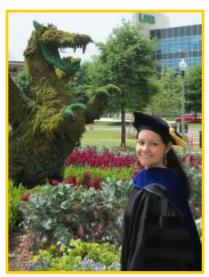
The end of an era

by Joshua Fried



Christopher Graham

I looked at the cell death mechanisms of 4-hydroxy tamoxifen (OHT) and BH3 mimetics in glioblastoma (GBM) and malignant peripheral nerve sheath tumor (MPNST) cells, respectively. I found that OHT reduces protein levels of EGFR and mediates GBM cell death via a caspase-independent mechanism that is attenuated by genetic inhibition of autophagy. Alternatively, BH3 mimetics appear to be significantly down-regulating CXCL12, a key secreted/extracellular signaling molecule that plays a role in an activated autocrine survival and growth promotion loop existent in MPNST cells. Further, data suggest that BH3 mimetic-mediated suppression of CXCL12 expression might result from liberating a key negative regulator of CXCL12 transcription, PARP1, from an inhibitory dimer complex with BCL-2.



Cara Schafer

My dissertation research focused on altering metabolism in the tumor microenvironment to enhance antitumor immunity for lung cancer. I assessed the preclinical efficacy and mechanism of action of a novel combination therapy consisting of a superoxide dismutase mimetic and gemcitabine chemotherapy. Using a mouse model of lung cancer, our combination therapy effectively targeted protumorigenic immune cells, especially myeloid-derived suppressor cells (MDSCs). Notably, combination therapy impaired tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase (IDO) expression in tumor-purified MDSCs and tumor cells. IDO-deficient CD8+ T cells and MDSCs isolated from the tumor microenvironment exhibited differential metabolic signaling pathway activation, further supporting a vital role for IDO in immune cell dependent metabolic reprogramming in mice. These findings were translated into an ongoing clinical study on peripheral blood samples from lung cancer patients before and after receiving different combination chemotherapy regimens. Not only was serum IDO activity significantly higher in lung cancer patients compared to healthy controls, but this was also associated with an increased frequency of circulating MDSCs. Following chemotherapy combination, we observed a reduction in MDSC frequency and IDO activity compared to pre-treatment values.



Alice Weaver

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease with high rates of recurrence and mortality. Unlike other cancer types, genome sequencing studies have failed to produce clinically actionable targets to improve HNSCC management. Therefore, alternative methods are needed to study the molecular mechanisms responsible for disease progression and response to therapy. The focus of this research was to determine how dysregulation of cell signaling pathways affects outcomes in HNSCC. Our results indicate that DNA repair and Notch signaling are dysregulated in HNSCC, leading to variability in characteristics such as therapeutic sensitivity and tumor progression. Importantly, we determined that DNA-Pk_{CS} and FGF1 are markers of signaling activity which should be studied further as potential therapeutic targets in this disease.

FIRST YEAR FOLLOW-UP 6

We're all set!

by Joshua Fried



Rachael Orlandella Dr. Lyse Norian's lab

Renal Cell Carcinoma (RCC) claims the lives of thousands of patients each year. Current therapeutic options are limited, but RCC has been shown to respond to immunotherapy. RCC also has a strong link to obesity; most patients are considered obese. An epidemic in itself, obesity continues to rise steadily in the United States. This trend will likely lead to an increase in RCC incidence. This makes studying RCC in the context of obesity essential to the development of more effective therapeutics. The Norian lab previously demonstrated that a T-cell based immunotherapy fails in obese mice, but clears renal tumors in lean mice. One possible explanation for this observation is a defect in T-cell activation kinetics in obese mice. This project aimed to characterize T-cell activation kinetics in lean mice with renal tumors. It was observed that both CD8+ and CD4+ T-cell tumor infiltration peaks on Day 14 post-tumor challenge, then falls again on Day 21. Future directions for this project will compare these results to obese mice with renal tumors.



Alyncia Robinson
Dr. SooryanarayanaVarambally s lab

Our study suggested that miR-101 loss results in increased STMN1 expression and subsequent activation of oncogenes, which in turn drives prostate cancer progression and metastasis. This study therefore demonstrated the functional role of STMN1 in prostate cancer and identified both its regulation and potential downstream therapeutic targets for aggressive prostate cancer.



Mateus Mota Dr. Lalita Shevde-Samant 's lab

The NF2 gene produces the protein, Merlin that acts as a tumor suppressor. In breast cancer, Merlin levels are decreased. Merlin is critical to the activation of the Hippo signaling pathway characterized by phosphorylation and subsequent inhibition of the co-transcriptional factors, YAP/TAZ, resulting in repression of cell proliferation and apoptosis. YAP/TAZ, when active, are involved in the activation of gene transcription. Our study shows that MCF7 breast cancer cells silenced stably for Merlin (shNF2) supported higher YAP/TAZ and SMAD reporter activity compared to control MCF7 cells. Furthermore, stable Merlin silencing was associated with an increase in the transcript levels of TAZ and TEAD 4 (transcription factor involved in YAP/TAZ binding to the DNA) and an increase in the levels of target genes. Cumulatively, our data demonstrate that loss of Merlin removes the check on Hippo signaling in breast cancer cells.

Shelly Nason Dr. Bob Kesterson's lab



Neurofibromatosis Type 1 (NF1) is one of the most common inherited neurological disorders, affecting about one in every 3,000 people. The disorder is characterized by the development of multiple benign Schwann cell tumors in the skin and large peripheral nerves. A specific form of NF1, called dermal neurofibroma, is a condition caused by mutations in the tumor suppressor protein, neurofibromin. Dermal neurofibromas are benign tumors that grow from small nerves in the skin. The goal of this project was to create a transgenic mouse model with the human mutation p.Arg1809Cys through CRISPR/Cas9 genome editing to study therapeutics for treating dermal neurofibromas.

Soniya Bastola Dr. Ichiro Nakano 's lab



Glioblastoma (GBM) is an aggressive type of intracranial tumor with median survival of patients is less than 2 years. One of the reasons for poor prognosis could be the tumor-initiating population in GBM that have enhanced resistance to chemotherapy and radiation-induced apoptosis. An inhibitor was designed (NPA 014.14) that selectively targeted extracellular domain of PDGFRβ. The goal of this project was to find out the PDGFRβ protein expression across different subclasses of GBM cells. Similarly, result was confirmed using ICC using confocal microscopy. Additionally, 8 different cell lines were used and looked at differential expression. Current data directs us towards the potential therapeutic strategies that could be used to design a more effective inhibitor against PDGFRβ.





My rotation project was to study the role of irradiated non-cancer stem cells that undergo senescence-associated secretory phenotype(SASP) on cancer stem cells. Glioblastoma (GBM) is an aggressive tumor of the brain with a high rate of recurrence. Within GBM there are a subset of cell population known as cancer stem cell (CSCs) that provide GBM resistance to chemotherapy and radioresistance in comparison to non-cancer stem cell population. We found that the CD133 negative non-GSCs undergo senescence indicated by increase in SASP factors that are composed of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-1α. Furthermore, non-GSCs also show a marked increase of immunostaining for β-gal and western blotting for p21 after irradiation. Co-culture experiments of non-CSC with CSC show growth promoting effect of irradiated non-CSCs on CSCs. This study would help us further elucidate the role of non-stem cells in the propagation of stem cells in GBM.

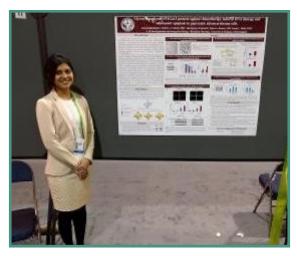
EVENTS

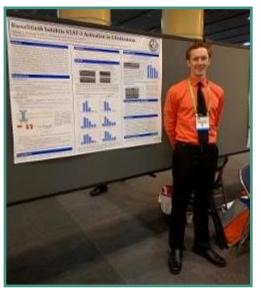
AACR Annual Meeting American Association for Cancer Research Annual Meeting 2016 · NEW ORLEANS

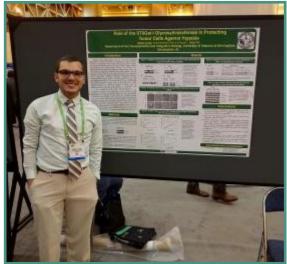
by Samuel Fehling

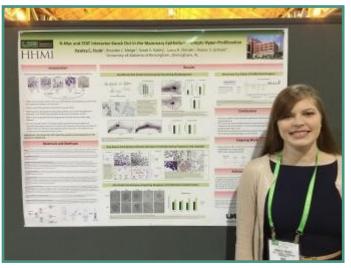
The American Association for Cancer Research, AACR, Annual Meeting 2016 was held April 16th – 20th in New Orleans, Louisiana. This year's theme, Delivering Cures Through Cancer Science, reinforces the monumental significance of research in both the understanding and elimination of cancer. Encompassing an extensive array of disciplines, hundreds of presentations by colleagues and friends, including those by our own Cancer Biology Theme

students, incited discussions regarding intriguing advances in patient care. In attendance was Vice President Biden who addressed nearly 4,000 attendees when he discussed the National Cancer Moonshot initiative and the importance of cancer research. This year marked the 100th anniversary of the AACR journals publication program and the 75th anniversary of Cancer Research.









EVENTS 8

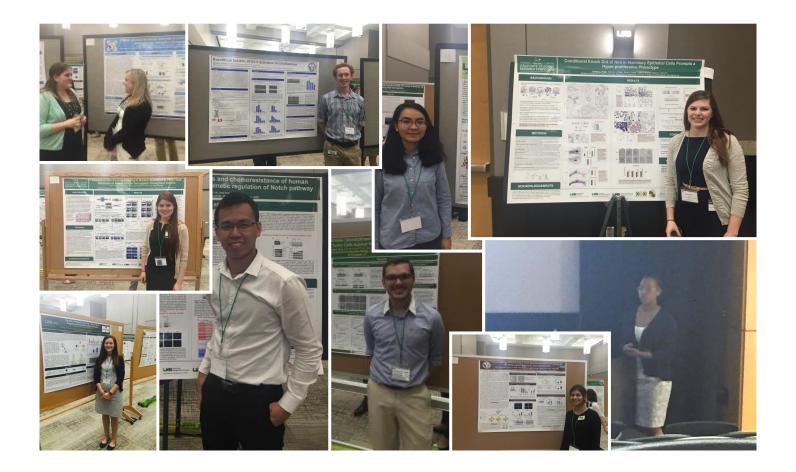
GRADUATE STUDENT RESEARCH SYMPOSIUM

by Hawley Pruitt

The GBS/JHS Graduate Student Symposium was a huge success this year, and the cancer biology theme students most definitely represented. There were approximately 300 attendees of the symposium with greater than 100 abstracts submitted and over 80 poster presentations at the new UAB Hill Student Center on May 13th 2016. Two oral presentations were awarded to cancer biology theme students

Anh Tran and Ashiya Buckels who gave talks on their dissertation projects looking at the role of nitric oxide signaling in brain tumor initiating cells of glioblastoma and the effects of growth hormone signaling on migration and invasion of melanoma respectively. The following students represented the cancer biology theme by presenting posters:

Asmi Chakraborty	GLYCOSYLTRANSFERASE ST6GAL-I PROTECTS AGAINST CHEMOTHERAPY INDUCED DNA
	DAMAGE AND SUBSEQUENT APOPTOSIS IN PANCREATIC ADENOCARCINOMA CELLS
Jia Cui	PTBP1 MODULATION OF MCL1 EXPRESSION REGULATES CELLULAR APOPTOSIS INDUCED BY
-	ANTITUBULIN CHEMOTHERAPEUTICS
Kaitlyn A. Dorsett	ST6GAL-I GLYCOSYLTRANSFERASE PROMOTES AN UNDIFFERENTIATED CELL PHENOTYPE
	AND ENHANCES C-KIT SIGNALING
Samuel Fehling	RUXOLITINIB INHIBITS STAT-3 ACTIVATION IN GLIOBLASTOMA
Kayla F. Goliwas	THE USE OF NON-INVASIVE IMAGING TO MONITOR GROWTH OF IN VITRO THREE DIMEN-
	SIONAL BREAST CANCER SURROGATES THROUGHOUT CULTURE
Ann Hanna	THE ROLE OF HEDGEHOG SIGNALING IN BREAST CANCER PROGRESSION THROUGH MACRO-
	PHAGE POLARIZATION
Brent Jones	ROLE OF THE ST6GAL-I GLOCOSYLTRANSFERASE IN PROTECTING TUMOR CELLS AGAINST
	HYPOXIA
Benjamin Y. Owusu	SRI31215, A NOVEL INHIBITOR OF ONCOGENIC HGF / MET SIGNALING
Hawley C. Pruitt	CONDITIONAL KNOCK OUT OF NMI IN MAMMARY EPITHELIAL CELLS PROMPTS A HYPER-
, and the second	PROLIFERATIVE PHENOTYPE
Trung Vu	STRAP MEDIATES THE CHEMORESISTANCE AND STEMNESSOF HUMAN COLORECTAL CAN-
=	CER CELLS BY EPIGENETIC REGULATION OF NOTCH PATHWAY



EVENTS

Pathology Research Day 2016

by Ann Hanna

The UAB Department of Pathology hosted its 11th Annual Trainee Research Day on Friday, March 18th. Trainees in the department including residents, postdoctoral fellows, and graduate students were invited to present their most recent advances in a variety of research areas. The Cancer Biology Theme was well represented during the event as several of our students showcased the exciting progress of their dissertation projects. Our students who participated in this event include Kayla Goliwas who presented a poster titled "Evaluation of in vitro Three Dimensional Breast Cancer Surrogates: The Use of Non-Invasive Imaging to Monitor Growth Throughout Culture", Ann Hanna who

presented "The Role of Hedgehog Signaling in Breast Cancer Progression through Macrophage Polarization", Will Jackson with his project "The Tumor Suppressor Protein Merlin Modulates the Breast Cancer Metabolome", and Monica Lewis who presented "SIN3A and SIN3B Differentially Regulate Breast Cancer Metastasis". Hawley Pruitt was selected to give an oral presentation discussing her project titled "Knock Out of N-Myc and STAT Interactor Gene in the Mammary Epithelium Prompts Hyper-Proliferation".

As the day concluded, both Hawley Pruitt and Monica Lewis won awards for Outstanding Research Presentation.



BRAGGING RIGHTS 10

Our New Publications

Krzywanski DM, Moellering DR, Westbrook DG, Dunham-Snary KJ, Brown J, Bray AW, Feeley KP, Sammy MJ, Smith MR, Schurr TG, Vita JA, Ambalavanan N, Calhoun D, Dell'Italia L, Ballinger SW. Endothelial Cell Bioenergetics and Mitochondrial DNA Damage Differ in Humans Having African or West Eurasian Maternal Ancestry. Circ Cardiovasc Genet. 2016 Feb;9(1):26-36.

- Pruitt HC, Devine DJ, Samant RS. Roles of N-Myc and STAT interactor in cancer: From initiation to dissemination. Int J Cancer. 2016 Aug 1;139(3):491-500. doi: 10.1002/ijc.30043. Epub 2016 Mar 11. Review.
- Libby EF, Liu J, Li Y, Lewis MJ, Demark-Wahnefried W, and Hurst DR. Globular adiponectin enhances invasion in human breast cancer cells. Oncology Letters. (2016) 11:633-641.
- Li Y, Libby EF, Lewis MJ, Liu J, Shacka JJ, and Hurst DR. Increased autophagic response in a population of metastatic breast cancer cells. Oncology Letters. (2016) 12: 523-529.
- Chakravarthi, B.V.S.K., Goswami M, Pathi S, Robinson A, Cieślik M, Chandrashekar D, Agarwal S, Siddiqui J, Daignault S, Carskadon S, Jing X, Chinnaiyan A, Kunju L, Palanisamy N, Varambally S. MicroRNA-101 regulated transcriptional regulator SUB1 plays a role in prostate cancer. Oncogene advance online publication, 6 June 2016.
- Goliwas KF, Miller LM, Marshall LE, Berry JL, Frost AR. Preparation and Analysis of In Vitro Three Dimensional Breast Carcinoma Surrogates. J Vis Exp. 2016 May 9;(111).
- Hanna A, Shevde LA. Hedgehog signaling: modulation of cancer properies and tumor mircroenvironment. Mol Cancer. 2016 Mar 18;15:24.
- Gilbert AN, Shevin RS, Anderson JC, Langford CP, Eustace N, Gillespie GY, Singh R, Willey CD. Generation of Microtumors Using 3D Human Biogel Culture System and Patient-derived Glioblastoma Cells for Kinomic Profiling and Drug Response Testing. J Vis Exp. 2016 Jun 9;(112).
- McFarland BC, Marks MP, Rowse AL, Fehling SC, Gerigk M, Qin H, Benveniste EN. Loss of SOCS3 in myeloid cells prolongs survival in a syngeneic model of glioma. Oncotarget. 2016 Mar 8.
- Vu T, Jin L, Datta PK. Effect of Cigarette Smoking on Epithelial to Mesenchymal Transition (EMT) in Lung Cancer. J Clin Med. 2016 Apr 11;5(4). pii: E44. doi: 10.3390/jcm5040044. Review.
- Tibbs ZE, Falany CN. An Engineered Heterodimeric Model to Investigate SULT1B1
 Dependence on Intersubunit Communication. Biochem Pharmacol. 2016 Jun 20. pii:
 S0006-2952(16)30137-X.

Presentation

 Asmi Chakraborty, Matthew Schultz, Hoa Quang Trummell, James Bonner and Susan Bellis, "Glycosyltransferase ST6Gal-I protects against chemotherapy induced DNA damage and subsequent apoptosis in pancreatic adenocarcinoma cells.", AACR Annual Meeting, April 2016.

New PhD Candidates

• Trung Vu and Ann Hanna

Awards and Honors

- Monica Lewis was elected to the Junior Board of Directors, Susan G. Komen North Central Affiliate, Birmingham, AL.
- Both Monica Lewis and Hawley Pruitt won Outstanding Research Presentation Awards at Pathology Trainee Research Day.
- Hawley Pruitt also won the Bertram Marx Student Research Endowment Travel Award.

#justphdthings

by Ann Hanna

HOLIDAY!

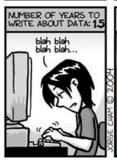




DATA: BY THE NUMBERS









Fun Fact:

Researchers have recently reported that in addition to glucose metabolism, gliomas rely on fat consumption to harness energy in order to advance. This potentially points to a novel target for brain tumor treatment. You can read more following this link: http://neuro-oncology.oxfordiournals.org/content/early/2016/06/29/neuonc.now128