RUTGERS
New Jersey Medical School

SUMMER STUDENT RESEARCH PROGRAM

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REPORT OF ACCOMPLISHMENTS

ACKNOWLEDGEMENTS

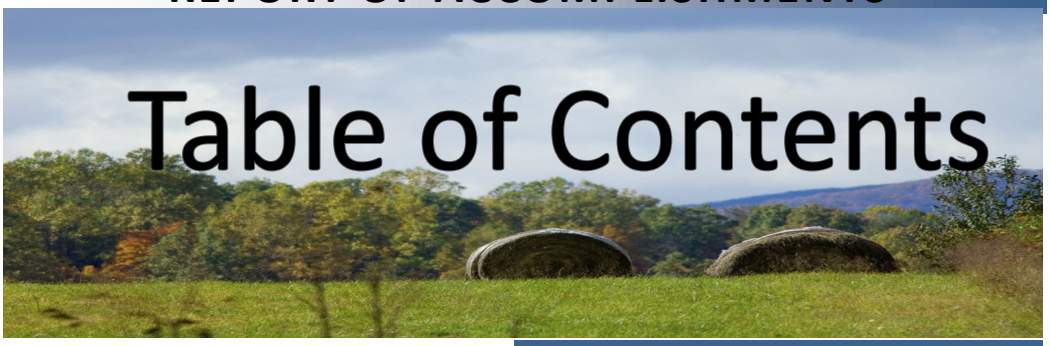
EXPRESSIONS OF APPRECIATION TO THE

RUTGERS, NEW JERSEY MEDICAL SCHOOL ALUMNI
AND
THE NEW JERSEY HEALTHCARE FOUNDATION, INC.
THANK YOU SO MUCH FOR YOUR CONTINUOUS FINANCIAL SUPPORT.
YOUR FINANCIAL SUPPORT ENABLES STUDENTS THE OPPORTUNITY
TO BROADEN THEIR RESEARCH SKILLS.

2015

STUDENT ABSTRACTS

REPORT OF ACCOMPLISHMENTS



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PREFACE

Since 1968 the New Jersey Medical School First-Second Year Students and Volunteers have participated in this organized research program. This program gives an opportunity for students and volunteers to work alongside an NJMS Faculty Mentor on a specific research project for a period of eight weeks. Over the eight week period the participants are exposed to the dynamic nature of biomedical science. During this time they learn about the methodology and results of laboratoclinical research; sharpen diagnostic skills, and learn the value and limits of experimental results. This program has been fortunate to have had an array of enthusiastic students seeking to broaden their research knowledge in the treatment of diseases.

This the forty-seventh edition of the Summer Student Research Program Abstracts summarizing research results generated by students, volunteers, and interns working thru this year's program. The Summer Student Research Program continues to provide a significant contribution to the training of our future clinicians and research scientists. It is the continued goal of this program to inspire the next generation of physicians and scientists.

We would like to thank the NJMS Faculty and Researchers who take time from their teaching and administrative responsibilities to mentor over the eight week period. We truly appreciate your continued support and exceptional commitment. It is also with pleasure that we thank the members of the faculty advisory committee…….for their assistance and commitment in developing the program guidelines, evaluating student abstracts, selection of student participants and participation during the poster symposium. This program could not be successful without your volunteerism! Many thanks to your for your kind consideration.

MANY THANKS TO THE FOLLOWING FACULTY FOR TAKING TIME TO SERVE AS JUDGES, SEMINAR SPEAKERS, AND TO MENTOR THE MEDICAL STUDENTS, INTERNS AND VOLUTEERS DURING THE 2015 SUMMER STUDENT RESEARCH PROGRAM.

2015 SEMINAR SPEAKERS

2015 KICK-OFF TO THE SSRP **SEMINAR PRESENTER** Stanley H. Weiss, M.D., FACP, FACE Professor-NJMS Preventive Medicine	2015 SSRP POSTER SYMPOSIUM **AM SEMINAR SPEAKER** Betsy Barnes, Ph.D., Associate Professor Microbiology, Biochemistry & Molecular Genetics
2015 SSRP POSTER SYMPOSIUM **PM SEMINAR PRESENTER** Maria L. Soto-Greene, M.D., MS-HPEd, FACP Vice Dean and Professor of Medicine Interim Chair, Department of Medicine Director, Hispanic Center of Excellence (HCOE) at Rutgers New Jersey Medical School	

NJMS FACULTY MENTORS

Purnima Bhanot, PhD., Assistant Professor Microbiology and Molecular Genetics	Soly Baredes, MD, Professor Neurological Surgery
Ziad Sifri, MD, Associate Professor Emergency Medicine	Ping-Hsin Chen, Ph.D.,Assistant Professor Family Medicine
Susan Feldman, Ph.D., Associate Professor Department of Radiology	Melissa Rogers, Ph.D., Associate Professor Biochemistry & Molecular Biology
Chirag Gandhi, MD, Assistant Professor Neurological Surgery	Sandra Scott, MD, Assistant Professor Emergency Medicine
Betsy Barnes, Ph.D., Associate Professor Biochemistry & Molecular Biology	Melissa Rogers, Ph.D., Associate Professor Microbiology, Biochemistry, and Molecular Genetics
Robert W. Ledeen, Ph.D., Professor Neurology & Neuroscience	James P. O'Connor, Ph.D., Associate Professor Microbiology, Biochemistry, and Molecular Genetics
Stanley Weiss, M.D., Assistant Professor Medicine	Sylvia Christakos, Ph.D., Professor Microbiology, Biochemistry, and Molecular Genetics
Chaoyang Xue, Ph.D., Assistant Professor Microbiology, Biochemistry, and Molecular Genetics	Elizabeth Moran, Ph.D., Professor Orthopedics
Lizhao Wu, Ph.D., Assistant Professor Microbiology & Molecular Genetics	Steven Schleifer, MD, Professor Psychiatry
Sue Ming, Ph.D., M.D., Ph.D., Professor Neurology and Neurosciences	Yongkyu Park, Ph.D., Assistant Professor Cell Biology and Molecular Medicine
Jean Anderson Eloy, M.D., Assistant Professor Otolaryngology	Charles Prestigiacomo, M.D., Professor Neurological Surgery
Antonios Mammis, M.D., Professor Neurological Surgery	Vijay Parashar, Ph.D., Assistant Professor Oral Biology

NJMS FACULTY MENTORS	
Bishambar Dayal, Ph.D., Adjunct Associate Professor Microbiology, Biochemistry, and Molecular Biology	Michael Lea, Ph.D., Professor Microbiology, Biochemistry, and Molecular Biology
Anna M. Barrett, M.D., Professor Physical Medicine and Rehabilitation	

JUDGES FOR POSTER COMPETITION	
Petros Levounis, MD, Professor & Chair Department of Psychiatry	Alex Bekker, MD, Ph.D., Professor & Chair Department of Anesthesiology
Susan Feldman, Ph.D., Associate Professor Department of Radiology	Elizabeth Moran, Ph.D., Professor Department of Orthopaedics
Vivian Bellofatto, Ph.D., Professor Microbiology, Biochemistry, and Molecular Genetics	Stanley Weiss, M.D., Assistant Professor Medicine
Melissa Rogers, Ph.D., Associate Professor Microbiology, Biochemistry, and Molecular Biology	Yongkyu Park, Ph.D., Adjunct Assistant Professor Cell Biology & Molecular Medicine
Deborah A. Lazzarino, Ph.D. Assistant Dean for Research Office of Research	Ziad Sifri, Ph.D., Assistant Professor Department of Psychiatry
Charles Spillert, Ph.D., Associate Professor Surgery	Mariana S. DeLorenzo, Assistant Professor Cell Biology & Molecular Medicine
James Dermody, Ph.D., Adjunct Assistant Professor Microbiology, Biochemistry, and Molecular Genetics	Ming Xiong, M.D., Associate Professor Anesthesiology

INTRODUCTION

The Summer Student Research Program provides an eight-week research experience for the New Jersey first-second year medical students, as well as undergraduate students enrolled in our combined BS/MD seven-year program. Students are required to participate in research activities in a basic science or clinical laboratory. On many occasions this has been the students first research experience. Participation allows students, interns and volunteers to develop a close working relationship with their mentor.

After completing eight weeks of research in the respective laboratories, students present their research projects at the Summer Student Research Poster Symposium held the last week of July. At the symposium students are interviewed and required to explain the results displayed in their poster presentation. The abstracts preceding is a reflection of the commitment, dedication and enthusiasm of every student who participated in the Summer Student Research Program who presented at the 2015 Poster Symposium.

Congratulations to all the students, interns and volunteers enrolled in the 2015 Summer Student Research Program! Wishing you all the best and my you have continued success in your future endeavors!

Congratulations to Mr. Karl Hoegler and Mr. Naveed Kamal the winners of the 2015 Summer Student Research Poster Competition!

CELESTE AZEVEDO (NJMS 2018)

PROJECT TITLE: **NEUROMODULATION THERAPIES FOR ALCOHOL ADDICTION: A LITERATURE REVIEW**
MENTOR: **ANTONIOS MAMMIS, MD, PROFESSOR**
DEPARTMENT: **NEUROLOGICAL SURGERY**

OBJECTIVES:

Alcohol abuse is an ongoing societal issue, yet indicated treatments remain largely insufficient. The goal of this review is to look at alternative neurological therapies including transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), electroconvulsive therapy (ECT), and the off-label use of the $GABA_B$ receptor agonist Baclofen in the treatment of alcohol use disorder. The recent development of a class of small molecule therapeutic agents that act as positive allosteric regulators of the $GABA_B$ receptor ($GABA_B$ PAMS) is also briefly explored as a promising future treatment of AUD.

METHODS:

A comprehensive literature search was conducted through EBSCOhost regarding the neurological therapies in the treatment of alcoholism discussed in this paper.

RESULTS:

To date, few studies have been conducted with regards to these therapies in the treatment of alcoholism, sample sizes are consistently small, and long-term abstinence appears a common problem. tDCS has shown to temporarily reduce alcohol cravings but with a high number of long-term relapses, ranging from 50-70%. DBS and TMS, similarly, fail to overcome high rates of long-term relapse in patient samples. In one DBS study, for example, only 2 of 5 patients were able to remain abstinent. ECT does in fact seem to avoid this problem and accomplish long-term abstinence, but only a single patient case study exists to date. As such, no solid conclusions can be made regarding its success in the treatment of alcohol abuse. Baclofen however, implicated in studies with much larger patient samples by comparison and higher efficacy rates, presents with great promise in the treatment of AUD, particularly those with more severe forms. In one of the largest observational studies to date, including 100 subjects, 92% of patients reported experiencing craving suppression upon administration and long-term relapse rates were low. The side-effects of oral baclofen (i.e. somnolence, insomnia, dizziness, paresthesia, nausea, etc.) though, pose one of the principle limitations to its administration in alcohol addiction.

CONCLUSIONS:

Further investigation and additional data are needed on the subject. However, based on current information, it is our conclusion that intrathecal baclofen administration be the next logical therapeutic option to be explored, as it is already used to treat patients with spasticity with very few side effects. In particular, those patients who suffer from severe AUD and require very high doses of the medication may benefit from this treatment, as it eliminates the systemic side effects associated with oral baclofen.

Keywords: Alcohol addiction, Baclofen, Transcranial direct current stimulation, Transcranial magnetic stimulation, Deep brain stimulation, Electroconvulsive therapy

Conflicts of Interest: None to report.

Support for this publication was provided by the New Jersey Medical School Hispanic Center of Excellence, Health Resources and Services Administration through Grant D34HP26020

LAUREN CUE (NJMS 2019)

PROJECT TITLE: **REGULATION OF THE PRO-CALCIFIC BONE MORPHOGENETIC PROTEIN (BMP) 2**
MENTOR: **MELISSA B. ROGERS, PHD, ASSOCIATE PROFESSOR**
DEPARTMENT: **MICROBIOLOGY, BIOCHEMISTRY AND MOLECULAR GENETICS**

PARTICIPATION DESCRIPTION:

Unless otherwise indicated, all the methods and protocols outlined in this abstract were performed by Annica Tehim, the other summer research student, and myself. Dr. Rogers performed the majority of the theoretical planning of the experiments and established the breeding schemes for the mice with Youhua Zhu long before Annica and I started our work this summer. The litters were ready by the time we arrived and we monitored the individual mice until we determined that they were sick enough to be sacrificed. Dr. Rogers, Youhua Zhu, and Tapan Shah taught Annica and me the various lab techniques we used in this project. Specifically, Youhua taught me how to dissect the mice, while Tapan taught me how to use the sonicator and guided the performance of the Western Blot and its analysis. Throughout the summer, Annica and I performed calcium and protein assays using the plate reader; performed necropsies on mice to isolate the heart, aorta, lungs, and kidneys; homogenized tissue using a sonicator; homogenized tissue using Laemmli buffer; performed Western Blots; and fixed tissue for future analysis.

OBJECTIVE:

BMP2, bone morphogenetic protein 2, is an essential molecule that acts at a distance to influence cell behavior in various processes, from embryonic development to adult physiology and calcification pathologies; however, elevated levels of BMP2 in the vasculature and valves promote pathological calcification. Pathological calcification, the conversion of soft tissue cells to bone cells, is a key feature of atherosclerosis, calcific aortic valve disease (CAVD), post-angioplasty restenosis, diabetes, high cholesterol, and chronic kidney disease—which are all major causes of stroke, amputation, heart disease, and death (Heart Disease and Strokes Statistics – 2010 Update, American Heart Association). The severity of these health problems impels the study of regulatory mechanisms of BMP2 expression. Dr. Rogers' lab has discovered that an ultra-conserved sequence (UCS) in the 3'untranslated region (UTR) of BMP2 mRNA post-transcriptionally represses BMP2 in vasculature [1-3]. Therefore, we hypothesized that mechanisms that prevent BMP2 synthesis are impaired in calcification pathologies.

Deletion of the UCS

One of our aims in this project was to compare calcification in the aorta of klotho null mice that lack the UCS to that of klotho null mice with 1 UCS. The UCS is conserved across distantly related species, including mammals and fishes, suggesting that it is crucial for survival. The lab used Cre-recombinase/loxP deletion to delete the UCS, which results in a short (sh) allele (as opposed to the wild type allele, +). We hypothesized that deleting the BMP2 UCS induces BMP2 which promotes calcification.

Klotho null mice as a model of pathological calcification

We additionally aimed to develop an *in vivo* model of age-related pathological calcification, which we modeled using klotho null mice. The klotho protein is a key regulator of calcium levels and a key player in the vitamin D/phosphate/calcium pathway [1]. Therefore, klotho insufficiency causes premature aging and kidney disease. Reduced kidney function in turn promotes calcification of heart valves, aorta, and kidneys in humans and mice. In order to determine whether these mice would effectively model pathological calcification, we compared calcium and protein levels as well as protein expression in the aortas of klotho null mice (kl/kl) and control heterozygous mice (kl/+) that carried a LacZ BMP2 reporter transgene with the intact 3'UTR. In terms of calcium levels, we hypothesized that calcium should be elevated in tissue from klotho null mice relative to

the heterozygous control mice. In terms of protein expression, we hypothesized that BMP2 is induced in aorta of kl/kl mice relative to control. We expected that there would be greater levels of BMP2 and phosphorylated Smad1/5/8 (signaling component) in tissue from kl/kl mice.

METHODS:

Klotho null mice as a model of pathological calcification

When a klotho null homozygous mouse presented signs of nearing death (heavy breathing, ruffling of fur, decreased movement and grooming), we sacrificed the mouse along with a heterozygous control mouse from the same litter. We then removed the heart, aorta, and 2 kidneys from each mouse. We performed this procedure repeatedly throughout the summer, and allocated multiple sets of tissue for various assays: calcium assay, protein assay, and Western Blots. Ms. Youhua Zhu genotyped the DNA via PCR & Gel Electrophoresis. The klotho null mice (kl/kl) have 1 intense 850bp band, while the klotho heterozygous mice (kl/+) have 2 bands (850bp and 470bp). WT mice only have the 470bp band.

We used the Cayman Chemical Calcium Assay kit to quantify calcium levels in the aorta from +/sh, Kl/+; +/sh, kl/kl; +/sh, Wt; sh/sh, kl/+; sh/sh kl/kl; sh/sh, Wt mice. Tissue was homogenized in a PBS/Heparin solution via a sonicator in preparation for the assay and protein levels were measured with Bradford Reagent and a plate reader to normalize the data. We then determined levels of calcium per mg protein inBMP2 Klotho mice (± SEM. Aorta: +/sh, Kl/+ n=4; +/sh, kl/kl n=5; +/sh, Wt n=1; sh/sh, kl/+ n=10; sh/sh kl/kl n=6; sh/sh, Wt n=6).

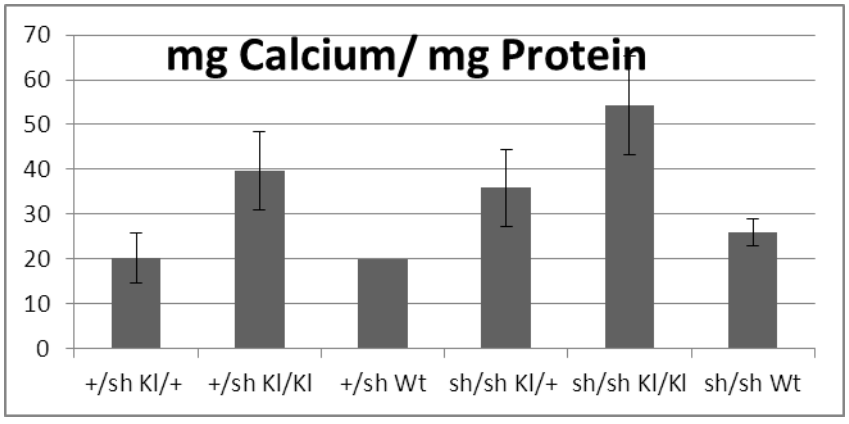
Guided by Tapan Shah, a PhD student in our lab, we performed a Western Blot on aortic tissue from pairs of kl/kl and kl/+ mice. We homogenized and lysed the tissue in PBS/Heparin via a sonicator. We then probed the resulting blots with anti-BMP2 and anti-phoshoSMAD (1/5/8) antibodies. We captured images of the probed blots using a GelDoc apparatus and then quantified the relative protein by obtained the relative band intensities using AlphaView Analysis Software. We normalized the relative band intensities to the levels based off of the lowest value in each dataset for BMP2 and pSMAD.

SUMMARY:

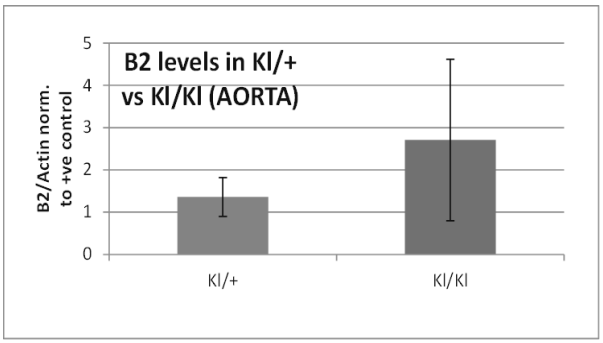
Klotho Mice as a Model for Pathological Calcification

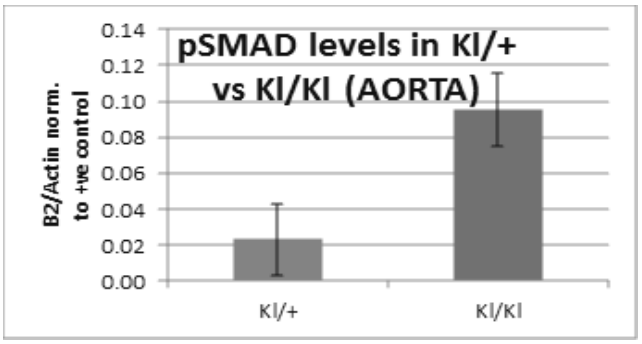
The control experiment confirmed that calcification is increased in Kl/Kl animals relative to heterozygous (+/Kl) animals. Additionally, calcium levels may be higher in sh/sh mice (those with a deleted BMP2 UCS) relative to those with an intact BMP2 UCS.

Average mg calcium per mg protein is shown below ± SEM



The Western Blots revealed the greater BMP2 and pSMAD levels in tissue from kl/kl mice (n=4). Relative signaling of BMP2 and pSMAD is shown below:





CONCLUSION:

Our hypothesis regarding increased BMP2 and pSMAD induction in the aorta of kl/kl mice relative to control heterozygotes was supported by the results of the Western Blot. Both BMP2, the protein of interest, and pSMAD, a protein involved in the same signal transduction pathway as BMP2, showed increased levels in tissue from kl/kl mice. However, our work is still in progress. Though the data gathered in this experiment demonstrates a trend, this trend was not statistically significant. The results of the calcium assay were similar in that they confirmed our hypothesis, but were not statistically significant. That is to say, though the control experiment confirmed increased calcification in Kl/Kl mice relative to heterozygotes (+/Kl) and suggested the possibility that calcium levels may be higher in sh/sh mice (those with a deleted BMP2 UCS) relative to those with an intact BMP2 UCS, these results were not statistically significant. This can be addressed by repeating both the Western blot and calcium assay several times with additional aliquots of sample from the same mice, or by repeating the experiment with new animals of the same genotype. Increasing the n value will yield results that are statistically significant and more accurate.

In sum, we have begun to establish that the klotho null homozygous mice function as an *in vivo* model of pathological calcification for studying regulatory mechanisms of BMP2. Though our hypothesis concerning the protein levels of BMP2 and pSMAD was confirmed by the Western Blot data, the experiment must be repeated to obtain statistically significant results. Furthermore, we demonstrated via calcium assays that the aorta tissue of kl/kl mice was more calcified than the tissue of kl/+ mice, and that calcium levels may be higher in sh/sh mice relative to those with an intact BMP2 UCS. This suggests not only that klotho mice serve as a good *in vivo* model of pathological calcification, but also that deleting the BMP2 UCS induces BMP2 which promotes such calcification. Having developed this model, we hope to study miRNAs predicted to bind the BMP2 3'UTR [4,5]. The regulatory proteins and miRNAs that mediate UCS-mediated repression may be reduced by the abnormal physiology associated with kidney disease, such as that exhibited by the klotho mice. Restoration of normal levels and function may pharmacologically reduce BMP2 repression in tissues undergoing pathological calcification in a clinical setting.

References:

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SOFIA GILELS (NJMS 2018)

PROJECT TITLE: ENDOSCOPIC ENDONASAL TRANSSPHENOIDAL REMOVAL OF RECURRENT PITUITARY AND PARASELLAR TUMORS
MENTOR: JAMES K. LIU, MD , ASSISTANT PROFESSOR
DEPARTMENT: NEUROLOGICAL SURGERY AND OTOLARYNGOLOGY-HEAD AND NECK SURGERY, CENTER FOR SKULL BASE AND PITUITARY SURGERY

OBJECTIVE:

The goal of the research was to assess the post operative results of patients undergoing endoscopic endonasal transsphenoidal skull base surgery for removal of recurrent pituitary and parasellar tumors. The patients studied in this research had all previously undergone previous transsphenoidal surgical treatment. The initial surgical operation of the patients was either a microscopic or endoscopic approach.

METHODS:

Patient files from the cases conducted by Dr. Liu were analyzed first to compile a data set of patients that underwent the surgical procedures outlined by the parameters of the study. The patient information was grouped by age, sex, preliminary surgical procedure as well as by the specific surgery performed. Consequently, the data assessment included analysis of the subsequent outcomes of the specific surgeries to include relevant post operative measures.

SUMMARY:

Patient data was assessed with focus on the following: post op outcomes, complications, investigation into primary surgical approach, assessment of outcomes across a variety of tumor types, functional patient improvements or areas of deficient.

This study compared the results of surgical outcomes following the removal of recurrent pituitary and parasellar tumors using an endoscopic endonasal transsphenoidal skull base approach. The patients analyzed were operated on by a multi-disciplinary skull base team comprised of a neurosurgeon and otolaryngologist.

CONCLUSION:

The endoscopic endonasal approach is a safe and viable approach for removing recurrent pituitary and parasellar tumors in patients who have previously undergone an endonasal approach (microscopic or endoscopic). It was noted that patients who underwent prior microscopic transsphenoidal surgery consistently had smaller sphenoidotomies, smaller bony sellar openings, and more residual tumor. Vascularized nasoseptal flap repair was effective in preventing postoperative CSF leakage.

Thirty-one patients were included in this study. 13 male and 18 female patients that averaged 54 years old. Amongst them, 21 were patients that underwent pituitary resection and 3 each underwent craniopharyngioma and meningioma surgical removal. There was 1 patient diagnosed with juvenile nasopharyngeal angiofibroma, 1 chordoma, 1 CSF leak and 1 with Rathke's cleft cyst. Of all 31 patients there were no complications with the surgery, and only 1 patient suffered from visual deficits.

LEANDRO GUTIERREZ (NJMS 2018)

PROJECT TITLE: **SUBNORMAL LEVELS OF GM1 GANGLIOSIDE IN COLON OF PARKINSON'S DISEASE (PD) PATIENTS SUPPORT THE CONCEPT OF SYSTEMIC GM1 DEFIENCY AS MAJOR ETOLOGIC RISK FACTOR IN IDIOPATHIC PD**

MENTOR: **ROBERT LEDEEN, PhD, PROFESSOR**

DEPARTMENT: **NEUROLOGY AND NEUROSCIENCES**

PARTICIPATION DESCRIPTION: I was involved in the preparation of colonic tissue samples, 11 PD and 11 age matched controls (non-PD). The preparation was followed by isolation, extraction and chromatography procedures in the attempt to detect lipid from the samples. The total duration of the procedures approximated 3-4 days; of which were performed for each set of samples consisting of 2 PD and 2 controls. I also developed the radiographic films to visualize the presence of ganglioside as bands; this was performed last. Often the procedures had to be repeated for various sample sets to validate previous results of the same sets. The quantification process was performed by a PhD student and me. The PhD student had previous knowledge on quantification and much of what I learned from this part of the research was from this individual.

OBJECTIVE: In contrast with familial Parkinson's disease (PD), sporadic PD has no known etiology. The purpose of this study is to explore the role of GM1 ganglioside in the onset of non-motor symptoms of sporadic PD. GM1 deficiency was modeled using genetically altered mice containing either one or two copies of mutated *B4galnt* 1 gene. Interestingly, it was heterozygote mice that experienced similar motor and non-motor (autonomic) symptoms and provided a superior model for PD. This suggested that PD patients could have experienced a systemic reduction in GM1 prior to onset. This is supported by findings in the substantia nigra and occipital cortex of PD patients demonstrating a deficit of GM1. GD1a, a metabolic precursor of GM1 was also reduced in the same areas of the brain of PD patients. Human colon tissues have now been analyzed in this summer project and found to manifest a similar deficiency in GM1 and GD1a. Colon tissue samples from PD patients and age matched controls were obtained from a tissue bank and analyses carried out for GM1 and GD1a. The results show that there is a significant reduction of GM1 and GD1a in colon tissues from PD patients when compared to age-matched controls. It was important to realize that GM1 (and GD1a) being deficient globally could account for the motor and non-motor symptoms of PD. It has been established that GM1 decreases gradually over age; however an abnormal reduction could place an individual below the GM1 threshold level and put them at risk for PD.

METHODS:

Preparation of Samples

11 PD and 11 age-matched control colon tissue samples were used. Each of the samples weighted approximately 50mg. The samples were mechanically lysed using shears until the tissue matter was suspended diffusely. Each sample was transferred into 10mL test tubes. Final volume of the samples was adjusted by adding chloroform/methanol/water(including tissue) (5:5:1), to extract lipids including gangliosides. Lipid was extracted with occasional sonication for 2 hours. The sample was then spun at 2300 rpm for 10 minutes. The resulting lipid supernatant was transferred into separate 10 mL test tubes. To each resulting pellet, 1mL of chloroform/ methanol (1:1) was added for re-extraction. The remaining supernatant was pooled to the previous one and stored. To each pellet, 3mL of SDS/1N NaOH (1:1) was added and allowed to sit for 24 hours for protein assay. The Lowery assay was carried out to determine total protein in each sample.

Thin Layer Chromatography and Densitometry

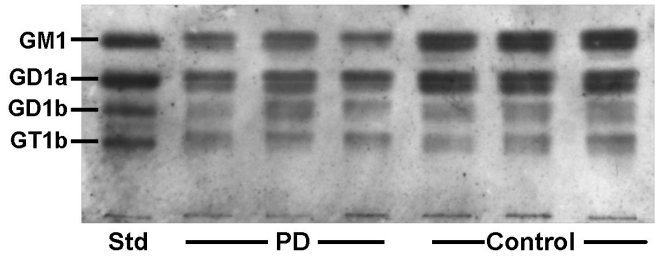
A 10X20 cm TLC plate was used. Lipid samples equivalent to 50µg protein from each sample were applied. Brain bovine gangliosides (BBG) were applied on the same plate as the standard. The TLC plate was placed within a closed vessel with approximately 150mL of chloroform/methanol/KCl (10:8:2) mixture and allowed to develop for an hour. The plate was treated with poly (isobutyl methacrylate) dissolved in chloroform/ hexane (1:8).

The following steps were followed in succession; acetic acid buffer bath for an hour, neuraminidase (0.4 units/mL) in acetic acid buffer for 2.5 hours, two washings with phosphate buffer saline solution (PBS) for 10 minutes, washing with 0.2g/mL solution of dry milk in PBS for 20 minutes, treatment with 0.5ng/1mL of cholera toxin subunit B-HRP solution in PBS for 1 hour and lastly two washings for 10 minutes with PBS. The plate was treated with Amersham ECL Western blotting detection reagents and exposed to radiographic film in a dark room. The developed ganglioside bands on the film were analyzed using densitometry, where the intensity of the darkness of each band was quantified according to BBG standards. A double-tailed Student t-test was used to determine significance in the difference between the PD and the control samples.

SUMMARY:

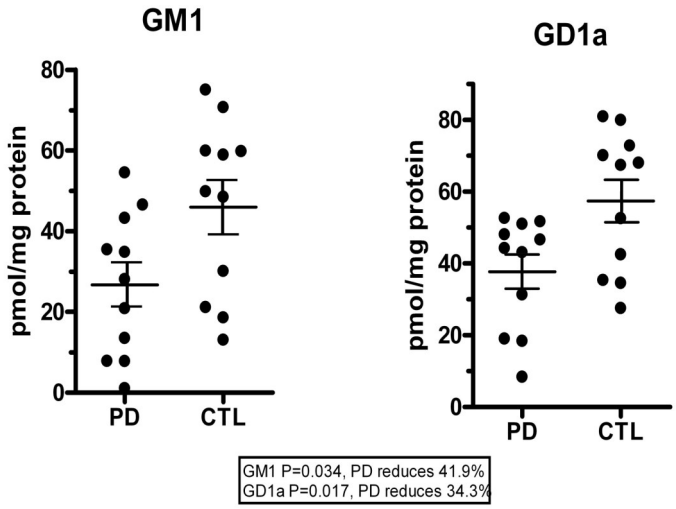
Several PD and control samples were grouped into one TLC plate. After development, the generated bands were observed on a photographic film. Visual analysis determined a difference in darkness intensity between the PD and control ganglioside bands as evident in figure 1. Three lanes were dedicated to standard ganglioside, bovine, applied at three distinct concentrations; this is not shown in figure 1. All the bands underwent densitometry, where darkness intensity was related to concentration of ganglioside.

Figure 1:



Following densitometry a standard curve was generated using the standard bands, from which the concentrations of gangliosides in the PD and control samples were calculated. All concentrations were plotted, Figure 2. The width of each of the data sets, particularity for GM1, was relatively large. Generally the average values of PD and control for GM1 did effectively differ, PD being less than control. There was a 41.9% reduction in GM1 ganglioside in PD samples as compared to control samples. The same pattern was observed for GD1a; a 34.3% reduction was observed in PD samples. P-values were calculated to determine whether the reduction percentages were significant. For the GM1 data sets P=0.034 and for the GD1a data sets P=0.017. Both values were below 5% and therefore it was considered that the reduction in both GM1 and GD1a should be defined as significant. For extensive purposes, the width of the data sets indicated the need for more samples and more data collection.

Figure 2:



CONCLUSION: The current study showed significant reduction in GM1 and GD1a in colon tissue of PD patients correlated with the non-motor symptom of constipation. These results are also consistent with the findings in the occipital cortex and SNPC, thus suggesting a systemic deficiency of GM1 and GD1a ganglioside as a risk factor of PD. This would make way for the development of methods to counteract significant depletion of corresponding ganglioside. The molecular mechanism of GM1 involved in neuro-protection is demonstrated in previous studies, GM1 is a co-modulator of the GDNF receptor complex. The GDNF complex is intimately involved in the viability of catecholaminergic neurons. Therefore death of said neurons, as a result of comprised GDNF receptor complexes from GM1 deficiency, in the colon of PD patients manifest as autonomic dysfunction .GM1 ganglioside has been used in clinical trials to treat PD patients and indicates administration of GM1 as a possible route of treatment for PD.

STEPHEN HANNAFORD (NJMS 2018)

PROJECT TITLE: **SYMPTOMATIC THROMBOSED DEVELOPMENTAL VENOUS ANOMALY**
MENTOR: **KRISHNA AMULURU, MD, HOUSESTAFF PGYVIII**
DEPARTMENT: **NEUROLOGICAL SURGERY**

PARTICIPATION DESCRIPTION:

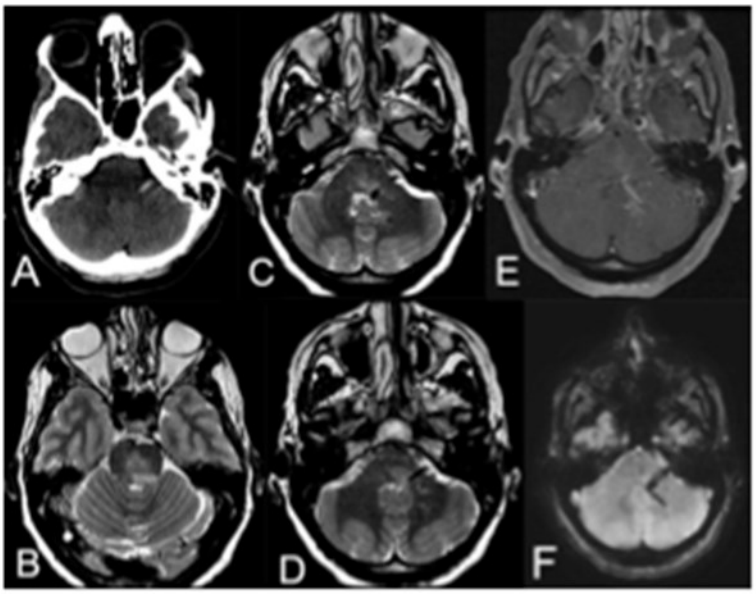
My participation in the case report included attending weekly research meetings with the Department of Neurological Surgery at University Hospital during which I would share my findings, and receive feedback and instruction from my faculty advisor. In collaboration with Dr. Amuluru, I conducted a review of the patient's medical record, including multiple imaging studies. I also conducted a review of the relevant neurosurgical, neurological, and radiological literature, which was integrated into the introduction and discussion sections of the report and poster presentations.

OBJECTIVE:

The objective of this research was to produce a case report concerning a patient who presented to the Neurological Surgery Department at University Hospital Newark with a rare cerebrovascular condition known as a symptomatic thrombosed developmental venous anomaly. Although developmental venous anomalies (DVAs) are known to occur with relative frequency in the population, it is rare that they should become symptomatic; in the vast majority of people, they simply provide normal venous drainage for a region of the brain. Symptoms may develop as a result of flow-related pathology such as occlusion (as in this case), or due to mechanical phenomena such as impact on neighboring nervous tissue.

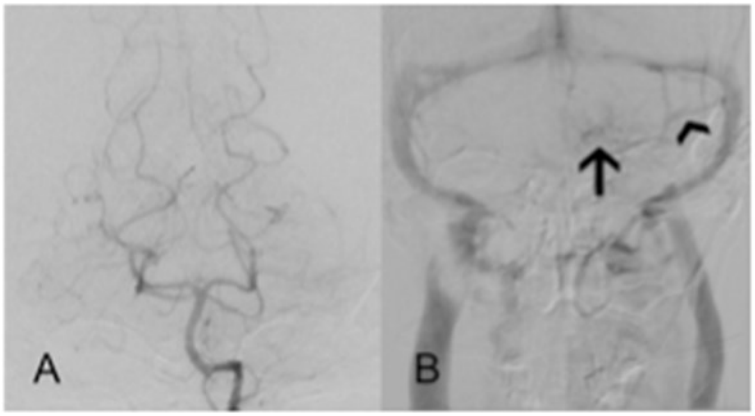
In our patient's case, computed tomography, magnetic resonance imaging, and angiography **(Figs.1&2)** showed that the DVA was located in both the cerebellum and pons, which along with its pattern of drainage, represented an uncommon presentation. Furthermore, the patient did not possess a cavernous malformation, which is a frequent co-occurrence with DVAs that become symptomatic. The presence of a cavernous malformation would have presented a risk for hemorrhage that may have precluded the use of anticoagulant drugs in the treatment of the patient's symptoms. The patient was thus treated with steroids and anticoagulants, and saw complete resolution of their symptoms. Due both to its rare anatomical location and presentation, as well as the successful treatment, the case warranted reporting to relevant journals of neurosurgery and interventional radiology. The report was to encompass the presentation, use of imaging modalities, treatment, outcomes, and relevant discussion about the case.

Figure 1



(A) Non-contrast CT scan of the head showing hyperdense vessel in the left cerebellopontine angle cistern. (B-D) Axial FLAIR sequences demonstrating increased signal in the pons extending caudally to involve the left middle cerebellar peduncle and dorsal medulla representing venous congestive edema. (E) Post contrast T1 sequence showing several enhancing vessels converging onto a large collecting vein draining into the vein of the lateral recess with increased susceptibility on (F) Axial 3D SWAN sequence representing thrombosis.

Figure 2



(A) Left vertebral artery angiogram showing no arterial nidus or early venous opacification. **(B)** Late venous phase of same showing infratentorial DVA(**arrow**) draining into the vein of the lateral recess (**arrowhead**).

METHODS:

In order to achieve the objectives of the symptomatic DVA case report, a thorough review of the patient's medical record was conducted. The information from the patient's record was integrated into the case presentation and treatment sections of the report. In addition, a thorough review of the literature on DVAs, symptomatic DVAs, venous drainage of the head, imaging of vascular malformations and cerebral venous thrombosis, and treatment of cerebral venous thrombosis – among other relevant topics – was conducted. This review was integrated into the introduction and discussion sections of the case report. Electronic and physical poster presentations based on the case report were also created. The review of the patient's medical record and the relevant literature, as well as the composition of the case report and poster presentations were all conducted with guidance and oversight by the faculty advisor, Dr. Amuluru.

SUMMARY:

In collaboration with Dr. Amuluru, the case of a symptomatic, thrombosed, cerebellopontine DVA was reviewed and reported upon. In addition, the relevant literature was consulted and integrated into the discussion of the case. An electronic poster was submitted to and accepted by the Society of Neurointerventional Surgery. The case report is still in the final editing process, and we anticipate submission to relevant publications during the Fall of 2015.

CONCLUSION:

This case provided an excellent subject for an instructive report on the treatment of a rare cerebrovascular condition. The report and poster should contribute to the body of literature on symptomatic DVAs and prove useful for those in the fields of neurology, neurosurgery, and neurointerventional radiology.

KARL HOEGLER (NJMS 2018)

PROJECT TITLE: **ASSESSMENT OF THE RELATIONSHIP BETWEEN SPATIAL NEGLECT AND MEMORY**
MENTOR: **ANNA M. BARRETT, MD, PROFESSOR**
DEPARTMENT: **PHYSICAL MEDICINE AND REHABILITATION**

PARTICIPATION DESCRIPTION:

For my summer project, I audited the data, performed statistic analysis using SPSS and Excel, and interpreted the results. Before doing the statistical analysis, I audited all of the data that was in the study. Auditing the data means that I had to ensure that all of it was inputted into the spreadsheet correctly and double check all of the total scores. During my summer project, Dr. Barrett and I met once a week to discuss how the project was progressing and the next step. In addition to working on the project, I observed the weekly neurology rounds at Kessler and was certified to perform the Kessler Foundation- Neglect Assessment Protocol for the Catherine Bergego Scale. I also learned how to administer and score the Behavioral Inattention Test and the Florida Mental Status Exam.

INTRODUCTION:

Spatial neglect is the failure to orient, respond to, or report stimuli in the contralesional space after a brain injury that is not explained by primary sensory or motor deficits. Neglect is an area of interest for clinicians and scientists because it occurs in approximately 50% of right hemisphere stroke survivors and is associated with increased family burden, longer average length of hospital stay, and greater requirements for assistance.[1]

A promising rehabilitative method for people with neglect is prism adaptation treatment (PAT), movement training sessions wearing prism goggles that displace vision 10-12 degrees horizontally. Initially, they misdirect their hand in the direction of the optical shift, but after multiple attempts their error is reduced. After removing the goggles, pointing error temporarily reverses direction, a phenomenon termed the aftereffect.[2] Improvements in neglect may last for one to three months. Recently, Chen *et al*. suggested that neglect patients who do not have lesions in the medial temporal lobe might be the best PAT candidates.[3]

The medial temporal lobe plays a critical role in acquiring two kinds of memory, declarative memory and motor learning.[4,5,6] Declarative memory is memory available as conscious recollection that can be brought to mind as an idea, sound, image, sensation, odor, or word.[7] Motor learning is a form of implicit, nondeclarative, memory that operates outside of awareness and is expressed through performance rather than conscious recollection.[8] It has been reported that disruptions in memory can occur following a unilateral right hemisphere stroke. Specifically, Cherney *et al*. observed that patients with a right hemisphere stroke presented with impairments in immediate and delayed verbal memory on the California Verbal Learning Test (CVLT). They also found that the patients had a decreased rate of learning across the CVLT trials.[9] Taken together, these findings suggest that memory and spatial function may interact.

OBJECTIVES:

We investigated whether memory impairment is associated with spatial neglect following a stroke. To investigate memory's relevance to stroke recovery, we examined the relationship between motor learning and neglect severity.

METHODS:

Participants

We examined behavioral data for 240 participants (121 males, 117 females) with left neglect following a stroke who took part in neglect research from 2008-2015. Most of the participants spoke fluent English (n=215). The mean age was 66.83 (SD=14.67), and the mean years of education was 13.49 (SD=3.18).

During this ongoing research, 15 (8 males, 7 females) of the 240 participants participated in the Prism Adaptation Treatment for Spatial Neglect. All of the patients spoke fluent English. The mean age was 61.13 (SD=15.17), and the mean years of education was 15.37 (SD=2.26).

Procedures

For all 240 participants, two tests were used to determine the severity of spatial neglect, and one instrument was used to evaluate memory. For the group of fifteen participants, motor learning was measured during treatment.

Kessler Foundation-Neglect Assessment Process for the Catherine Bergego Scale (CBS). A rater observes a patient performing 10 basic daily activities (e.g. eating, grooming, and dressing), and scores them from 0 to 3, where 0 indicates no neglect and 3 indicates severe neglect. A score of $\leq$25 was used to define spatial neglect on this assessment.[10]

Behavioral Inattention Test (BIT). The BIT includes six tests, line crossing, letter cancellation, star cancellation, figure/shape copying, line bisection, and representational drawing, and is scored from 1 to 146, where higher scores indicate better function. A cutoff score of < 130 was used to define spatial neglect on this assessment.[11]

Florida Mental Status Exam (FMSE). The FMSE includes multiple components of mental status, such as attention, memory, and visuospatial. It also includes the Hopkins Verbal Learning Test. Points are earned by successfully completing a task, and partial credit is given. Higher scores indicate better function.

Prism Adaptation Treatment (PAT). During PAT, the participants wore prismatic lenses that displaced their vision 10-12 degrees horizontally and made repeated movements in the center, right, or left space with their hand and arm obscured from view except for the final few degrees of movement. Following treatment, the participants' error from the center of the object was measured. Zero is marked at the center of the object. A positive score indicates deviation to the right, while a negative score indicates deviation to the left (relative to the patient).

Data Analysis.

Objective 1. In order to assess the relationship between memory and neglect, a total memory score was compiled from the Hopkins Verbal Learning Test Immediate Recall (HVLT-IR), Orientation, Short-term and Long-term Recall from the FMSE and correlated with CBS Total Correct scores and BIT Total scores using SPSS software. Additionally, a principal component analysis with a promax rotation was performed to determine the underlying factors among the BIT, CBS, and memory items.

Objective 2. In order to further investigate the relationship between memory and neglect, we examined whether patients with neglect have impaired motor learning by comparing motor learning speed with neglect severity.

SUMMARY:

Objective 1. Correlation. We observed a significant relationship between CBS Total Correct score and **Memory** (r = .35, p = .01). Similarly, there is a significant relationship between BIT Total score and **Memory** (r = .48, p = .01). Taken together, these two findings show that as memory declined, the severity of neglect increased, and vice versa. Although for the group this relationship between neglect and memory is strong, it does not apply to every patient. As observed in the graphs, some of the patients with the best memory had neglect, while some of the patients with an impaired memory had no neglect.

Factor Analysis. In order to determine the underlying factors among the BIT, CBS, and memory item scores, we performed a principal component analysis with a promax rotation. Since the factors were intercorrelated, we decided to use a promax rotation (Table 1). In the analysis, three factors were extracted that accounted for 66.3% of the variance. All of the variables had primary loadings over .5, while none of them had a cross-loading above .3. Items from each of the tests loaded onto one particular factor. For example, all of the CBS items loaded onto factor 1, while all of the BIT items loaded onto factor 2 (Table 2). This indicates that none of the items behave as if they could be included on more than one test.

Factor Correlation Matrix

Factor	1	2	3
1	1.00	-.63	-.34
2	-.63	1.00	.44
3	-.34	.44	1.00

Table 1. Factor correlation matrix showing that the three factors extracted are intercorrelated.

Pattern Matrix[a]

	Factor		
	1	2	3
BIT: Line Total	-.11	**.80**	.00
BIT: Letter Total	-.05	**.80**	.11
BIT: Star Total	-.07	**.83**	.06
BIT: Figure/Shape Copying	.04	**.89**	-.07
BIT: Line Bisection	-.02	**.85**	-.15
BIT: Representational Drawing	.08	**.74**	.16
CBS: Dressing	**.80**	-.03	.03
CBS: Grooming	**.84**	.17	-.12
CBS: Gaze Orientation	**.79**	-.05	.17
CBS: Limb Awareness	**.76**	-.08	.09
CBS: Auditory Attention	**.77**	.02	-.01
CBS: Collisions	**.76**	-.05	.05
CBS: Navigation	**.73**	-.11	-.04
CBS: Difficulty Finding Belongings	**.69**	-.18	.00
CBS: Eating	**.81**	-.11	.00
CBS: Cleaning After Meal	**.82**	.18	-.18
FMSE: HVLT-IR	.10	.19	**.77**
FMSE: Orientation	-.00	.26	**.54**
FMSE: Short-Term Recall	-.05	-.18	**.89**
FMSE: Long-Term Recall	-.03	-.04	**.81**

Table 2. Factor loadings based on a principal components analysis with promax rotation for 6 BIT, 10 CBS, and 4 memory variables. [a]Rotation converged in 5 iterations

Objective 2. A correlation between verbal memory and spatial function suggests that motor memory and the speed of motor learning might also be influenced by spatial neglect. To determine whether patients with more severe neglect demonstrated less motor learning during prism adaptation, we computed two comparisons. First, we divided patients into those with decreasing errors (good motor learning) and those whose errors increased over the sessions (poor motor learning), and compared spatial neglect scores between these groups. Those with good motor learning had less neglect (CBS mean = 9.84) than those with poor motor learning (CBS mean = 12.41, Mann-Whitney U, one-tailed $p < 0.05$). Similarly, the rate of motor learning (error slope) tended to be correlated with CBS score (Spearman's rho = 0.36, $p < .10$) There was no difference, however, in BIT scores between patients with good and poor motor learning (Good motor learning BIT mean = 89.87; poor motor learning BIT mean = 62.93; Mann-Whitney U, one-tailed $p = .45$, n.s), and BIT scores were not correlated with the rate of motor learning (error slope; $p = 0.70$, n.s.).

Eight patients who received prism adaptation therapy had the HVLT completed. Consequently, we were able to evaluate the rate of verbal learning in this group by calculating the slope of the best-fit line for each participant's HVLT Immediate Recall Trials. We observed that the person with the lowest slope (whose memory did not improve at all over the three trials) had the lowest CBS Total correct score, i.e. the worst neglect, while the person with the steepest slope (best learning) had the highest CBS Total Correct score, i.e. the least neglect. The others were intermediate.

CONCLUSION:

Objective 1. As others have reported[12,13,14], we found that memory was impaired following a right hemisphere stroke. We also found that memory impairment is directly related to neglect severity. This relationship suggests that memory and neglect may be drawing on the same neural substrates, i.e. the medial temporal lobe. Although the medial temporal lobe is involved with memory and possibly neglect, the specific

neural networks that involve memory and neglect are probably different. Although there is a strong relationship between neglect and memory for the entire group, the relationship is not significant for individuals. Some of the patients who had the best memory had moderate neglect. Future research could evaluate medial temporal lobe activation during memory and spatial function tasks using fMRI and brain connectivity parameters.

Objective 2. The Spearman correlation and Mann-Whitney U test suggest that motor learning is also related to the severity of spatial neglect. This is important clinically, because stroke rehabilitation's goal is to increase the accuracy of patients' motor tasks. Therefore, if patients' motor learning is decreased, they may need to remain in therapy longer. Future research could evaluate how other forms of implicit, automatic learning are related to neglect because these functions are important in daily life. Additionally, it will be interesting to further evaluate the relationship between the rate of verbal learning and the severity of spatial neglect.

Acknowledgements/Disclosures:

We thank Jenny Masmela for being the research coordinator on the neglect research projects and maintaining the datasets; the project scientists, Kelly Goedert, PhD, Peii Chen, PhD, Mooyeon Oh-Park, MD, PhD, and Cristin McKenna, MD, for planning and executing the neglect research study operations; and the research assistants for collecting the data. We also thank Peii Chen, PhD for reading and commenting on a previous version of the results, which inspired an additional analysis.

No disclosures apply. This work was funded by the National Institutes of Health/NICHD/NCMRR, Rutgers-New Jersey Medical School, Kessler Foundation, Healthcare Foundation of New Jersey, Wallerstein Foundation for Geriatric Life Improvement, and National Institute on Disability, Independent Living, and Rehabilitation Research.

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RYAN HOLLAND (NJMS 2017)

PROJECT TITLE: **PUBLIC INSURANCE USAGE AND DIFFERENCES IN LENGTH OF STAY FOR CERVICAL FRACTURE PATIENTS RECEIVING SPINAL FUSIONS**

MENTOR: **RACHID ASSINA, MD, ASSISTANT PROFESSOR**
DEPARTMENT: **NEUROLOGICAL SURGERY**

INTRODUCTION:

The cervical spine consists of seven vertebrae and can be fractured in motor vehicle accidents, neck injuries, or other types of trauma. There is a bimodal distribution for the age of patients with these fractures with the first peak between 15-24 years old and the second in patients over 55. Classifying the specific vertebrae that are fractured helps to ensure appropriate treatment. Some of these patients are indicated to receive spinal fusions. This operation creates a solid union between two or more vertebrae in order to improve spinal stability. Accurately predicting patient length of stay following surgery allows hospitals to effectively manage resources and increases efficiency of patient care. This study assessed the proportion of these patients that used public insurance (Medicaid or Medicare) and the association between using public insurance and total length of stay at the hospital.

METHODS:

Discharge data for patients with Diagnosis-Related Groups (DRGs) 471-473 was obtained from the 2008-2011 Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. These DRGs are for cervical spinal fusions. All patients in this analysis had elective surgeries. Further selection occurred for patients with closed cervical fractures. The associated ICD-9 diagnostic codes were 805.01-805.07 (closed fractures of C1 to C7, respectively). The variables studied were insurance type and length of stay. Insurance type was divided into Public Insurance (Medicaid and Medicare) and Private Insurance. All data was weighted using HCUP's algorithm for estimating discharges for all hospitals nationwide. National Census data was obtained for years 2008-2011 in order to compare the proportion of publicly insured patients with these diagnoses with the proportion of insured patients that use publicly funded insurance in the general population. SPSS and Microsoft Excel were used to summarize and graph the data. A linear regression analysis was used to compare the proportion of each ICD-9 group that used public insurance and the mean length of stay for that same group.

Results:

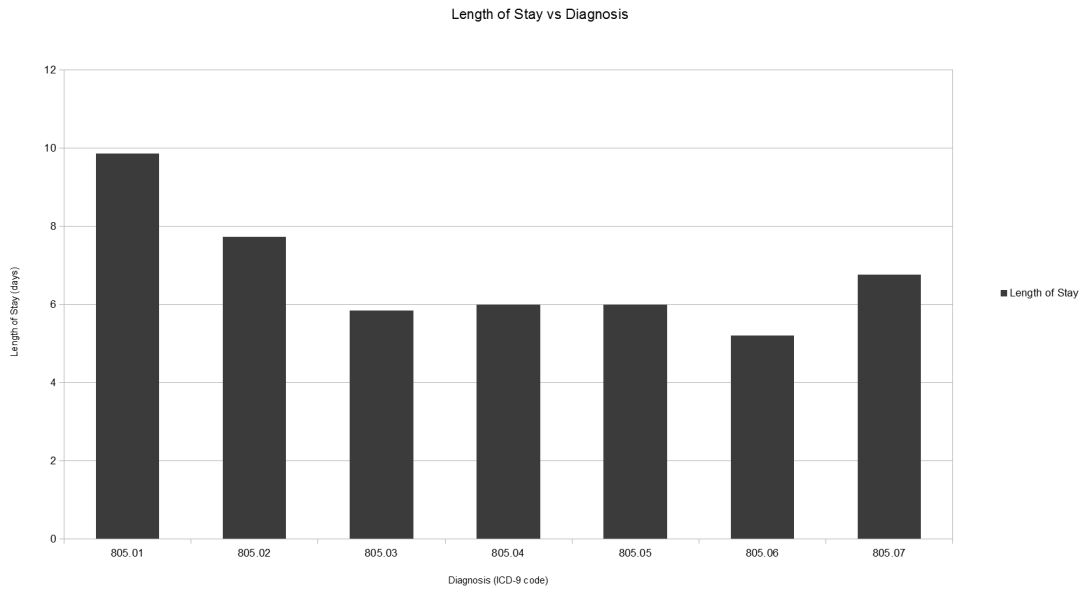

Figure 1: Mean Length of Stay for patients with each specific cervical vertebrate fracture following spinal fusion.

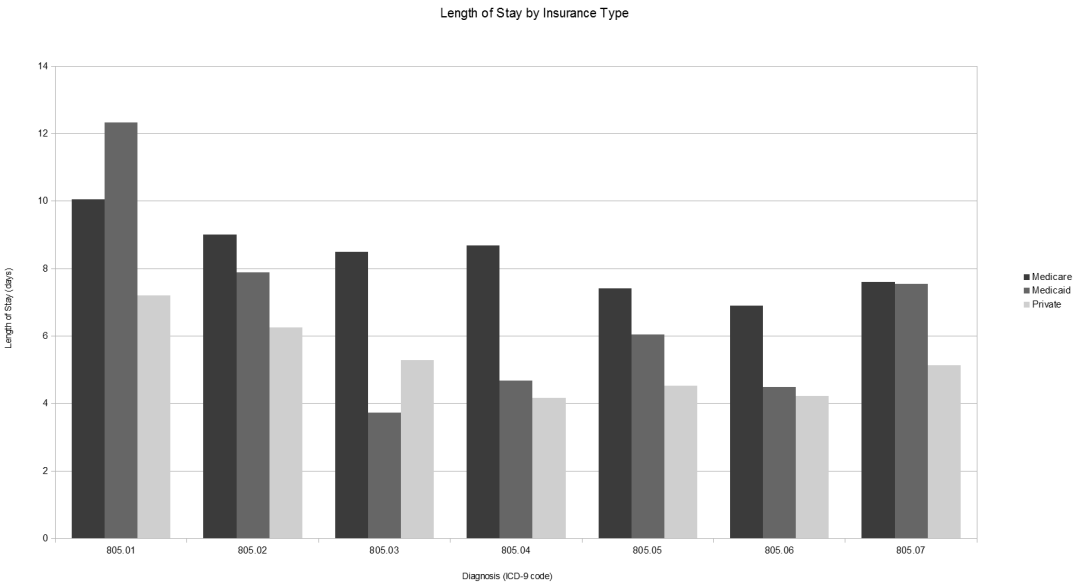

Figure 2: Mean Length of Stay categorized by specific fracture and insurance type.

Diagnosis	% Publicly Insured
805.01	69.1
805.02	70.5
805.03	40.3
805.04	38.1
805.05	38.5
805.06	32.2
805.07	32.1
CENSUS	31.3

Table 1: Percentage of publicly insured (Medicare or Medicaid) patients for each cervical fracture compared to general population according to Census data for given years.

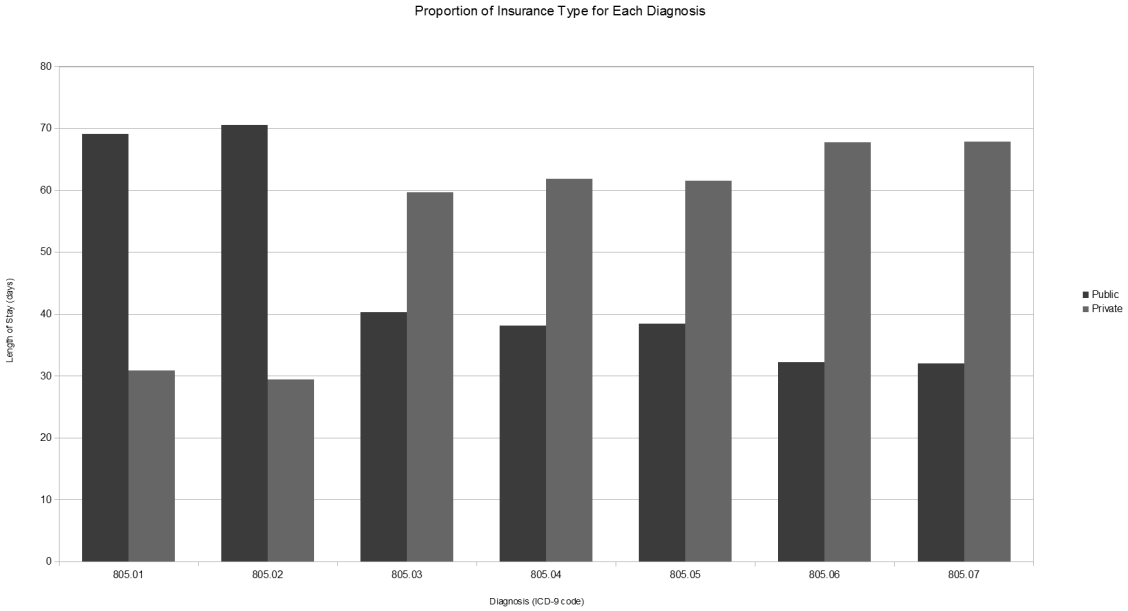

Figure 3: Proportion of insurance type (public vs private) for each specific cervical fracture.

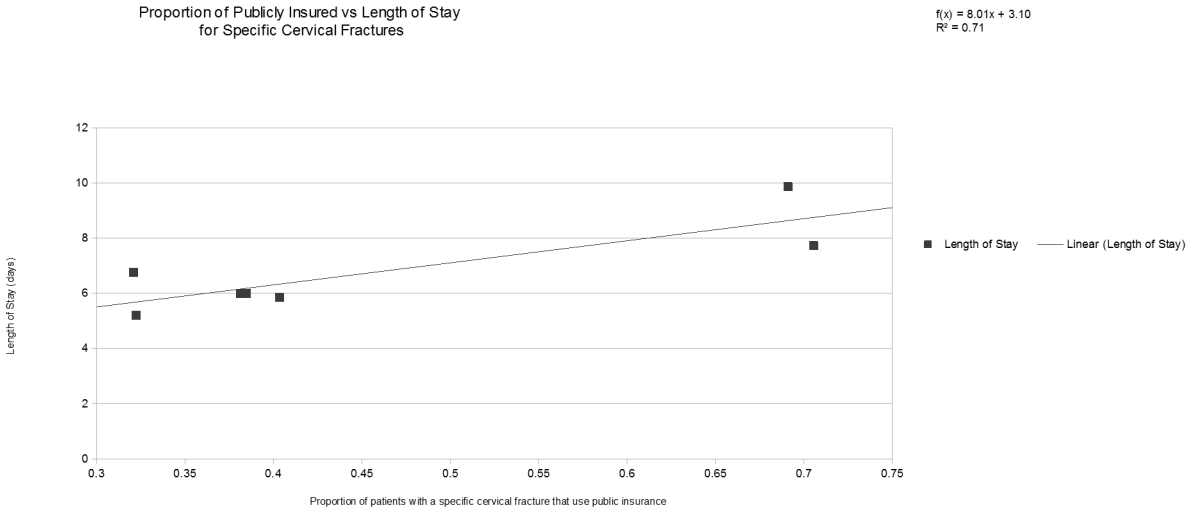

Figure 4: Linear model of length of stay vs proportion of publicly insured cervical fracture patients.

DISCUSSION:

There was a wide range in lengths of stay for patients with closed cervical fractures. Means fell between 5.2 and 9.9 days depending on which cervical vertebrate was fractured. All of the diagnoses had a greater proportion of publicly insured patients compared to the general population according to the US Census for the given years. Furthermore, patients with C1 or C2 fractures had the longest lengths of stay and also the greatest proportion of publicly insured patients. A linear regression analysis showed a direct correlation (R-squared = .71) between the percentage of patients with each diagnosis that used public insurance and their length of stay.

CONCLUSIONS:

Because of the variance in length of stay among patients with closed cervical fractures that received spinal fusions, it may be beneficial to stratify data by specific ICD-9 codes before analysis. Fractures of each vertebrate should be analyzed independently. Because the diagnoses with the longest lengths of stay also had the highest proportion of publicly insured patients, those without private insurance may present a particularly high burden on hospital resources. The proportion of publicly insured patients for a given group with the same ICD -9 code was directly correlated to how long they stayed at the hospital. This relationship may be useful when assessing how to best manage hospital resources.

NAVEED KAMAL (NJMS 2018)

PROJECT TITLE: **THE ROLE OF FIESTA MRI FOR ASSESSMENT OF DELAYED ENHANCEMENT OF FAT GRAFT PACKING ON POST-OPERATIVE IMAGING AFTER ACOUSTIC NEUROMA SURGERY**

MENTOR: **JAMES K. LIU, MD, ASSISTANT PROFESSOR**

DEPARTMENT: **NEUROLOGICAL SURGERY**

PARTICIPATION DESCRIPTION:

I worked with Dr. James Liu, M.D. to evaluate the efficacy of FIESTA imaging for fat graft analysis on 20 patients after they underwent acoustic neuroma resections. I completed a literature review on postoperative imaging post acoustic neuroma resection. I was responsible for developing the image sets and organizing the data for all patients after retrospective chart review. I also went through the first pass of data interpretation by analyzing the radiographs. Dr. Liu then went through another pass interpreting the images to catch any errors in radiograph analysis. Lastly, I wrote the discussion and created a poster for this study to be presented at the NJMS SSRP poster symposium.

OBJECTIVE:

The goal of this study was to show the utility of FIESTA imaging in conjunction with Contrast T1 MRI with fat suppression for the assessment of fat grafts. We compared image sets and reported the clinical indication of FIESTA imaging after seeing enhancement on the contrast MRI.

METHODS:

We identified 20 patients who underwent retrosigmoid and translabyrinthine acoustic neuroma resection from 2009-2015 at University Hospital. Patients who had at least two sets of imaging were included in the study. Radiograph images were collected at different time points: preoperative, Immediate postoperatively (24-48 hours), 3-6 months postoperatively, and yearly postoperatively (if available). The image sets contained T1, T2, Fat Suppressed T1 with Gadolinium, and FIESTA. The radiographs were analyzed for postoperative enhancement on the fat suppressed T1-weighted image. Then, they were compared with the T2 and FIESTA images.

SUMMARY:

All of the patients exhibited delayed enhancement of the fat graft on the post-gadolinium fat-suppressed T1-weighted MRI at 3 months and thereafter. This enhancement raised the suspicion of possible early tumor recurrence with gadolinium image. 3 of the patients showed enhancement on the immediate post-operative image set, 14 patients showed enhancement on imaging done 3-6 months postoperatively, and 3 of the patients showed enhancement after 1 year post-operative imaging.

FIESTA imaging showed hyperintensity at the site of the fat graft and hypointensity around the graft structures. When comparing the FIESTA image with the post-gadolinium fat-suppressed T1-weighted MRI, the enhancing signal within the fat graft correlated with signal characteristics of the fat graft, and not with tumor recurrence. The enhancement of the fat graft was likely due to delayed neovascularization of the fat graft. FIESTA was very useful in clarifying whether enhancing signal was due to recurrent/residual tumor versus postoperative changes. In one case, there was a recurrent tumor which was in the enhanced fat graft bed. FIESTA imaging showed hypointensity around the tumor with hyperintensity showing fat.

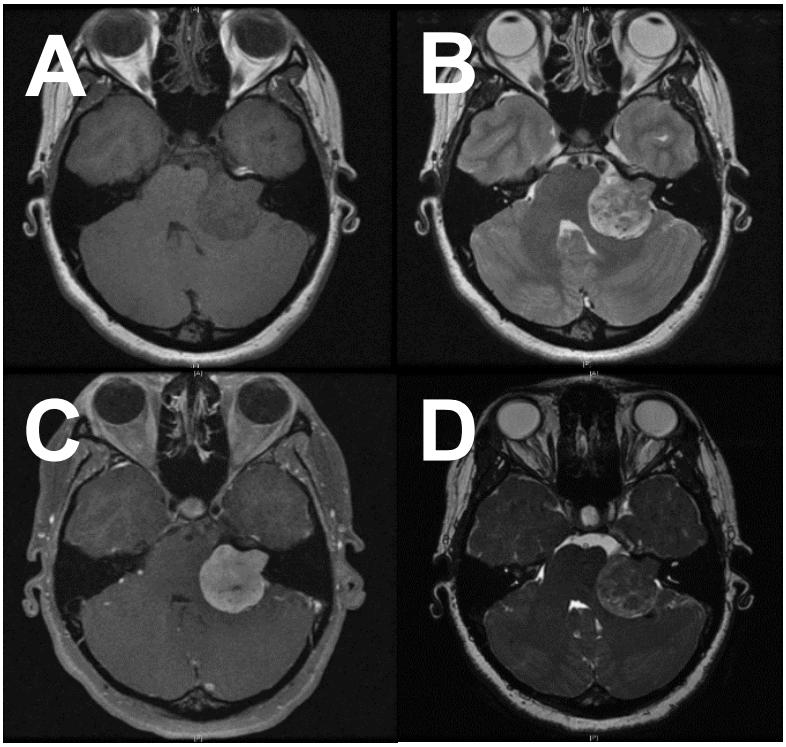

Fig. 1. Preoperative axial MRI showing left acoustic neuroma. A: T1-weighted MRI, tumor is hypointense. B: T2-weighted MRI, tumor is hyper- and hypointense. C: Post-gadolinium T1-weighted MRI, tumor is enhancing and hyperintense. D: FIESTA MRI, tumor hyper- and hypointense.

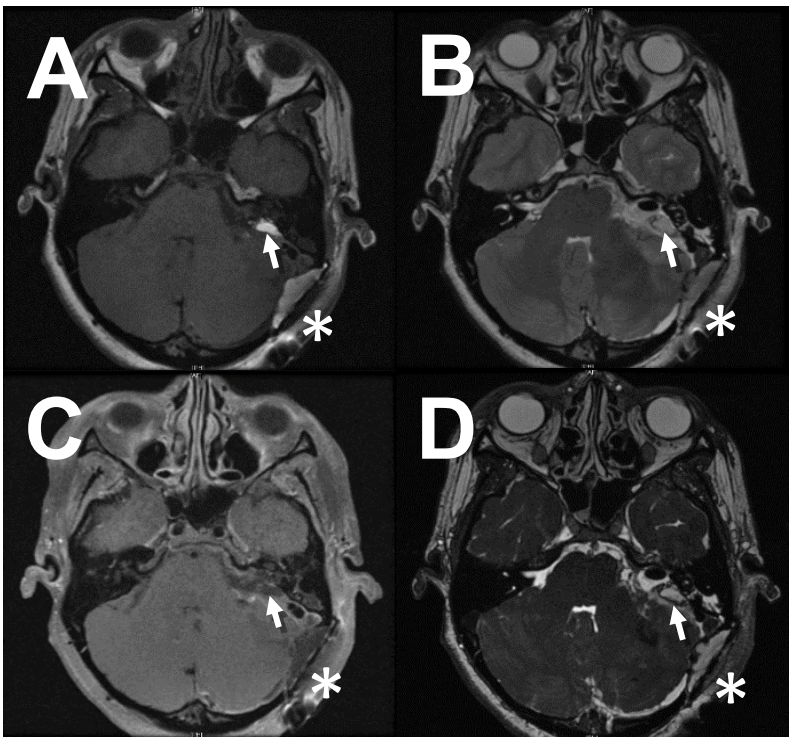

Fig. 2. Immediate postoperative day 1 axial MRI after retrosigmoid transmeatal resection of left acoustic neuroma. Fat graft is placed in the internal auditory canal (IAC) defect (white arrow) and over retrosigmoid dural closure (asterisk). A: T1-weighted MRI, fat is hyperintense. B: T2-weighted MRI, fat is hyperintense with rim of hypointensity. C: Post-gadolinium fat-suppressed T1-weighted MRI, fat signal drops out and there is rim of hyperintensity from postoperative blood products. D: FIESTA MRI, fat is hyperintense with a rim of hypointensity.

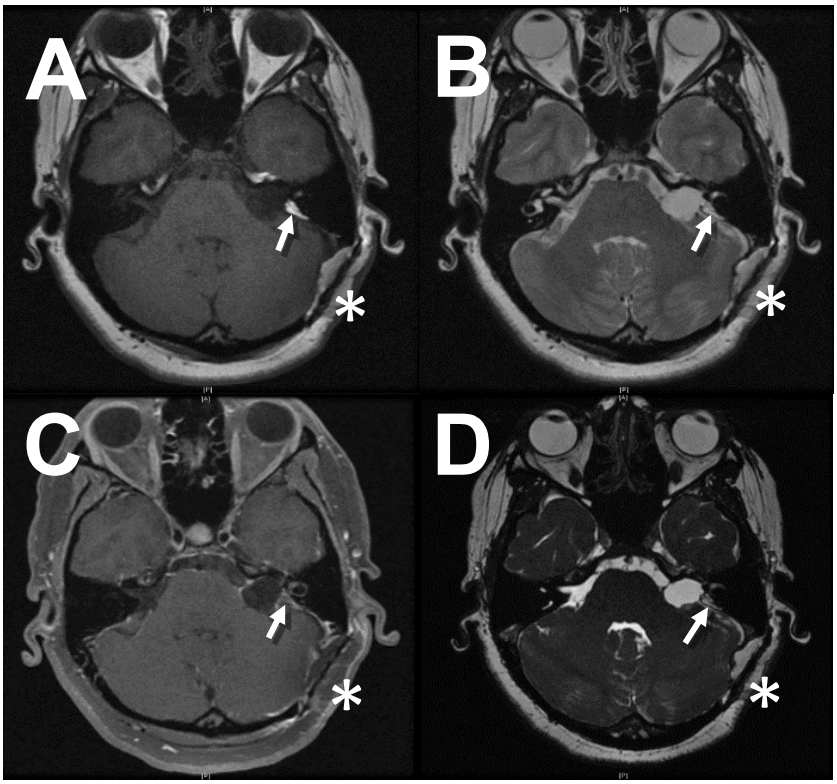

Fig. 3. Delayed postoperative axial MRI at 3 months after retrosigmoid transmeatal resection of left acoustic neuroma. Fat graft is in the internal auditory canal (IAC) defect (white arrow) and over retrosigmoid dural closure (asterisk) have both shrunken in size. There is delayed enhancement in the fat graft with gadolinium administration (arrow, C). FIESTA imaging (D) shows clarifies that the enhancing signal is actually fat graft signaling, and that there is no evidence of tumor recurrence. The enhancement is likely postoperative changes from neovascularization. A: T1-weighted MRI, fat is hyperintense. B: T2-weighted MRI, fat is hyperintense with rim of hypointensity. C: Post-gadolinium fat-suppressed T1-weighted MRI, fat signal drops out and there is rim of hyperintensity from postoperative changes. D: FIESTA MRI, fat is hyperintense with a rim of hypointensity.

CONCLUSION:

This study demonstrates the utility of FIESTA imaging in providing additional information and insight to standard imaging modalities when assessing tumor recurrence after acoustic neuroma surgery. Post-gadolinium fat suppressed T1-weighted MRI can show delayed enhancement in the fat graft by 3 months after surgery due to neovascularization of the fat graft. FIESTA can help resolve whether this delayed enhancement represents tumor versus postoperative changes.

CHRISTOPHER D. LEE (NJMS 2018)

PROJECT TITLE: **ETHNIC VARIATION IN PRESENCE AND LOCATION OF COLORECTAL LESIONS FOUND IN SCREENING COLONOSCOPIES: A RETROSPECTIVE STUDY IN A MINORITY SCREENING POPULATION**
MENTOR: **STANLEY H. WEISS, MD, ASSISTANT PROFESSOR**
DEPARTMENT: **MEDICINE**

PARTICIPATION DESCRIPTION:

I, Chris Lee, worked to analyze and expand on an existing dataset of all colonoscopies done at UH from 2005 -2006. I cleaned data, structured data, defined and created new variables, generated and tabulated statistics, performed statistical tests, interpreted results, and wrote up findings. I was guided on data structure, statistical analysis, and interpretations.

OBJECTIVE:

In the United States, colorectal cancer (**CRC**) is the 4th most common cancer and will have an estimated 133,000 new cases in 2015 (SEER). The lifetime risk for CRC is about 6% (Giovannucci and Wu). The most recent SEER data (2005-2011) show an overall 5-year survival rate of 65%. When cancer is detected early and localized to primary site, 5-year survival rate is over 90%. But when cancer has metastasized, 5 year survival is about 13%. Only 40% of CRCs are diagnosed in the localized stage, with 20% in distant or metastatic stage (SEER). Screening rates for CRC have doubled from 20%-30% in 1997 to 55% in 2008; but screening is still underused. Screening methods include fecal occult blood test (FOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy, CT colonography, and colonoscopy.

In the colon, adenomatous polyps are benign growths in the lining of the gastrointestinal tract that are of special interest because 70-90% of CRC develops from adenomatous polyps (with the remaining 10-30% developing from sessile adenomas) (Rudy and Zodon, 2000). There are different types of adenomatous polyps with varying prevalence and malignancy potentials, or the likelihood of becoming malignant: Tubular adenomas (**TA**) are 83% of polyps but have only about a 4% malignancy potential. Tubulovillous adenomas (**TVA**) are 12% of polyps and have 16% malignant potential, while villous adenomas (**VA**), the most dangerous polyps, are 5% of polyps but have 21% malignant potential (2000). Size is also a potent predictor of subsequent malignancy—large polyps (>1cm) have increased malignancy potential. The largest polyps (>2cm) have about 50% malignancy potential (2000). The presence of multiple polyps increases risk of cancer by 4.8 times what is expected with one polyp (2000).

Finally, the sub-site of the cancer and polyps is important clinically. One third to one half of all CRC arise in the proximal colon (caecum through splenic flexure). E.g., in one sample from 1992-1997 in the US, there was an estimated 45% proximal and 55% distal cancers (Giovannucci and Wu). In all CRC diagnosed at NJMS/University Hospital from 2000-2010, there were approximately 30% proximal and 70% distal cancers. In addition, there are demographic and racial differences in incidence, mortality, and survival. African Americans have the highest incidence and mortality rates, while Asians and Hispanics have the lowest rates (SEER). Some evidence suggests that African Americans are at increased risk for proximal cancers compared to whites (Nelson et al., 1997). Several screening techniques, including FOBT and flexible sigmoidoscopy, have limitations that do not allow for adequate screening of the proximal colon. We here examine differences in cancer, adenomas, and polyp location, size, and frequency in a largely minority screening population.

METHODS:

Data for this study was obtained by retrospectively reviewing all colonoscopies performed by the NJMS/University Hospital gastroenterology division during 2005-2006. Overall there were 2,697 colonoscopies performed. These included persons referred to NJMS from other clinical sites. Key demographic and clinical information was obtained, including sex, race, ethnicity, age, indication for colonoscopy, number of polyps, and for each polyp, size, location, and pathology. We limit this study to those colonoscopies that were complete (N=2,323), which is defined as reaching the terminal ileum or caecum and having colon preparation as adequate or better. Thus this ensures examination of the entire colon with maximal detection sensitivity.

We analyzed four outcomes—cancer, adenomas, presence of polyps >10mm, and presence of more than one polyp—overall, proximally and distally. Carcinoids and lymphomas were excluded from analysis. Adenomas, including TA, TVA, and VA, are a potential cancer risk. Hyperplastic lesions pose little risk of developing cancer and hence were not included in the present analysis. Note that the proximal colon includes the caecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure, while the distal colon includes the descending colon, sigmoid flexure, and rectum.

We stratified based on ethnicity with particular attention to Non-Hispanic (**NH**) Blacks, Hispanics, and NH Caucasian. When defining ethnicities, Portuguese (N=18), Brazilian (N=1), Asian/Pacific Islanders (N=92), and Caribbean (N=40) were collapsed into an 'other' category. We also stratified by indication for colonoscopy. The indication for colonoscopy was hierarchically organized, with the least severe being screening in asymptomatic persons, followed by screening of persons with a family history, followed by screening in those presenting with nonspecific symptoms (hematochezia, change in bowel habits, discomfort, etc) that don't necessarily indicate cancer, then by those with increased risk (personal history, surveillance, etc), and finally by those with significant clinical findings or clinical conditions that indicate increased risk of cancer. If someone had multiple indications, the most severe was used; thus, for example, someone with both family history and specific clinical indications would be assigned to the specific clinical indications category because the latter is more severe. We also combined the indications for colonoscopy into two larger groups: (1) Screening broadly defined (N=1,986), which includes asymptomatic persons, family history, or presenting with nonspecific symptoms; (2) Specific increase in risk (not analyzed here), which include those with personal history, surveillance, and specific clinical findings. All analyses were done using SAS Software.

SUMMARY:

In the asymptomatic screening group (N=630, mean age 58.4), NH blacks have higher rates (5.3%, 14/265) of proximal polyps > 10 mm compared to NH Whites (0%, 0/59) and Hispanics (2.0%, 5/250). In addition, NH blacks have higher rates of any polyps >10mm (7.9% vs 2.8%), multiple polyps (19.6% vs 12%), distal multiple polyps (9.4% vs 4.8%) compared to Hispanics. This corroborates previous work by Grover et al. (2007) that showed that NH blacks have higher rates of large colonic polyps and proximal large colonic polyps than Hispanics.

In our screening group with presenting symptoms (N=1314, mean age 53.7) as seen in Table 1 (below), NH blacks have higher rates of adenomas (16.6% vs 11.9%), proximal adenomas (9.4% vs 5.8%), and distal adenomas (9.4% vs 6.5%) compared to Hispanics. Similar to our asymptomatic group, NH blacks also have higher rates of proximal polyps >10mm (2.6% vs 1.0%), multiple polyps (16.1% vs 11.1%), and proximal multiple polyps (5.6% vs 3.3%) compared to Hispanics. However, NH blacks in the presenting symptom group have lower rates of cancer (0.2%, 1/620) compared to Whites (1.4%, 2/138) and Hispanics (1.3%, 6/479). Notably, asymptomatic persons have a higher rate of adenomas compared to persons with nonspecific

symptoms; this is perhaps due to mean age difference.

Overall, when we collapse our three screening populations, as noted in Table 2 (below), trends found in individual screening groups persist. In this less restrictively defined screening group, we continue to corroborate some findings by Grover et al. (2007) that NH blacks are more likely to have large polyps (5.6% vs 4.0%) and proximal large polyps (3.0% vs 1.2%) compared to Hispanics. In contrast, more NH blacks have any adenomas (15.2% vs 13.1%), proximal adenomas (9.3% vs 7.1%), multiple polyps (14.6% vs 10.1%), proximal multiple polyps (5.1% vs 3.4%), and distal multiple polyps (7.6% vs 5.2%) compared to Hispanics. In addition, opposite to the trend that NH blacks have worse outcomes, blacks had lower proximal cancer rates (0% vs 0.4%).

Conclusion:

This study confirms the results of the prior Grover et al. study that purely asymptomatic NH blacks and Hispanics have similar risk profile for cancers and adenomas but NH blacks are at a higher risk for polyps>10mm, particular proximal polyps>10mm, and for multiple polyps. The analyses were here extended beyond the previously considered "pure" screening group and now include those with family history and presenting symptoms, such as diarrhea, hematochezia, change in bowel habits, or discomfort. We observe higher overall and proximal rates of adenomas, large polyps, and multiple polyps in NH blacks compared to Hispanics.

While we do not observe that NH blacks have increased cancer risk compared to Hispanics or whites, perhaps related to study size limitations, our data corroborate a general trend that NH blacks are at more risk for cancers, particularly proximal cancers (Nelson et al., 1997). We show that, in screening colonoscopies in asymptomatic persons and those with non-specific presenting symptoms, more NH blacks have adenomas, polyps > 10mm, and multiple polyps both overall and proximally. These are all known risk factors for CRC. This is clinically significant because proximal colon lesions are known to have poorer outcomes than distal lesions, partially due to veiled symptoms (e.g., delayed detection) (Rudy and Zodon, 2000). Further examination of those with incomplete colonoscopy or inadequate preparation is continuing and may be incorporated into future analyses. It is also notable that the mean ages of those with presenting symptoms or with family history are younger than in asymptomatic persons. Overall, we stress the significant risk borne by NH blacks of screening age, and the importance of early screening in those with family history or presenting symptoms.

Table 1: Occurrence of Cancer, Adenomas, Large Polyps & Multiple Polyps, Overall, Proximally & Distally: by Race -Ethnicity for Screening of Pts with Presenting Symptoms

Includes only patients with nonspecific presenting symptoms	**NH Black (N=620) (Reference Group)**	NH White (N=138)	Hispanic (N=479)	Other (N=77)	*Total of all races / ethnicities (N=1314)*
Cancer	1 (0.2%)	2 (1.4%)*	**6 (1.3%)****	**3 (3.9%)****	*12 (0.9%)*
Proximal Cancer	0 (0.0%)	**2 (1.4%)****	3 (0.6%)*	0 (0.0%)	*5 (0.4%)*
Distal Cancer	1 (0.2%)	0 (0.0%)	3 (0.6%)	**3 (3.9%)****	*7 (0.5%)*
Adenomas	103 (16.6%)	22 (15.9%)	**57 (11.9%)****	12 (15.6%)	*194 (14.8%)*
Proximal Adenomas	59 (9.5%)	12 (8.7%)	**28 (5.8%)****	5 (6.5%)	*104 (7.9%)*
Distal Adenomas	58 (9.4%)	13 (9.4%)	31 (6.5%)*	8 (10.4%)	*110 (8.4%)*
Polyps >10mm	37 (6.0%)	11 (8.0%)	24 (5.0%)	7 (9.1%)	*79 (6.0%)*
Proximal Polyps>10mm	16 (2.6%)	3 (2.2%)	5 (1.0%)*	0 (0.0%)	*24 (1.8%)*
Distal Polyps >10mm	22 (3.5%)	9 (6.5%)	20 (4.2%)	**7 (9.1%)****	*58 (4.4%)*
Multiple Polyps	100 (16.1%)	20 (14.5%)	**53 (11.1%)****	11 (14.3%)	*184 (14.0%)*
Proximal multiple Polyps	35 (5.6%)	6 (4.3%)	16 (3.3%)*	2 (2.6%)	*59 (4.5%)*
Distal multiple Polyps	54 (8.7%)	9 (6.5%)	31 (6.5%)	7 (9.1%)	*101 (7.7%)*

Reference group for comparison is Non-Hispanic African American patients (N=620)

* indicates $0.05 < p < 0.10$. ** indicates $p < 0.05$ **(Fisher exact test, two-tailed)**

Table 2: Occurrence of Cancer, Adenomas, Polyps > 10mm, and Multiple Polyps — Overall, Proximally, and Distally — by Race-Ethnicity for All Screening Colonoscopies (Broadly Defined)

Includes asymptomatic, family history, and with presenting symptoms	**NH Black (N=903) (Reference**	NH White (N=204)	Hispanic (N=744)	Other (N=135)	*Total of all races / ethnicities (N=1986)*
Cancer	2 (0.2%)	2 (0.7%)	6 (0.7%)	**3 (2.0%)****	*13 (0.6%)*
Proximal cancer	0 (0.0%)	**2 (0.7%)****	3 (0.4%)*	0 (0.0%)	*5 (0.2%)*
Distal cancer	2 (0.2%)	0 (0.0%)	3 (0.4%)	**3 (2.0%)****	*8 (0.3%)*
Any adenomas[a]	162 (15.2%)	35 (12.8%)	109 (13.1%)*	19 (12.6%)	*325 (14.0%)*
Any proximal adenomas	99 (9.3%)	19 (6.9%)	**59 (7.1%)****	9 (6.0%)	*186 (8.0%)*
Any distal adenomas	86 (8.1%)	19 (6.9%)	61 (7.3%)	11 (7.3%)	*177 (7.6%)*
Any polyps >10mm[a]	60 (5.6%)	13 (4.7%)	33 (4.0%)*	10 (6.6%)	*116 (5.0%)*
Proximal polyps >10mm	32 (3.0%)	3 (1.1%)	**10 (1.2%)****	3 (2.0%)	*48 (2.1%)*
Distal polyps >10mm	31 (2.9%)	11 (4.0%)	25 (3.0%)	7 (4.6%)	*74 (3.2%)*
Multiple Polyps[b]	156 (14.6%)	29 (10.6%)	**84 (10.1%)****	16 (10.6%)	*285 (12.3%)*
Proximal multiple polyps	54 (5.1%)	10 (3.6%)	**28 (3.4%)****	**2 (1.3%)****	*94 (4.0%)*
Distal multiple polyps	81 (7.6%)	14 (5.1%)	**43 (5.2%)****	10 (6.6%)	*148 (6.4%)*

a. Colonoscopies with (proximal adenomas + colonoscopies with distal adenomas) > colonoscopies with any adenomas & similarly for polyps > 10mm: some colonoscopies show these findings in both proximal & distal colon

b. Colonoscopies with multiple proximal polyps + colonoscopies with multiple distal polyps < colonoscopies with multiple polyps because some people have a single polyp in in each proximal and distal.

Reference group for comparison is Non-Hispanic African American patients (N=903)

* Indicates a possible trend, with $0.05 < p < 0.10$. **** indicates a statistically significant difference in comparison to the reference group (NH Blacks), with $p \leq 0.05$ (Fisher exact test, two-tailed)**

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KAMIL LUPICKI (NJMS 2018)

PROJECT TITLE: **EPIGENETIC MECHANISMS INVOLVED IN THE REGULATION OF INNATE IMMUNITY BY VITAMIN D**

MENTOR: **SYLVIA CHRISTAKOS, PhD, PROFESSOR**

DEPARTMENT: **MICROBIOLOGY, BIOCHEMISTRY AND MOLECULAR GENETICS**

PARTICIPATION DESCRIPTION:

My participation in this research in Dr. Christakos's lab involved planning the 4 individual experiments in this abstract, performing the experiments, optimizing the protocols for the experiments, and analyzing the data. Ran Wei, a Ph.D. student in Dr. Christakos's lab, also served as my mentor. I became proficient in cell culture, RT-PCR, gel electrophoresis assays, and western blot assays. I did not perform the *Mycobacterium tuberculosis* infection of the Beas2B cells; infection of cells was performed by the Rutgers NJMS Department of Medicine. I created all figures and charts included in this report.

OBJECTIVE:

The respiratory epithelium is the first line of defense against inspired pathogens. A defining component of this defense system is the protective immunologic activity of antimicrobial peptides against bacteria and other pathogens. Cathelicidin antimicrobial peptide (CAMP, LL37), encoded by the *CAMP* gene, was previously shown to increase antimicrobial activity against airway pathogens. Cathelicidin was also shown to be induced by $1,25(OH)_2D_3$ in lung epithelial cells; however, we do not yet fully understand the mechanisms by which $1,25(OH)_2D_3$ regulates *CAMP* transcription. In this study we aimed to investigate three regulatory components that may cooperate with the vitamin D receptor (VDR) in the transcriptional regulation of *CAMP* in lung epithelial cells: PU.1, BRG-1, and PRMT5.

PU.1 is a transcription factor responsible for the differentiation of myeloid and B cells, and has been reported to play a role in the regulation of the innate immune system. We aimed to investigate dominant negative (DN) PU.1's effect on the induction of CAMP mRNA expression by $1,25(OH)_2D_3$. Additionally, we investigated the induction of PU.1 by $1,25(OH)_2D_3$ and C/EBPα, the CCAAT-enhancer binding protein alpha, which is also known to cooperate with VDR in promoting *CAMP* transcription.

BRG-1 is one of two homologous ATPases of the SWI/SNF chromatin remodeling complex. The SWI/SNF complex facilitates gene transcription using the energy of ATP hydrolysis to remodel chromatin. Our objective was to understand its effect on *CAMP* mRNA expression by investigating the effect of DN BRG-1 on the induction of CAMP mRNA expression by $1,25(OH)_2D_3$. We further aimed to study BRG-1's mechanism of action.

Recent publications have also shown interaction between histone modifying enzymes and chromatin remodelers. Protein arginine methyltransferases (PRMTs) are histone modifying enzymes implicated in transcriptional activation and repression. Our objective was to understand the effect of PRMT5, a type II PRMT that dimethylates histone 3 at arginine 8 (H3R8) and histone 4 at arginine 3 (H4R3), on $1,25(OH)_2D_3$ induction of CAMP mRNA expression.

Lastly, we aimed to investigate the role of *Mycobacterium tuberculosis* infection in the induction of CAMP mRNA expression in order to gain insight into the effects of bacterial infection on CAMP mRNA induction.

METHODS:

Culturing Beas2B lung epithelial cells

Beas2B lung epithelial cells were cultured in DMEM supplemented with 10% heat-inactivated fetal bovine serum. Cells were grown in a humidified incubator with atmosphere of 95% air-5% CO_2 at 37 ^{o}C. Cells were grown to desired confluence prior to beginning treatments.

Determining the effects of DN BRG-1, DN PU.1, and PU.1 on the induction of CAMP mRNA expression by 1,25(OH)$_2$D$_3$ using RT-PCR analysis

Beas2B cells were transfected using Lipofectamine 2000 (Invitrogen) with 1.7 ug of DN BRG-1 plasmid, 1.7 ug of DN PU.1 plamid, or 1.7 ug of PRMT5 plasmid. The cells were then left untreated or treated with 1,25$(OH)_2D_3$ (10 nM) for 24 hours. Total RNA was extracted from the Beas2B cells using the RiboZol RNA Purification Kit (Amresco) following the protocol provided. Total RNA was for each sample was measured using NanoDrop, and concentrations were normalized prior to RT-PCR. RT-PCR was performed, and DNA from RT-PCR was analyzed using gel electrophoresis to assess mRNA expression.

Assessing BRG-1's mechanism of action using RT-PCR analysis

Beas2B cells were transfected using Lipofectamine 2000 (Invitrogen) with 1.7 ug of DN BRG-1 plasmid. The cells were then left untreated, treated with 1,25$(OH)_2D_3$, or treated with 1,25$(OH)_2D_3$ and 1 mM sodium butyrate (NaB) or 10 nM trichostatin A (TSA) for 24 hours. Total RNA was extracted and mRNA expression was assessed as described above.

Assessing induction of PU.1 protein expression using Western blot assay

Beas2B cells were transfected using Lipofectamine 2000 (Invitrogen) with vehicle or 4.5 ug of C/EBPα plasmid, and were left untreated or treated with 1,25$(OH)_2D_3$ for 24 hours. Cells were lysed, treated with protease inhibitor, and cellular debris was cleared using centrifugation. Bradford assay was performed to determine total protein concentration. 50 µg of protein from each lysate were separated using SDS-PAGE. Proteins were electrophoretically transferred to nitrocellulose membrane in transfer buffer. Western blot assay was used to test for PU.1 expression.

Assessing CAMP mRNA expression after infection with Mycobacterium tuberculosis

Beas2B cells were infected with varying concentrations of *Mycobacterium tuberculosis* at the same time of treatment with vehicle or 1,25$(OH)_2D_3$ for 24 hours. Total RNA was extracted and mRNA expression was assessed as described above.

SUMMARY:

Transfection of DN BRG-1, DN PU.1, and PRMT5 inhibited the induction of CAMP mRNA expression by 1,25$(OH)_2D_3$ in Beas2B cells as compared to nontransfected Beas2B cells treated with 1,25$(OH)_2D_3$ for 24 hours (Figure 1).

Treatment of 1,25$(OH)_2D_3$-treated DN BRG-1-transfected Beas2B cells with the histone deacetylase inhibitors (HDACi), 1 mM NaB or 10 nM TSA, reversed the CAMP mRNA inhibition by DN BRG-1 after 24 hour treatment (Figure 2).

PU.1 protein expression was independently induced by C/EBPα transfection and 1,25$(OH)_2D_3$-24 hours treatment in Beas2B cells (Figure 3). These preliminary data are pending GAPDH results.

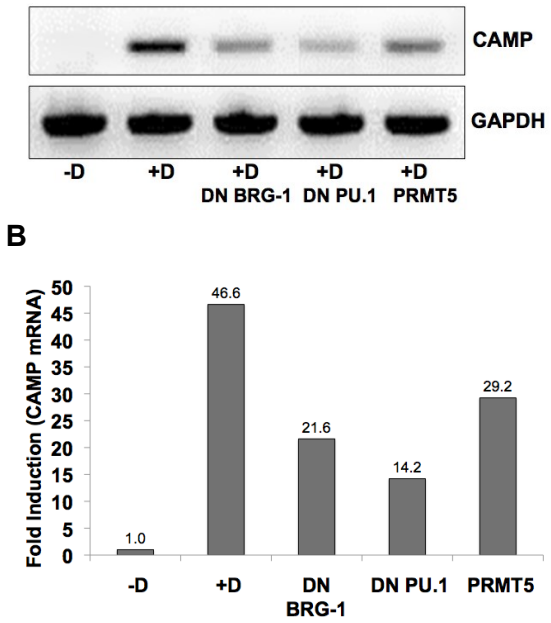

Figure 1. Effect of DN BRG-1, DN PU.1, and PRMT5, on $1,25(OH)_2D_3$ induction of CAMP mRNA expression. (A) Gel electrophoresis was performed to visualize CAMP mRNA from RT-PCR of total mRNA in Beas2B cells treated with (+D) or without (-D) $1,25(OH)_2D_3$ for 24 hours and no transfection or transfection with DN BRG-1, DN PU.1, or PRMT5. (B) Fold induction of CAMP mRNA as compared to untreated and nontransfected Beas2B cells.

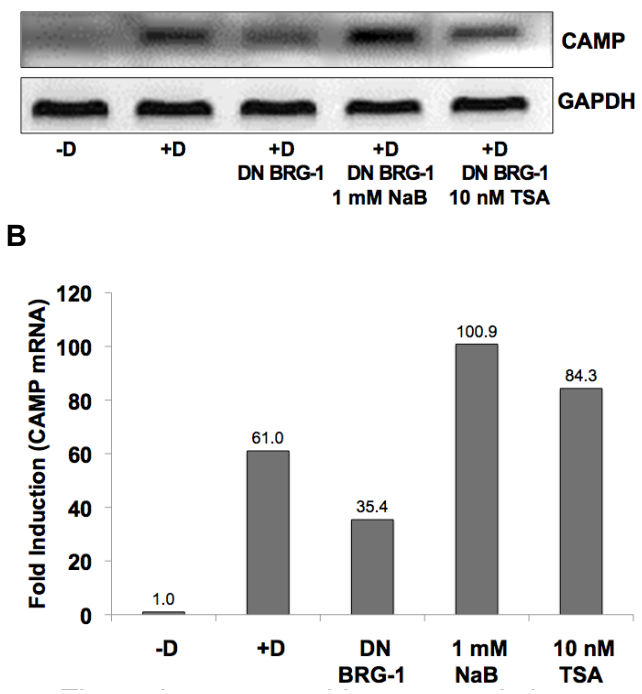

Figure 2. Effect of NaB and TSA on BRG-1 inhibition of of CAMP mRNA expression. (A) Gel electrophoresis was performed to visualize CAMP mRNA from RT-PCR of total mRNA in Beas2B cells treated with (+D) or without (-D) $1,25(OH)_2D_3$, as well as 1 mM NaB or 10 nM TSA for 24 hours, and transfected with DN BRG-1. (B) Fold induction of CAMP mRNA as compared to untreated and non-transfected Beas2B cells.

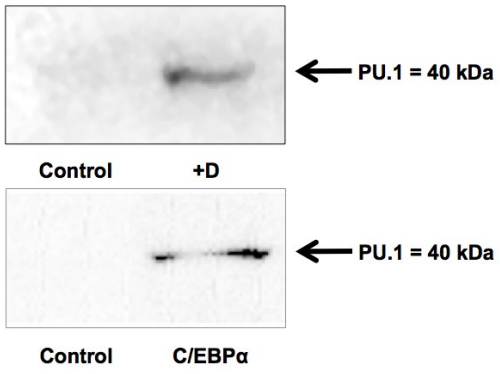

Figure 3. PU.1 protein expression. Western blot assay for PU.1 in Beas2B cells untreated, treated with $1,25(OH)_2D_3$ (+D), or C/EBPα for 24 hours.

SUMMARY (continued):

Expression of $1,25(OH)_2D_3$ induced CAMP mRNA expression was enhanced after infection with *Mycobacterium tuberculosis* (*Mtb*) for multiplicities of infection of 1:1, 3:1, and 10:1. The greatest fold increase in CAMP mRNA expression was seen in $1,25(OH)_2D_3$-treated cells infected with a 10:1 multiplicity of infection (Figure 4).

CONCLUSION:

In this study, we show that DN BRG-1 inhibits the induction of *CAMP* mRNA expression by $1,25(OH)_2D_3$ suggesting BRG and the SWI/SNF complex cooperate with VDR in CAMP upregulation. Furthermore, we found that, DN BRG-1's inhibition of CAMP mRNA expression is reversed by the histone deacetylase inhibitors sodium butyrate and trichostatin A. These data suggest that, in addition to BRG-1's known role in histone remodeling, BRG-1 may contribute to the upregulation of CAMP mRNA expression through promoting histone acetylation in lung epithelial cells.

We also show that DN PU.1 inhibits the induction of *CAMP* mRNA expression by $1,25(OH)_2D_3$, and, for the first time, that PU.1 is induced by $1,25(OH)_2D_3$ alone in lung epithelial cells (pending GAPDH results for the Western blot assay). These findings suggest a role for PU.1 in the VDR-mediated regulation of CAMP in lung epithelial cells, in addition to its known role in myeloid cells.

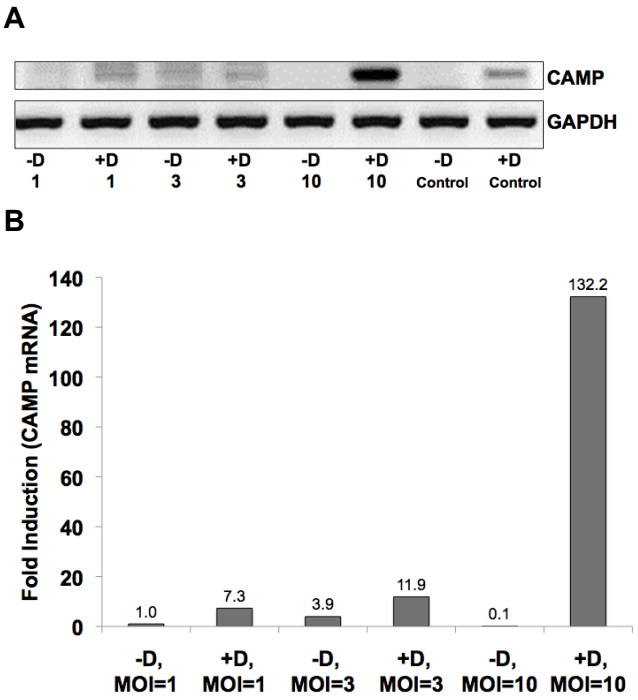

Figure 4. Expression of CAMP mRNA after *Mycobacterium tuberculosis* infection. A) Gel electrophoresis was performed to visualize CAMP mRNA from RT-PCR of total mRNA in Beas2B cells treated for 24 hours with (+D) or without (-D) $1,25(OH)_2D_3$ and infected with *Mycobacterium tuberculosis* at the time of treatment. Numbers 1, 3, and 10 indicate the multiplicity of infection (MOI) such that 1 corresponds to a MOI of 1:1. (B) Fold induction of CAMP

We found that PRMT5, a type II PRMT that dimethylates histone 3 at arginine 8 (H3R8) and histone 4 at arginine 3 (H4R3), inhibits $1,25(OH)_2D_3$ induction of *CAMP* mRNA.

Lastly, we found that $1,25(OH)_2D_3$ induced CAMP mRNA expression is enhanced after infection with *Mycobacterium tuberculosis*. This finding suggests an important role for $1,25(OH)_2D_3$ in the promotion of the innate immune response after infection. Further investigations are needed to determine how the specific transcription factors involved in CAMP regulation are affected by *Mycobacterium tuberculosis* infection.

The mechanisms involved in the regulation of the CAMP gene suggest potential candidates, including vitamin D, in the development of innate immune responses to augment current therapies to treat bacterial airway infection.

APEXA MEHTA (BDS, Research Intern)
ASHUTOSH PANDEY, PhD (Postdoctoral Researcher)
SAGAR PATEL, MD (Research Intern)
BIREN, PATEL, MD (Research Intern)

PROJECT TITLE: **DESIGN, SYNTHESIS AND MASS SPECTRAL CHARACTERIZATION OF A NOVEL CURCUMIN-METFORMIN ADDUCT: A POTENTIAL ANTI-DIABETIC AGENT**

MENTORS: **BISHAMBAR DAYAL, PhD, ADJUNCT ASSOCIATE PROFESSOR**
MICHAEL LEA, PhD, PROFESSOR
PATRICK O'CONNOR, PhD, ASSOCIATE PROFESSOR
DEPARTMENTS: **MEDICINE AND MICROBIOLOGY, BIOCHEMISTRY AND MOLECULAR GENETICS**

We have recently studied binding and modification of proteins: human serum albumin (HSA) and lysozyme (Lys) by methylglyoxal under physiological conditions (ACS 247, 248, 249) . Inhibition of the formation of advanced glycation end products (AGEs) from MGO-modified ribonuclease by Okra Seed Extract (OSE) bioactives was also reported from our laboratory. The analysis of HSA-MGO and MGO-Lys was achieved by various spectroscopic methods and their inhibitory effect with structurally-defined flavonoids present in okra-seed extract and curcumin was assessed via AGEs associated absorbance changes and SDS-PAGE analysis . Furthermore comparative efficacy studies using different well-established AGE inhibitors: Metformin, aminoguanidine, phenformin with OSE and yellow curcumin were studied and analyzed via SDS-PAGE and fluorescence measurements. The results exhibited 70-80% antiglycosylation activity of OSE extract while yellow curcumin inhibitory activity ranged from 45-50%. But the combinations of metformin, phenformin and aminoguanidine with OSE or yellow curcumin further enhanced the antiglycosylation (antiglycation) activity in a dose dependent manner.

Rationale:

The commonly used drug metformin (1,1-dimethylbiguanide) for type-2 diabetes reduces cancer risk and tumor growth. The mechanisms by which this happens are not completely understood. One of the proposed mechanisms suggest activation of AMP-activated protein kinase (AMPK), inhibition of m-TOR activity, Akt dephosphorylation, disruption of UPR transcription and cell cycle arrest.

> *Therefore our studies are aimed at studying development of more potent anti-cancer drugs and their mechanisms. Our previous observations have suggested that synergistic anti-diabetic effect of metformin or phenformin with curcumin shows a much better and enhanced antiglycation activity. We have combined metformin with curcumin not only to prevent side-effects lactic acidosis a major effect of biguanidies but also may show synergistic anti-diabetic and anti-cancer effects.*

A Facile Synthesis and Characterization of Curcumin-Metformin Adduct:

We recently synthesized and characterized the hydrazino derivative of curcumin (249th ACS AGFD abstract 69). Present studies describe synthesis of curcumin-metformin adduct molecule.

Briefly, Curcumin (6mg) was dissolved in methanol (2ml) and 20 mg of metformin hydrochloride was added followed by 200µl of triethylamine and catalytic amount of glacial acetic acid (200µl). The reaction mixture was vortexed for 45 seconds and left stirring at room temperature for 5 minutes. The progress of the reaction was monitored by analytical TLD plates in the solvent system: $CHCl_3$:CH_3OH (24:4 v/v). The major extremely

polar metformin curcumin adduct (85%, R_f = 0.53) and the minor isomer (15%, R_f = 0.69) were visualized only in Iodine chamber. The parent curcumin metabolites were visualized under UV light. ESI-MS in +ion mode did not exhibit molecular ion peak M/Z at 461but a major M/Z at 265 (100% , M-149-OCH3-NH2) was exhibited. Other prominent peaks at M/Z 237 (M^+-149-$N(CH_3)_2$ –OCH_3) and 179 (fragment 265- N=C- $(CH_3)_2N$-NH_2) indicative of the metformin-curcumin adduct were observed.

Since substitution of 1,3 dicarbonyl moiety in curcumin by pyrazole has been shown to inhibit gama-secretase activity and its affinity to polymeric Aβ amyloid protein aggregates. The reaction of a biguanide, metformin a well- known diabetes drug, may also have the potential to bind Aβ-oligomers and disaggregate fibrillar formation in Alzheimers disease as well. Insights into the mechanism of the formation of metformin adduct with curcumin will be discussed in a future communication.

PETER NAKAGAMI (NJMS 2018)

PROJECT TITLE: **SCREENING FOR CASPOFUNGIN SENSITIVITY IN *CRYTOCOCCUS NEOFORMANS***
MENTOR: **CHAOYANG XUE, PhD, ASSISTANT PROFESSOR**
DEPARTMENT: **MICROBIOLOGY, BIOCHEMISTRY, AND MOLECULAR GENETICS**

PARTICIPATION DESCRIPTION:

Over the summer, I was involved in the planning and execution of my project, under the guidance and advice of Dr. Xue and the other members of the Xue Lab. I personally ran each experiment, from setting up cultures and plates, to each round of screening (3 times), running phenotypic analyses, and imaging each plate. As a member of the lab I also helped make media for the lab and attended lab meetings every Monday afternoon. Furthermore, I helped transition 2 projects over the summer from one member of the lab who was leaving to the end of August; this entailed making mating plates, as well as running large scale genomic DNA extractions, cutting and ligating samples, and running PCR's and gels to examine the results of the ligation.

OBJECTIVE:

Cryptococcus neoformans is an opportunistic infection that is naturally resistant to the echinocandin class of antifungal agents, which is thought to target 1,3-β-glucan synthase. Even though 1,3-β-glucan synthase is found in *C. neoformans* and 1,3-β-glucan is found in its cell wall, echinocandins are still ineffective in treating infections caused by *C. neoformans*. With the mechanism of resistance still unknown, this study seeks to try and identify genes responsible for echinocandin resistance by screening a gene knock-out library. If strains are found that are susceptible to caspofungin, the target gene deleted in the mutant strain will be identified by comparing to known identified genes in *Cryptococcus* or BLAST search on a protein sequence database. Further phenotypic analyses will also be performed on these susceptible strains.

METHODS:

A library of *Cryptococcus neoformans* gene deletion mutants comprising 2111 strains was obtained from the Fungal Genetics Stock Center; the library was generated by the Madhani lab at UCSF. An initial minimum inhibitory concentration (MIC) test was done on the wild-type strain (H99) to provide a benchmark for caspofungin working concentration for the screen. Our results showed the growth was not inhibited at 32 µg/mL; the screen was done at 8 µg/mL. The screen was repeated 3 times, with each round selecting those strains that had inhibited growth, with the screen repeated on those strains. Each screen was checked after 48 hours in a 30 ^{o}C incubator. A 10 times serial dilution of caspofungin in dH_2O was then performed with initial dilutions set at 1.000 from OD600, starting at 32 µg/mL for caspofungin; strains showing reduced growth versus the wild-type H99 were then selected for the next round of screening of caspofungin at 8 µg/mL and 16 µg/mL on solid media. A YPD solid plate without caspofungin was used as a control to separate strains with sensitivity to caspofungin from strains that have growth defects as a result of their gene knockout. Several other antifungal agents were also tested on these strains, including antimycin at 5 µg/mL, fluconazole at 4 µg/mL, and amphotericin B at 4 µg/mL. Phenotypic testing included growth on YPD at pH 4.0, 100mM $CaCl_2$, 1.5M NaCl, and 0.04% SDS. Melanin production was examined on L-DOPA plates.

The resultant identified strains were searched using UCSF's provided gene knock-out list and searched on the Broad Institute's H99 genome database. Gene products with unknown function were searched in the National Center for Biotechnology Information's BLAST search tool, using the protein search to look for analogous sequences. Further inquiry was done to learn more about the functions of each gene product, particularly in yeast if the information was available.

SUMMARY:

From the initial 2111 strains, four strains were ultimately found in the final serial dilution test that were susceptible to caspofungin when compared to wild-type growth after 48 hours in incubation at 30 ^{o}C.

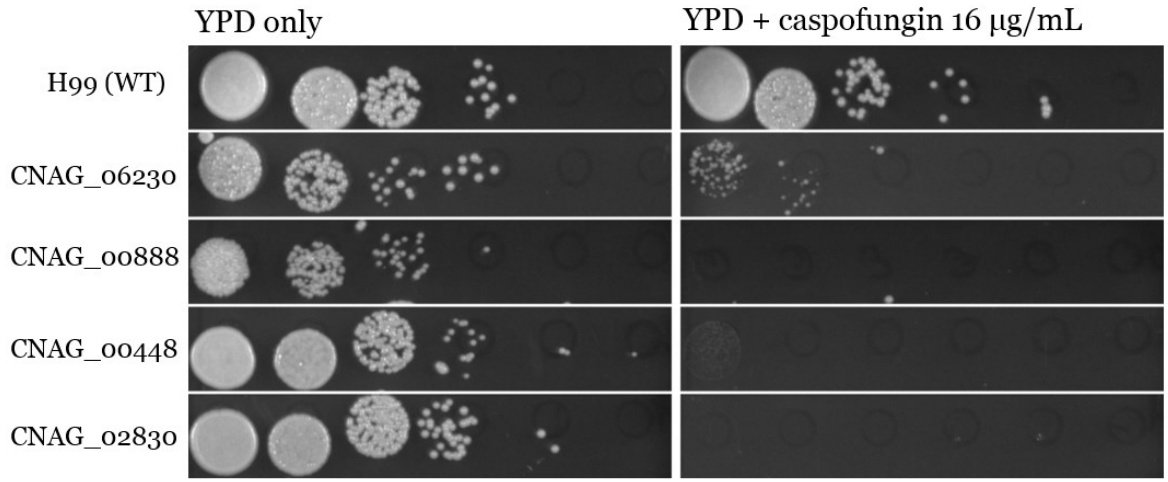

Figure 1: 10x serial dilutions; 4 strains found sensitive to caspofungin at 16 μg/mL

After the four strains that were susceptible to caspofungin were identified, further tests were done to phenotype the strains. Shown below are serial dilution tests done on those strains with 3 different agents known to inhibit fungal growth.

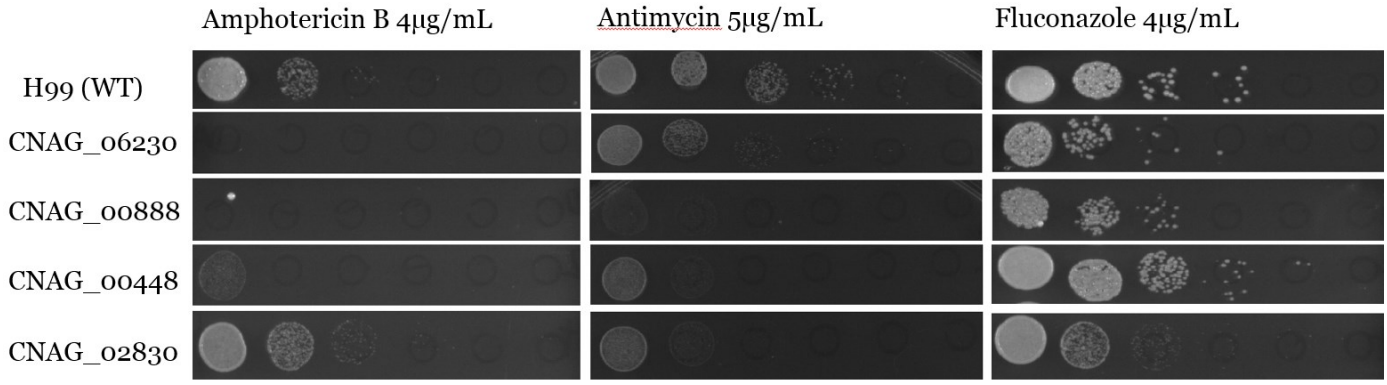

Figure 2: 10X serial dilutions; 4 strains susceptible to caspofungin tested with other agents on solid YPD media

The full results of the serial dilution test with caspofungin, as well as the phenotypic analysis on the four identified susceptible strains are listed in the table 1:

Table 1: Results from phenotypic analysis on the four identified caspofungin-sensitive strains

Test:	**CNAG_06230**	**CNAG_00888**	**CNAG_00448**	**CNAG_02830**
Morphology	Pale and creamy with isolated dry-appearing colonies	Pale and creamy	Pale and creamy	Pale and creamy
Caspofungin (16 µg/mL)	-	-	-	-
Caspofungin (8 µg/mL)			+	+
Amphotericin B (4 µg/mL)	-	-		+
Antimycin (5 µg/mL)		-		
Fluconazole (4 µg/mL)			+	+
pH 4.0	+	+	+	+
$CaCl_2$ 100mM	+	-		+
NaCl 1.5M	-	-	-	
SDS .04%	-	-	-	-
L-DOPA	Normal melanin	Normal melanin	Normal melanin	Normal melanin

Note: '+' = same growth as H99 (WT)
'-' = less growth than H99 (WT)
'- -' = minimal/no growth

CONCLUSION:

From our initial screening process, we have identified 4 strains from the UCSF library that are sensitive to caspofungin.

CNAG_06230 was found to be similar in sequence to the EamA superfamily of transporters, which is a membrane transporter involved primarily in nucleotide sugar transport, but has been linked to drug/metabolite transport as well. For caspofungin, we hypothesize that this may be exporting caspofungin out of the cell, preventing a minimum necessary concentration from building up in the cell.

CNAG_00888 was identified to be the gene encoding calcineurin subunit B. Calcineurin is a calcium/calmodulin-activated protein phosphatase involved in the cell cycle, homeostasis, and changing morphology in fungi. Other studies show that calcineurin may be key in *C. neoformans* virulence due to its role in morphologic changes and high temperature growth. Because calcineurin is involved in many cellular signaling processes and is important for fungal growth, further investigation of its role in caspofungin resistance is needed to yield a better understanding of a calcineurin-mediated drug resistance mechanism in *C. neoformans*.

CNAG_00448 is a gene involved in a V-type H-transporting ATPase. This ATPase is typically found on the membrane of an intracellular vacuole and pumps protons from the cytosol into the organelle, and is used in pH regulation. Furthermore, this ATPase has been linked to a multitude of cellular functions in yeast including protein sorting, zymogen activation, transmembrane transport, storage of metabolites, and osmotic control. For its role in caspofungin resistance, we hypothesize that disruption of this ATPase may affect vesicle formation, preventing the cell from isolating caspofungin into a vesicle and out of the cytosol.

Finally, CNAG_02830 is a gene involved in delta24-sterol reductase. This reductase is a key part of the ergosterol synthesis pathway; ergosterol is a key component of the fungal cell membrane and is specific to fungi. For caspofungin, we hypothesize that disruption of cell membrane components may be allowing easier entrance of caspofungin into the cell, where it can disrupt 1,3-β-glucan synthase.

These four identified genes illuminate avenues of exploration that may not only help further our understanding of caspofungin's mechanism of action and range of effects, but also future targets for combination therapies.

Future directions include further phenotypic testing of our identified strains. Testing has already been done on amphotericin B, antimycin, and fluconazole, as well as YPD at pH 4.0, 100mM $CaCl_2$, 1.5M NaCl, .04% SDS, and L-DOPA. Further testing will be done on capsule formation, 250 µg/mL CFW, 0.5% Congo Red, 5mM H_2O_2, 1M KCl, and 1M sorbitol. The end goal would be to identify an agent that targets one of these identified proteins, which could lead to sensitivity to caspofungin when administered in conjunction with the antifungal agent.

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ALVIN NYABOGA (NJMS 2018)
SHMILAH CHOUDHARY (SETON HALL UNIVERSITY 2018)

PROJECT TITLE: **EFFECT OF DVT PROPHYLAXIS ON THROMBOEMBOLISM IN NEUROSURGERY: A RETROSPECTIVE ANALYSIS OF VARIOUS PATIENT SUBGROUPS**

MENTOR: **CHIRAG D. GANDHI, MD, ASSISTANT PROFESSOR**

DEPARTMENT: **NEUROLOGICAL SURGERY**

PURPOSE:

The purpose of this retrospective study is to determine, within our institution, whether DVT prophylaxis has helped reduce the risk of venous thromboembolism (VTE) in neurosurgical patients, and what prophylactic regiment has shown to best decrease incidence of VTE. We will also investigate whether a specific subgroup of neurosurgical patients has a higher incidence of VTE, and whether complications arose from giving anticoagulation for VTE prophylaxis. Furthermore, our secondary aim is to determine the effectiveness of the various DVT prophylactic methods in lowering VTE rates and whether it would be cost-effective to be screening all neurosurgical patients or just a subgroup of patients that have higher than normal incidences.

STUDY DESIGN:

This study is a retrospective chart review of neurosurgery patients who have had or were at risk for thromboembolism with or without DVT prophylaxis. These patients were admitted at University Hospital Newark hospital from January 1, 1989 through June 30, 2014. We will query the case logbook for the Neurosurgery Department at University Hospital Newark to obtain the list of patients. Key words used when looking up patients in the database were “CT PE, LED, Duplex, PE.” Data will be obtained by chart review by the principle investigator. We will obtain the following data for the patients meeting our inclusion & exclusion criteria.

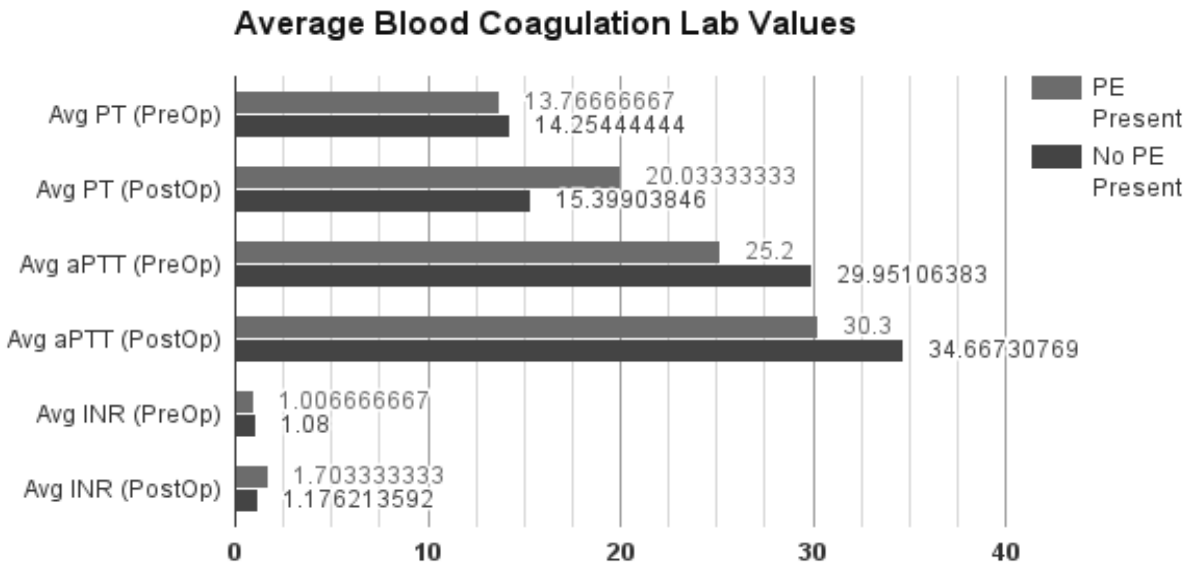
Variables that would be collected include:

1. Patient demographics (age, gender, race)
2. Admission date
3. Length of Stay
4. Mortality
5. Past Medical History
6. Home medications (Plavix, Aspirin, Coumadin, etc.)
7. Hospital Medications (subcutaneous heparin, lovenox)
8. Neuroimaging findings (CT/MRI/Angiogram)
9. Blood product transfusions from hospital record
10. Blood Tests (PT/PTT/INR)
11. Neurological examination and operative notes from chart

12. Technical aspects of the surgery (type of surgery, placement of IVC filter, duration of surgery, DVT prophylaxis)
13. List of complications of the surgery during hospital stay (thromboembolism, DVT)
14. If any complications arose from initiating anticoagulation for DVT prophylaxis (i.e. ICH, spinal hematoma, etc.).

RESULTS

Figure 1: Prepared by Alvin Nyaboga and Shmilah Choudhary



CONCLUSION:

The blood coagulation lab values show that prior to operation individuals whom would later develop VTE had lower PT (Prothrombin time), aPTT (Activated Partial Thromboplastin time) and INR (International Normalized Ratio) values than their counterparts. However, as we approach the date of discharge for each patient the PT and INR of those that developed VTE was higher than their counterparts. PT and INR are values that show the clotting time of blood via the extrinsic pathway of coagulation. APTT values showcase clotting time in relation to the intrinsic pathway. Post-operative differences in aPTT values between those that develop VTE and those that do not may be of value to look further into. On the other hand, anti-coagulation therapy and the timing of post-operative blood coagulation tests can also be playing a large role in shifting the lab values.

This study is still currently underway. Data collection for the other subgroups, as well as further analysis of currently gathered data will need to be completed in order to better understand any possible correlations between VTE and anti-coagulation prophylaxis.

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AKASH PATEL (NJMS 2018)

PROJECT TITLE: **IMPULSIVE & VIOLENT BEHAVIORS IN LONG TERM PSYCHIATRIC INPATIENTS: IMPULSIVE SWALLOWING & OTHER BEHAVIORS**

MENTOR: **STEVEN J. SCHLEIFER, MD, PROFESSOR**

DEPARTMENT: **PSYCHIATRY**

PARTICIPATION DESCRIPTION:

I examined all the nursing reports, ADN reports, and incident reports needed for this study and compiled all of this data onto a spreadsheet. I also did preliminary analysis on patterns that could be observed relating to the initial hypothesis. Finally, I generated graphs from this data so that the observed patterns could be visualized

OBJECTIVE:

This project is a component of a Greystone Park Psychiatric Hospital (GPPH) Performance Improvement project. It aims to seek causes and interventions for Foreign Body Ingestion (FBI) in adult psychiatric inpatients. By 2012, the hospital had noted a large increase in the number of patients with FBI, an uncommon behavior that often requires continued psychiatric hospitalization due to its high morbidity and mortality. The literature did not reveal any evidence-based practices for treating such patients. The goal of the project was to better understand FBI behaviors and to develop patient-specific interventions. Preliminary clinical observations suggested that there may be three subgroups of nonpsychotic FBI patients, the group of primary interest. The first includes patients with cognitive disorders such as developmental disabilities and traumatic brain injury. The second group includes patients without cognitive disorders who are hypothesized to include two subgroups. These include one hypothesized subgroup who manifest a variety of self harming impulsive behaviors, of which FBI may be either a preferred or occasional opportunistic behavior. The second subgroup includes patients without cognitive disorders for whom FBI is a specific compulsive behavior, not associated with other impulsive behaviors. As a first step toward understanding FBI behavior patterns and subtypes, daily clinical records were examined to identify FBI and other self harming patients and their patterns of self harm behaviors. It was hypothesized that some subgroups of impulsive swallowers of foreign objects could be identified based on the relative presence or absence of other impulsive behaviors.

METHODS:

FBI and other self harm behaviors were examined retrospectively for one area of the hospital between the months of May and September of 2014. The primary resources used were the 24-hour nursing reports (a communication vehicle not included in the regular patient chart), which reported on notable patient events for each unit. The selected time frame consisted of 153 days for six hospital units: a total of 918 unit-days. Of these, 873 had available 24-hour nursing reports. Two units had blocks of time with no available nursing reports and there were also several isolated unit-days which did not have them. For these 45 unit-days with missing nursing reports, 33 had available ADN reports (another type of nursing communication). Next, incident reports (generated only when there is a notable activity) for that time period were examined in order to supplement the previous data and to fill in any gaps. These records were reviewed to identify self harm impulsive behaviors, including FBI, among all patients on the six units during that interval. The present data for this work in progress summarize currently available information.

SUMMARY:

Of 277 patients hospitalized in this area during the period of May and September of 2014, 35 were found to have at least one self harm event. Of the 35 patients, 11 were found to have ingested a foreign body on at least one occasion. Fig. 1 shows that, of patients with at least 2 self harm events, about 52% included FBI behaviors, a seemingly high proportion. Several patterns are suggested as seen for 3 units with active events. On the A unit (Fig. 2a), FBI was relatively frequent and tended to occur concurrently with other self harm behaviors. On the B unit (Fig. 2b), there were numerous self harm behaviors but FBI did not appear to have a strong correlation with other self harm behaviors. On the C unit (Fig. 2c), self harm is frequent but FBI is not; the FBI events on this unit are clustered into a two week span.

Fig. 1:

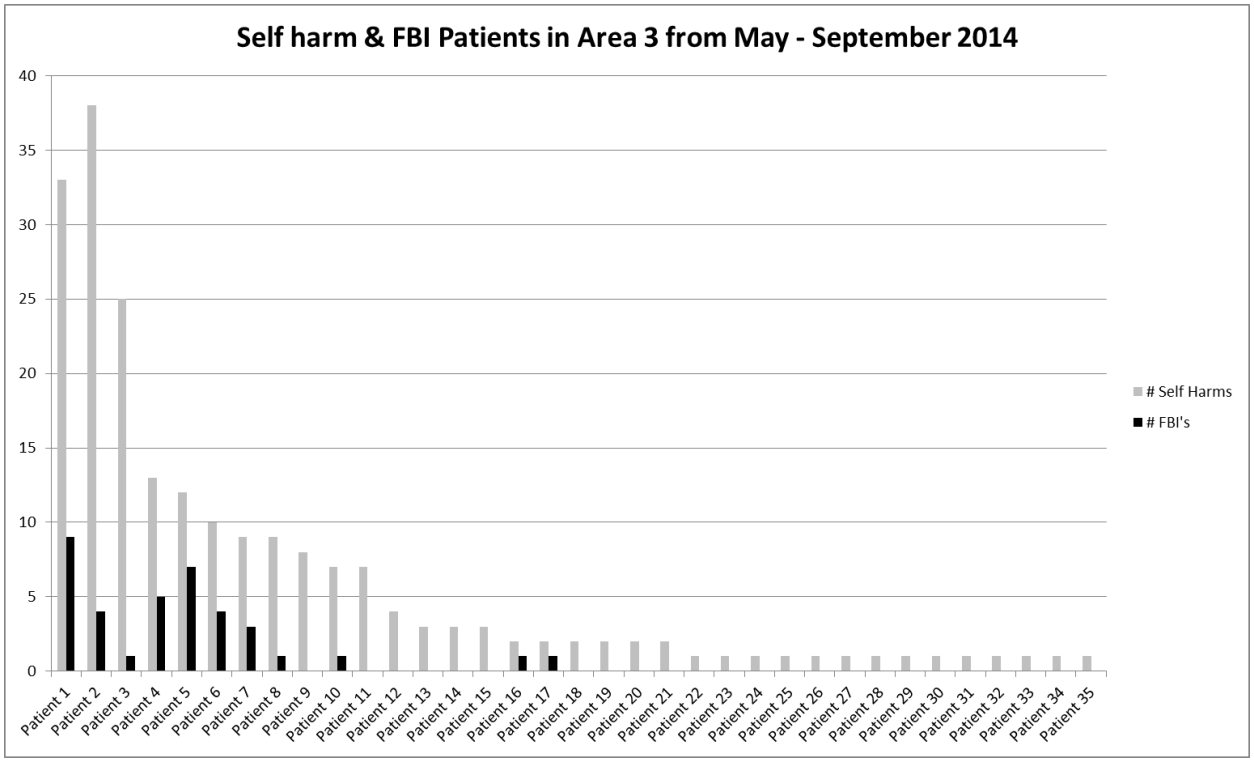


Fig. 2a:

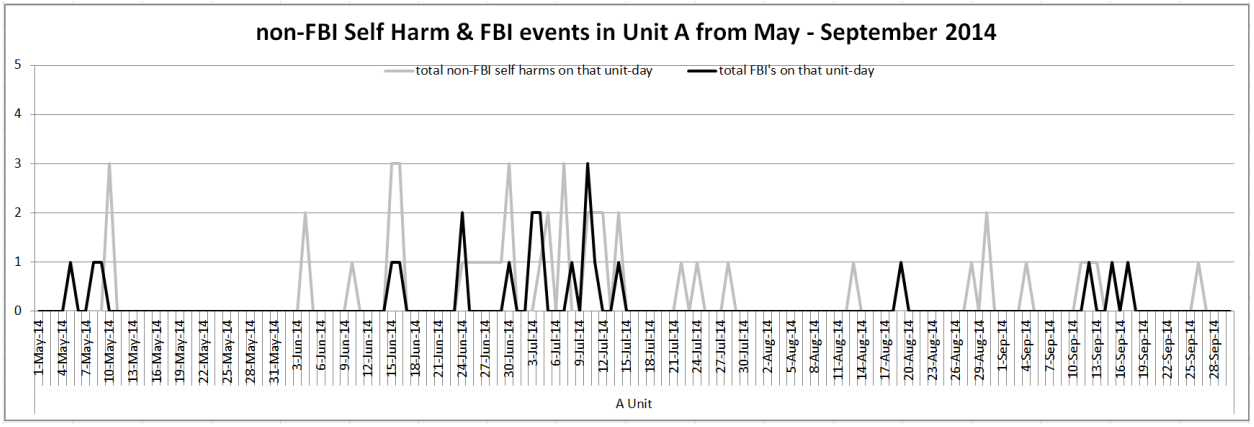


Fig. 2b:

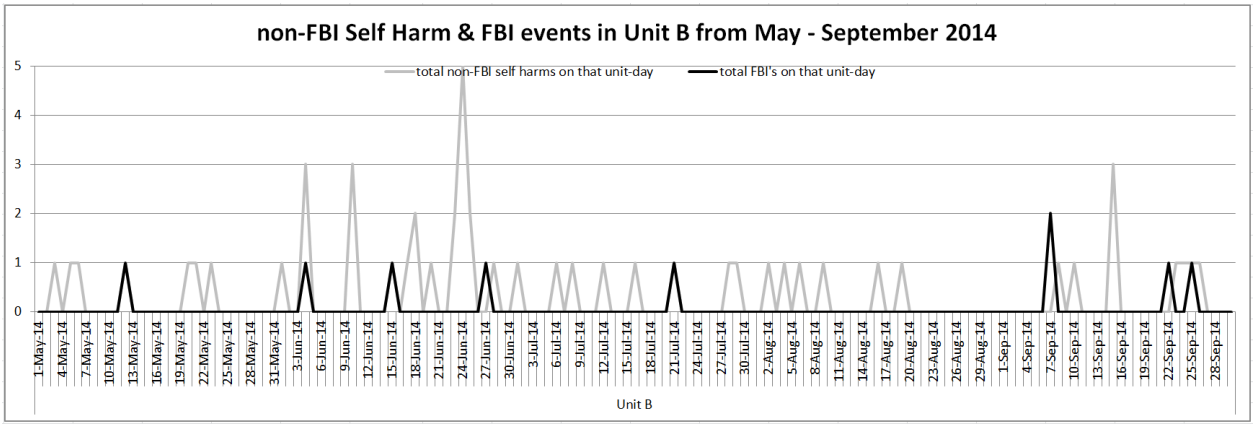
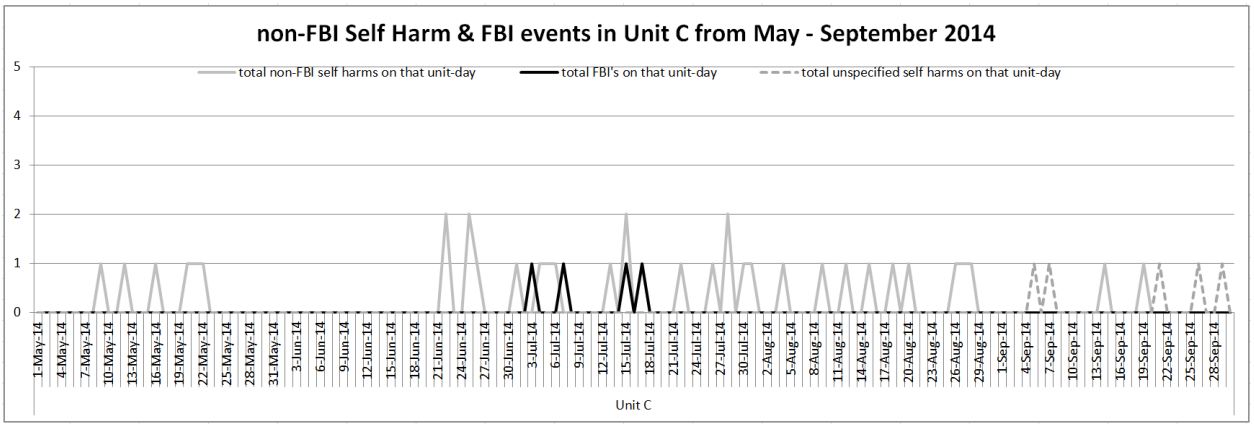


Fig. 2c:



CONCLUSION:

These preliminary data suggest that there are several patterns of FBI behavior. This is suggested first by the patient characteristics seen in Fig 1, which appear to fall into two categories: those for whom FBI is just one out of many self harm impulsive behaviors and those for whom FBI seems to represent a large portion of their self harm behavior. In unit A, there appears to be a correlation between FBI and other self harm events; the pattern and high frequency of FBI suggests a possible “infectious” spread among the patients on that unit. This pattern is not seen on the other units and will be further explored by identifying the specific patients involved in the different patterns of behavior on the several units. It is of note that unit A showed a concentration of FBI and other self harm behaviors clustered in a 3 week span; this may have been associated with identified changes occurring throughout the hospital at the time. After additional clinical information and patterns have been identified in this ongoing project, statistical as well as descriptive approaches will be used to generate more specific hypotheses that may be used to test clinical interventions, both pharmacologic and behavioral, for hypothesized patient subgroups.

AMY PATEL (NJMS 2018)

PROJECT TITLE: **INTIMATE PARTNER VIOLENCE IN CLINICAL SETTINGS: PREVALENCE & WILLINGNESS TO RECEIVE INTERVENTION**
MENTOR: **PING-HSIN CHEN, PhD, ASSISTANT PROFESSOR**
DEPARTMENT: **FAMILY MEDICINE**

PARTICIPATION DESCRIPTION:

I was the medical student described in the methods. As such, I was responsible for screening all of the patients in all three locations (University Hospital Ob/Gyn clinic, New Jersey Family Practice Center, and the Pediatrics Clinic). If any patient screened positive and was identified as a victim of IPV, I referred her to the attending physician and, in Ob/Gyn, to the social worker, as well. Then, I contacted a local domestic violence agency on the victim's behalf. I also contacted the agency a few weeks later to make sure that the victims had been given a call by one of their representatives. I constantly updated the results from the screenings and, when it came time to analyze them, I decided how that should be done. I also interpreted the results and determined what conclusions could be drawn for them.

OBJECTIVE:

In the United States, an estimated 12-35% of female patients in emergency departments and family medicine offices experienced intimate partner violence (IPV) within the past year. Further, an estimated 4-8% of women experience IPV during pregnancy.[1-4] These numbers may be under-reported because of the barriers to disclosure. Nevertheless, the consequences of IPV are staggering and include immediate and long-term effects. There negative effects include injury, death, chronic mental and psychological health conditions, sexually transmitted diseases, and unintended pregnancies.[1] Medical costs for IPV have approached $6 billion annually.[3] As such, the United States Preventative Services Task Force (USPSTF) established more proactive recommendations for IPV screening in 2013 that clinicians screen all women of child-bearing age and refer women screening positive to intervention services.[1]

The objective of this study is to assess the prevalence of IPV in clinical settings and the willingness of women identified as victims to receiving an intervention.

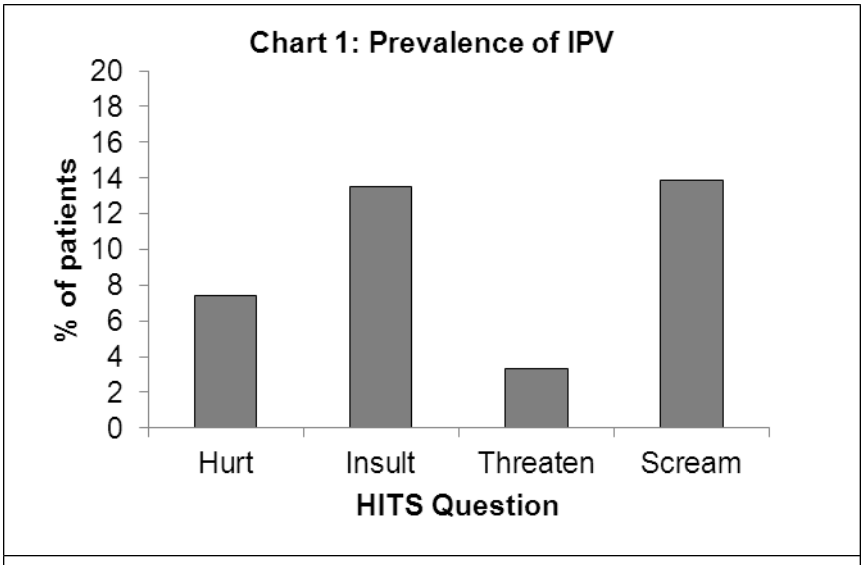
METHODS:

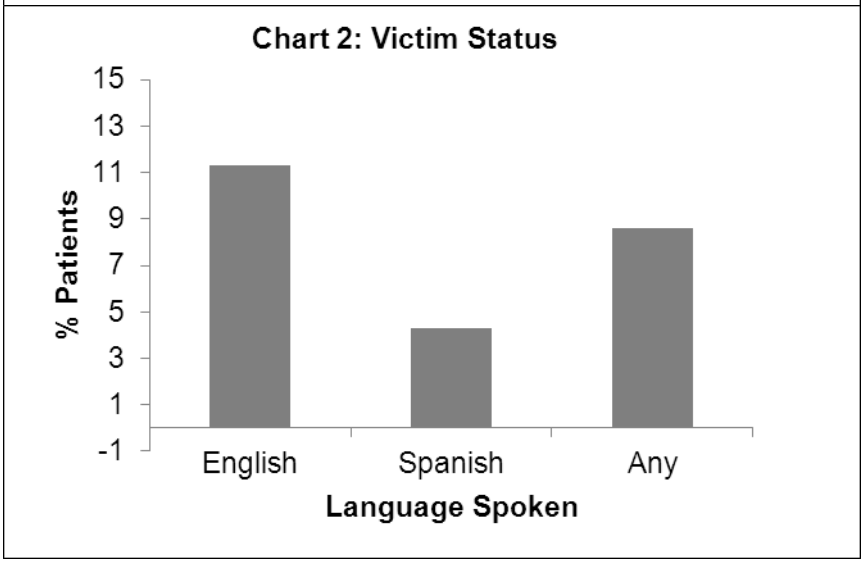
Between June 1st and August 7th, 2015, 244 women were screened for IPV at the University Hospital Ob/Gyn clinic (n=208), New Jersey Family Practice Center (n=28), and the Pediatrics Clinic (n=8). Of the women screened, 61.9% (n=151) spoke English and 38.1% (n=93) spoke Spanish. In the exam room, before the patient was seen by the doctor, a medical student asked patients the HITS (**H**urt, **I**nsult, **T**hreaten, **S**cream) questions. The HITS tool screens for IPV and different forms of abuse: with the H indicative of physical abuse, the I and T of psychological abuse, and the S of verbal abuse. In situations where the patient was Spanish-speaking, she was asked to fill out the HITS Spanish form and a phone translation line was used where available. A standard cutoff score of >6 was used to determine victim status. The medical student reported any woman who screened positive to the attending doctor and, in Ob/Gyn, the social worker. Victims were offered four different intervention programs: (1) children's therapeutic program, (2) parent education program, (3) support group, and (4) counseling services. If the victim expressed interest in an intervention, a community domestic violence agency was contacted on her behalf. A representative of the agency would later contact the patient directly at a phone number deemed safe by the patient. A follow-up phone call was made to assure the patient had been contacted. In Ob/Gyn, a social worker was also present, so patients who screened positive

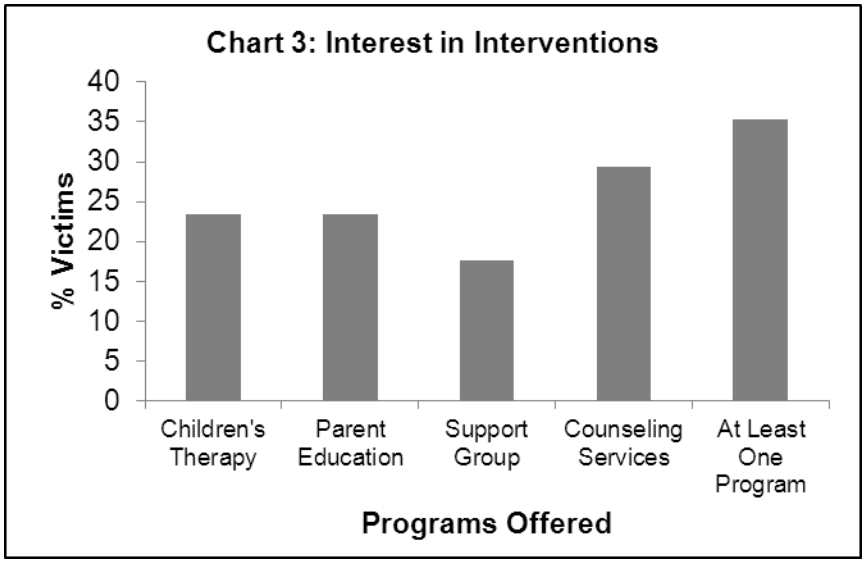
were referred to the social worker, who then worked with the medical student to contact the community domestic violence agency.

Summary:

Screening results indicated that 7.4% of women were physically hurt, 13.5% were insulted, 3.3% were threatened, and 13.9% were screamed or cursed at by their partners (Chart 1). Overall, 8.6% of the women screened were identified as victims of IPV (Chart 2). Of those that spoke English, 11.3% were identified as victims; 4.3% of Spanish-speakers were identified as victims (Chart 2). There was no significant difference in the prevalence of victims between English- and Spanish-speaking women (p=0.06). Though no pediatric or family medicine patients were interested in programs, overall 35.3% of the victims were interested in at least one program, with 23.5% interested in the children's therapeutic program, 23.5% interested in the parent education group, 17.6% interested in the support group, and 29.4% interested in the counseling services (Chart 3).







CONCLUSION:

Overall, 8.6% of women screened were identified as victims and 20.5% experienced at least one form of abuse. This number may be an underestimate the actual prevalence of IPV in this population. This may be because, in this study, a medical student, with whom the patients had never had any previous contact, was the one to ask the HITS questions. Furthermore, there are a considerable number of barriers to the disclosure of abuse, which lead to the under-report of IPV. These include language barriers, the demeanor of the provider, and the readiness of the victim for change.[2] Some victims of IPV stated that they were never asked about abuse by their healthcare providers, and, if they were asked, they never felt comfortable enough to answer questions about abuse truthfully. More programs are needed for healthcare professionals to become adept and comfortable with asking about IPV. Physicians who are more practiced at asking these questions are also more likely to make their patient comfortable and be able to elicit disclosure about abuse.

Among the 8.6% of women identified as victims, only 35.3% were interested in an intervention program. Previous studies have shown that victims of IPV undergo five stages of change (precontemplation, contemplation, preparation, action, and maintenance). However, it can take victims months to years to progress from the precontemplation stage, in which they are not aware of or deny the fact that they are in an abusive relationship, to the action stage, in which they actually effect change in their lives.[4] Victims of IPV stated that they required some event to trigger a need for change in their lives. For example, a victim can be in an abusive relationship, but still be hopeful that her situation would improve and that she could deal with whatever was happening. However, possible injury to their children, often serves as a sort of trigger episode for many victims of IPV and propels them through the five changes of stage. Another explanation for the low interest in intervention amongst the identified victims was that the study only included a one-time screening and, so, the patients may not have been ready or comfortable enough at that point in time to disclose abuse and accept an intervention. This raises the issue of the importance of follow-up. Routinely asking about IPV not only builds the patient-provider relationship, which increases the patient's comfort with disclosure, but also brings awareness to the patient that her doctor is able to help victims of IPV.

The population screened was diverse and a large proportion was comprised of Spanish-speaking patients. Due to the screening process, Hispanic patients were probably less likely to disclose IPV. Rather than the personal, one-on-one interaction with English-speaking patients, the interaction with Spanish-speaking patients involved either the Spanish version of HITS that the patients were required to fill out themselves without any discussion with the medical student or a translation line which required the medical student to talk to an interpreter on the phone, who would subsequently speak to the patient. Both methods of communication diminished the rapport between the provider and the patient, making disclosure less likely. A previous study has already shown that 53% of Spanish-speaking women are more likely to disclose abuse if their provider also speaks Spanish.[2] As such, more attention needs to be paid to language and cultural barriers to disclosing and further studies are needed to determine the best screening process in these diverse populations.

The prevalence of IPV may be underestimated due to various barriers to disclosure. More provider training and patient education may be helpful in promoting disclosure and willingness to accept intervention.

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MICHAEL PICO (NJMS 2018)

PROJECT TITLE: **AMELIORATING THE NEGATIVE EFFECTS OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS THROUGH BRM TARGETING**
MENTOR: **ELIZABETH MORAN, PhD, PROFESSOR**
DEPARTMENT: **ORTHOPEDICS**

PARTICIPATION DESCRIPTION:

I began working on my project in April. Under the guidance of Dr. Moran and Stephen Flowers, I helped plan experiments to test the effects of glucocorticoids on mouse preosteoblast cells.

My responsibilities included:

Culturing 3 preosteoblast cell lines. Each cell line was cultured for 28 days. Because I started in April, I was able to culture my cells for 3 cycles of 28 days.

Staining my cells with Alkaline Phosphatase and Alizarin Red S. Each cell line was stained at days 0, 7, 14, 21, and 28. I performed 3 rounds of staining for each cell line.

Conducting real-time PCR assays. I tested my cell lines for expression of the following genes: osteocalcin, osteoprotegerin, and BRG-1. I performed 3 rounds of PCR assays for each gene.

Statistical analysis of my PCR results. This included finding averages, standard errors, and p-values for my results.

Performing ChIP assays. I performed 2 rounds of ChIP assays for my cells.

INTRODUCTION:

Despite their therapeutic potential, glucocorticoids can have profound effects on bone cell differentiation and function. Patients taking glucocorticoids typically experience bone loss within the first few months of treatment. Even modest doses of glucocorticoids greatly increase the risk of fractures of the spine and hip (Henneicke et al. 2014. Trends Endocrinol Metab. 25(4):197-211).

- Prior studies in this lab reveal that BRM knockout mice are resistant to age induced osteoporosis because of an increased osteoblast progenitor pool Nguyen et al., 2015 Stem Cells 2015 Jun 8. doi: 10.1002/stem.2064.
- From this, we hypothesize that BRM deficient preosteoblasts might be resistant to the effects of glucocorticoids.
- BRM and BRG1 are two alternative ATPases of the mammalian SWI/SNF chromatin remodeling complex. They control gene expression during differentiation.
- In mesenchymal stem cells, knockout of BRM causes accelerated progression towards the osteoblast phenotype. Conversely, knockout of BRM in mesenchymal stem cells impedes adipocyte differentiation.

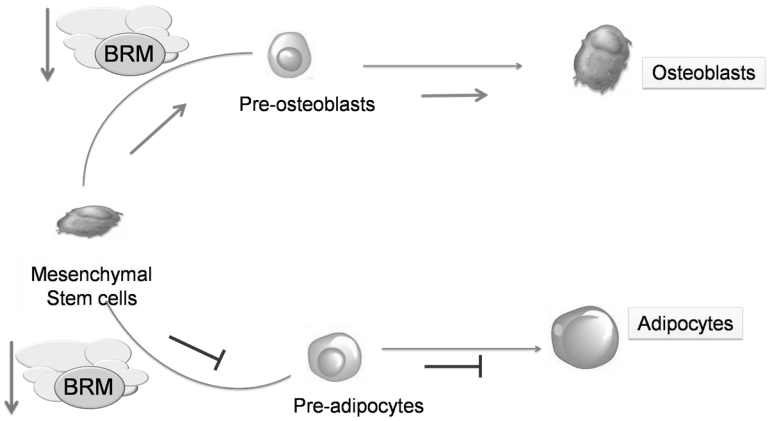


Figure 1. BRM deficiency in mesenchymal stem cells favors **osteoblastogenesis** over adipogenesis.

OBJECTIVE:

- Using the MC3T3-E1 preosteoblast cell line as a model, osteocalcin (OSC) expression and alkaline phosphatase staining as indicators of bone cell differentiation, and mineralization assays as an indicator of mature bone cell formation, we intend to study the interactions between BRM and the glucocorticoid receptor (GR) in differentiating osteoblasts.

- Osteocalcin expression is blocked by dexamethasone treatment (a glucocorticoid) in MC3T3-E1 parental cells. (Stromstedt et al., 1991, Mol Cell Biol 11(6): 3379-83)

- We hypothesize that in BRM-depleted MC3T3-E1 cells, the negative effects of glucocorticoids will be negated due to the loss of BRM repression of differentiation. This will be tested over the course of osteoblast differentiation, which takes up to 4 weeks.

METHODS:

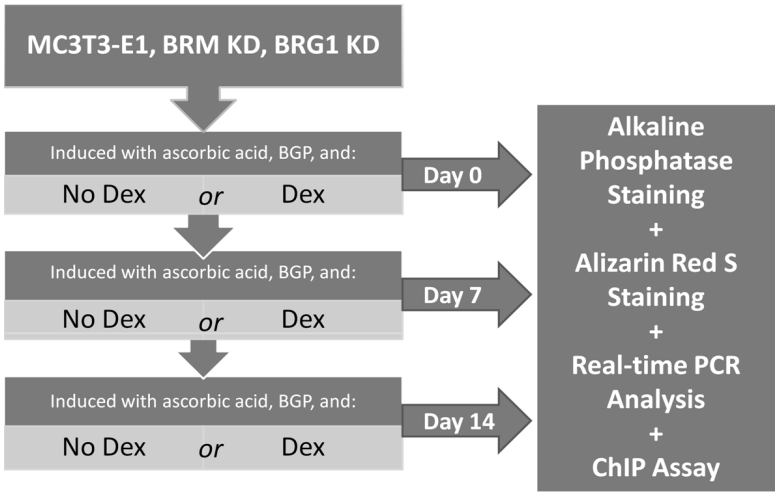
- Cell culture - MC3T3-E1 parental, BRM-depleted, and BRG1-depleted cell lines were cultured in α-MEM with 10% FBS and 1% Penicillin/Streptomycin. G418 was used to maintain selection for the siRNA sequences. Generation of the knockdown lines was described previously (Flowers et al., 2009. J Biol Chem 284(15): 10067-75). Cells were induced with .05 mM ascorbic acid and 10 mM β-glycerol phosphate. Half of the cells were treated with 1 μM dexamethasone at the time of induction. Cells were harvested for analysis at days 0, 7, and 14 after induction.

- Alkaline Phosphatase Staining—Cell monolayers were rinsed in PBS, fixed in 100% methanol, rinsed with PBS, and then overlaid with 1.5 ml of 0.15 mg/ml BCIP plus 0.3 mg/ml NBT for 30 minutes, and rinsed again with PBS three times.

- *Mineralization Assay*—Cell monolayers were washed with PBS, covered with 0.1% alizarin red S for 10 min, and then rinsed with PBS three times.

- Real-time PCR assays were performed according to established lab protocols. Data were analyzed using the PCR Array Data Analysis Web Portal.

- Chromatin immunoprecipitation (ChIP) assays were performed with the EZ ChIP™ system, according to established lab protocols.



SUMMARY OF RESULTS:

- Alkaline Phosphatase staining reveals differentiation is blocked by dexamethasone treatment in parental cells, but BRM knockdown cells resist the effects of dexamethasone

Figure 2. Alkaline phosphatase staining is an early indicator of differentiation; positive cells stain purple-black.

- Mineralization is a biological indicator of mature osteoblast function. Mineralization is blocked by dexamethasone treatment in parental cells, but not in BRM knockdown cells

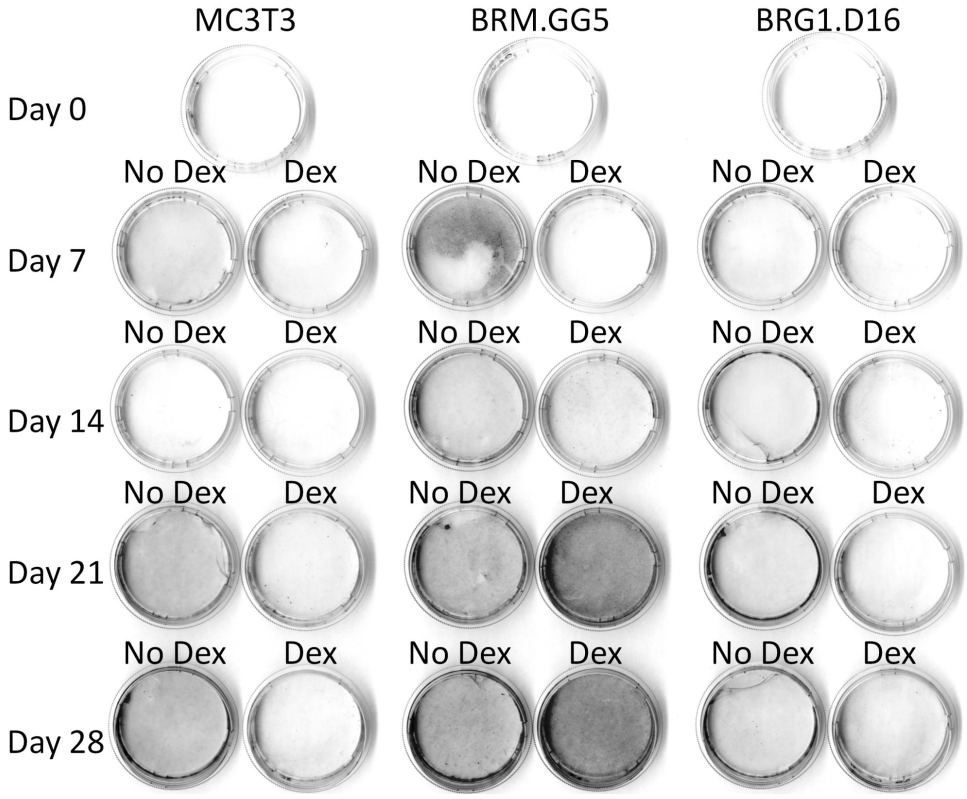


Figure 3. Alizarin Red S indicates the presence of mineralized calcium-containing compounds in the cell matrix.

Osteocalcin gene expression is a quantitative indicator of osteoblast differentiation, and BRM depleted cells resist the negative effects of dexamethasone.

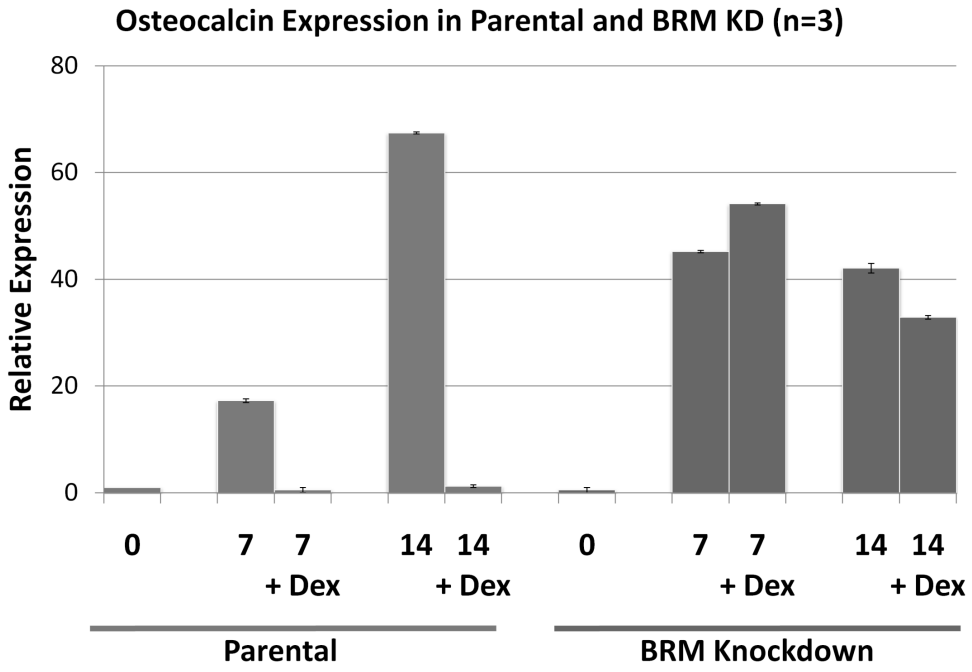


Figure 4. Real-time PCR analysis from three independent experiments was conducted to measure osteocalcin expression, normalized to glyceraldehyde-3-phosphate dehydrogenase expression.

CONCLUSION:

- Alkaline phosphatase staining, and real-time PCR analysis indicate BRM depleted cells are resistant to the negative effects of glucocorticoids.

- The mineralization assay is an end point biological assay that further indicates BRM depleted cells are resistant to the negative effects of glucocorticoids.

- Chromatin immunoprecipitation (ChIP) assays are currently being completed to determine whether glucocorticoid treatment will cause the glucocorticoid receptor to maintain association with the osteocalcin promoter even after differentiation has been induced, and whether BRM is required for such an effect.

- In vivo studies are being conducted to study the effects of glucocorticoid induced osteoporosis in BRM KD mice.

- Long term goals involve BRM targeting as a potential therapy for glucocorticoid induced osteoporosis.

VARSHA RADHAKRISHNAN (NJMS 2018)

PROJECT TITLE: **GENDER DIFFERENCES IN ADOLESCENT SLEEP HEALTH AND THE EFFECTS OF INSTANT MESSAGING AND CHRONIC HEADACHE IN MALES VS. FEMALES**
MENTOR: **SUE MING, PhD, MD, PROFESSOR**
DEPARTMENT: **NEUROLOGY AND NEUROSCIENCES**

PARTICIPATION DESCRIPTION:

I was personally involved in proposing the hypothesis and distributing surveys to high school students at Linden High School. I collected approximately 246 surveys to add to the preexisting data. I organized the data for statistical analysis, conducted the literature search, and authored both the presentation and abstract for this study.

INTRODUCTION:

Pubertal shifts in circadian rhythm, sleep-wake cycle, and social pressures can lead to the development of sleep health problems in adolescents, including impaired concentration, fatigue, and memory problems.[1,2] Emerging studies suggest gender differences in adolescent sleep health, with females citing worse sleep health, gastrointestinal problems, anxiety, and depression than males.[3-6] Another factor affect adolescent sleep health is the electronic use, which contributes to late sleep onset due to light exposure induced delay in melatonin release, adolescent females report greater use of texting while males report greater use of videogames.[4,7,8] Furthermore, headaches such as migraine tend to onset or exacerbate during adolescence. Chronic headache also plays a role in sleep health, and current literature also suggests that females suffer from more severe headaches in greater frequency than males due to increased central sensitization to pain.[9-11] Nevertheless, a degree of contention exists in the literature, with some studies suggesting no gender difference while others cite that females suffer from worse sleep health.[4,7,11-13]

OBJECTIVES:

The study aimed to determine whether there is a difference in sleep health between males and females and whether there is a gender difference in terms of texting after lights out or headache occurrence. Furthermore, of those who text after lights out, we aim to determine whether there is a gender difference in terms of academic performance and daytime sleepiness. Likewise, of those suffering from chronic headaches, we will determine whether there is a gender difference in terms of academic performance, late-night texting, and daytime sleepiness.

METHODS:

Anonymous self-complete sleep surveys modelled after Ming et al.[14] were distributed to high school students in grades 9-12 across New Jersey and the Wen Zhou Science Academy High School in the People's Republic of China. A total of 7223 surveys were collected over the span of 4 years. New questions were added to subsequent versions of the questionnaires. Common questions found on all surveys included sleep quantity, quality, and academic performance, while updated questionnaires asked for additional information on technology use before vs. after lights out and headache chronicity. Questions were formatted in multiple choice, yes or no, or filling the blanks. Surveys with blank responses were excluded, leaving a total of 6042 surveys (3183 females and 2859 males). The 6042 high school surveys were analyzed to compare between weekdays vs. weekend, for sleep duration, sleep adequacy, daytime sleepiness, and in general sleep onset, sleep maintenance, and napping. A hypersomnolence score was generated by tally of hypersomnolence symptoms experienced by the student (whether the student napped, had daytime sleepiness, and reported

sleep adequacy during the weekday). Chronic headache (N=872) and instant messaging after lights out (N=4715) were further analyzed. Analysis was performed on SPSS v21. Contingency tables and Mann Whitney U tests were used to compare females vs. males and mean rank was calculated accordingly. The study was approved by the Institutional Review Board of Rutgers New Jersey Medical School and the governing structures of all participating high schools.

SUMMARY:

There was a significant difference in sleep health between males and females. Females reported having significantly less adequate sleep, more daytime sleepiness, poorer sleep maintenance, more texting after lights out, and more headaches than expected whereas males reported significantly more adequate sleep, less daytime sleepiness, better sleep maintenance, less texting after lights out, and fewer headaches than expected. There was no difference in weekend sleep duration or sleep onset between females and males.

As expected, females text more often than males after lights out. However, of those who texted after lights out, females had better academic performance than males. Further exploration of texting habits and frequency is needed to determine differential effects of texting on gender. Contrary to what was expected, there was no difference in daytime sleepiness, messaging after lights out, or academic performance between males and females with chronic headache.

CONCLUSIONS:

There are gender differences in sleep health, texting habits, and headache occurrence, and the impact of late night texting may be different on males vs. females with respect to school performance. However, gender differences in daytime sleepiness, texting habits, and school performance are not apparent in students with chronic headache in this cohort of adolescents. Females likely suffer from poor sleep health from psychosocial and pubertal shifts prior to or during high school and are affected more adversely than adolescent males. The findings that female high school students have worse sleep has many applications, as poor sleep health is associated with depression and anxiety which females are also more prone to developing. Headache severity is also associated with anxiety and sleep problems. It could be worthwhile to explore these gender differences further to see whether varied forms of media affect males vs. females differently or whether frequency of cell phone use or frequency of headache is associated with observable gender difference in sleep health. Lastly, sleep education could be part of high school curriculum to promote healthy sleep hygiene and Behavioral Sleep Modification may be used for students with sleep health problems and headache[15].

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RADHIKA RAGAM (NJMS 2019)

PROJECT TITLE: **ENHANCING LIFESPAN AND STRESS RESISTANCE IN *DROSOPHILA MELANOGASTER* THROUGH FURTHER HEART-SPECIFIC DOWNREGULATION OF RPD3 PROTEIN**

MENTOR: **YONGKYU PARK, PhD, ASSISTANT PROFESSOR**

DEPARTMENT: **CELL BIOLOGY AND MOLECULAR MEDICINE**

PARTICIPATON DESCRIPTION:

Although I was not involved in the original design of this project, I was directly involved with each part of the project tasks. This includes learning and performing all methods (GFP Imaging, quantitative PCR, oxidative stress tests, heartbeat measurements, and aging assays, in addition to baseline fly maintenance. I was also responsible for teaching incoming students about the objectives, hypothesis, and learning the methods in this project, and data interpretation of the results.

OBJECTIVE:

Downregulation of Rpd3, homologue of mammalian Histone Deacetylase 1 (HDAC1), extends lifespan in *Drosophila melanogaster*. However, previous experiments indicated that heart-specific Rpd3 downregulation (rpd3/tinG4) flies did not sustain increased longevity throughout aging in spite of higher resistance to stress. The objective of this project is to investigate whether greater Rpd3 downregulation in the heart would maintain improved stress resistance and/or lifespan. This current project uses the UAS-Gal4 system to regulate heart-specific downregulation of Rpd3. Specifically, this project uses an additional UAS-Gal4 transgene in order to sustain levels of Gal4 and therefore increase stress resistance and lifespan, throughout the aging process. Investigation of the effects of further heart-specific Rpd3 downregulation on lifespan and stress resistance in *Drosophila melanogaster* will be performed via GFP Imaging, quantitative PCR, oxidative stress tests, heartbeat measurements, and aging assays. The hypothesis is that further heart-specific Rpd3 downregulation will consistently increase lifespan and stress resistance throughout aging in Drosophila melanogaster.

METHODS:

GFP Imaging

Three different genotypes (GFP/tinG4,UASG4; GFP/tinG4; GFP/GMRG4) were observed under fluorescent light for GFP staining in different parts of the fly body.

Quantitative PCR

Gene expression of several anti-aging genes in flies with genotypes rpd3Ri/+ and rpd3Ri/tinG4,UASG4 was measured.

Oxidative Stress Test

Five vials of 20 flies per genotype (rpd3Ri/+, +/tinG4,UASG4, rpd3Ri/tinG4,UASG4) were initially starved in vials containing only 300µl distilled water for 6 hours. The flies were then subjected to oxidative stress by adding 300µl of 20mM paraquat solution in 5% sucrose solution. Vials were kept in 25°C and counted for surviving flies.

Heartbeat Measurements

Flies from aging tests were collected and used for heartbeat measurement. Flies from each genotype were anesthetized with 40µl FlyNap and mounted onto glass slides. Heartbeats were then videotaped for 20 seconds at 10x magnification under Olympus microscope, and later counted.

Aging Assay

200 flies from each genotype were collected and placed accordingly into 10 standard cornmeal medium vials, and kept in a 25°C incubator. The surviving flies were counted, and transferred into new vials every 3-4 days.

SUMMARY:

GFP Imaging

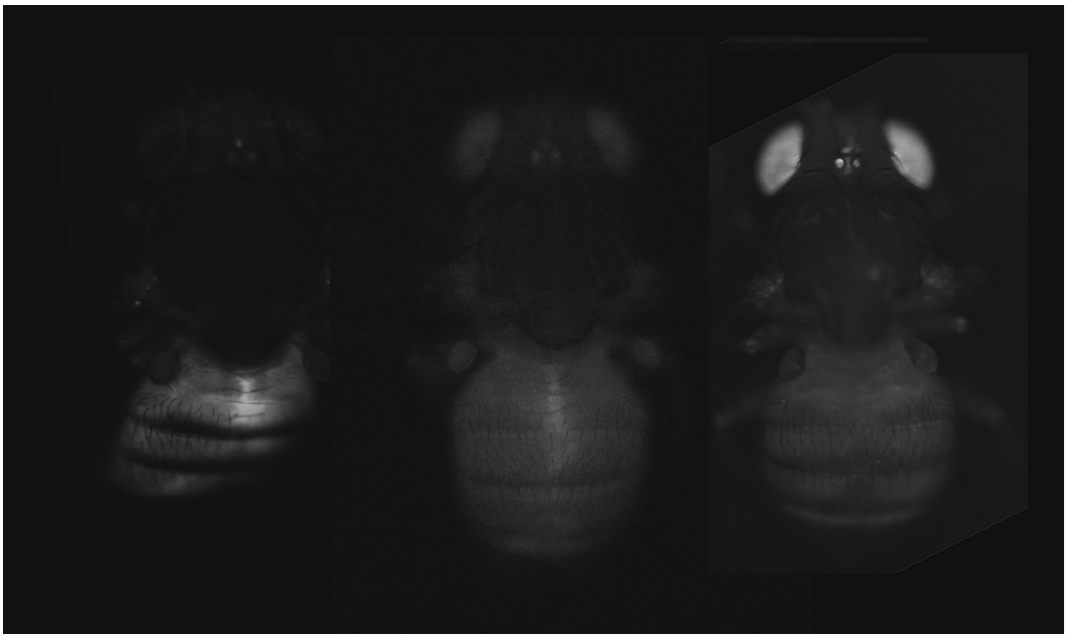

Figure 1. GFP expression in heart is stronger in flies with added UASG4 transgene (GFP/tinG4,UASG4) relative to GFP/tinG4 flies, indicated by stronger GFP signal. GFP/GMRG4 flies show strong GFP signal in fly eye.

Anti-aging gene expression

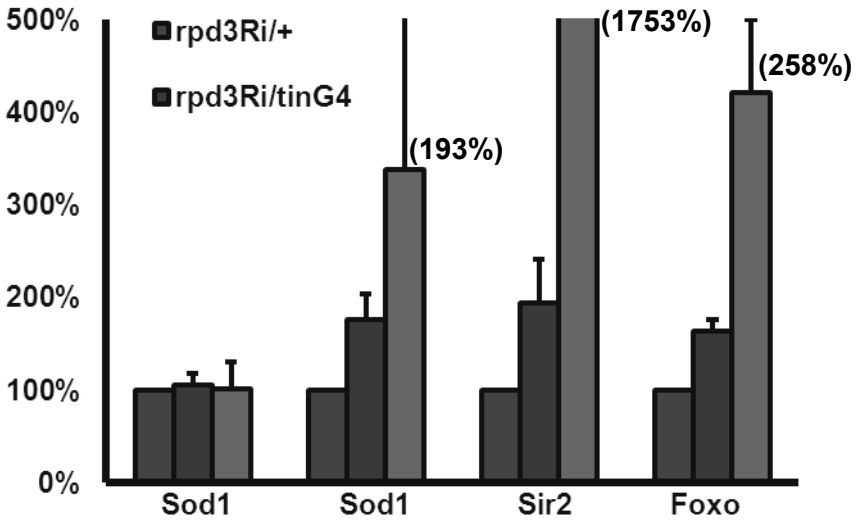

Figure 2. Increased expression of Superoxide dismutase 2 (Sod2), Silent Information Regulator 2 (Sir2), and Forkhead box (Foxo) transcription factor was observed in further heart-specific Rpd3 downregulation (rpd3Ri/tinG4,UASG4) flies. However, Sod1 expression was not affected, showing a specificity of heart-specific Rpd3 downregulation effect.

Oxidation

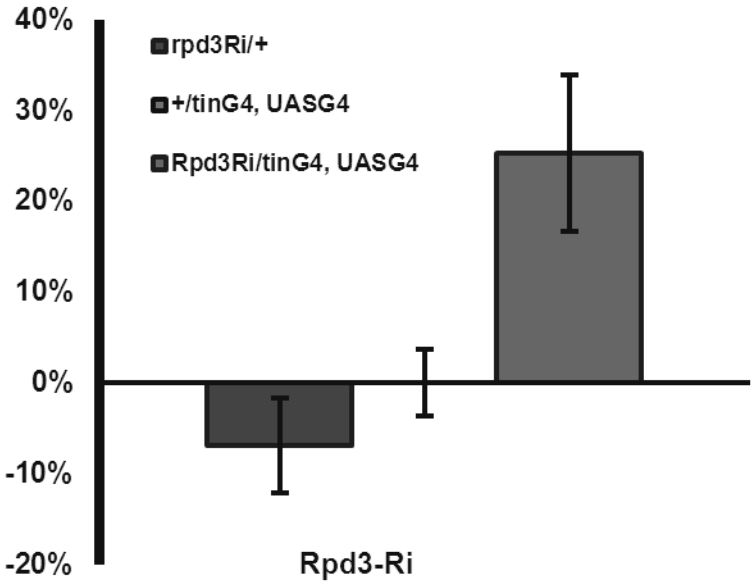

Figure 3. The experimental, Rpd3Ri/ tinG4,UASG4, showed an increased resistance to oxidative stress compared to the two controls (rpd3Ri/+ and +/tinG4,UASG4).

Heart Rate in Aging

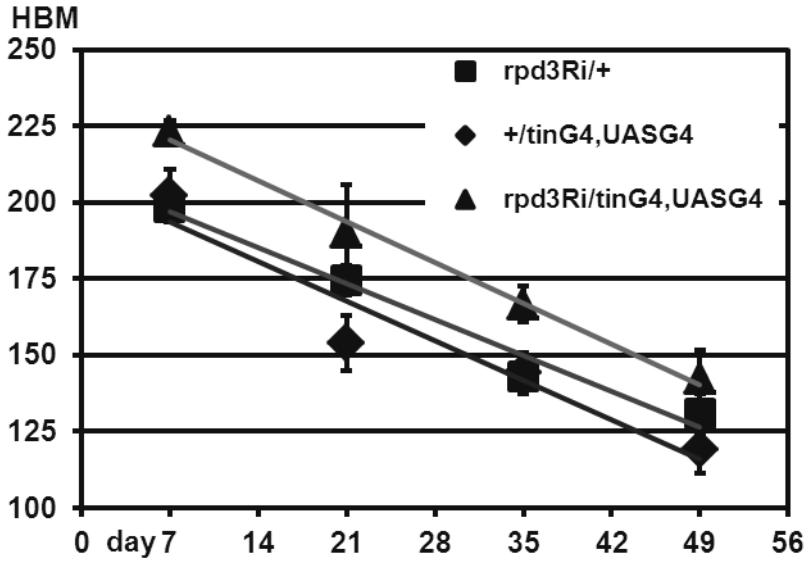

Figure 4. Greater downregulation of rpd3Ri in the heart (rpd3Ri/tinG4,UASG4) showed enhanced cardiac function compared to the two controls (rpd3Ri/+ and +/tinG4,UASG4).

Aging

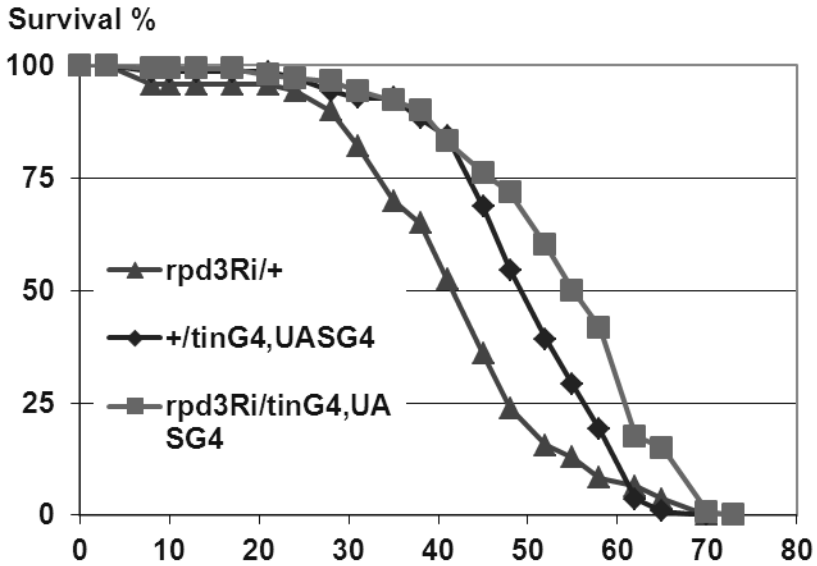

Figure 5. Flies with genotype rpd3Ri/tinG4,UASG4 showed increased survival throughout aging in comparison with control flies (rpd3Ri/+and +/

CONCLUSION:

Heart-specific downregulation of Rpd3 through RNA interference and the UAS-Gal4 system was the approach used in this project. Through these series of experiments, it was concluded that further heart-specific Rpd3 downregulation results in flies with increased resistance to oxidative stress, improved cardiac function, and longer lifespan. Quantitative PCR, a method used to measure gene expression, indicated that there was increased expression of anti-aging genes Sod2, Sir2, and Foxo, in rpd3Ri/tinG4,UASG4 flies compared to the mild heart-specific Rpd3 downregulation (rpd3Ri/tinG4) flies, implying that more downregulation of Rpd3 in heart tissue has more benefits for cardiac function and longevity mechanism. Further studies will focus on why these specific anti-aging genes have an increased expression with decreased Rpd3 expression, and elucidate the pathway(s) responsible for these increased stress resistance and lifespan through heart-specific Rpd3 downregulation in *Drosophila melanogaster*.

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AUGUSTINE J. TAWADROS (NJMS 2018)

PROJECT TITLE: **LOCAL VANADYL ACETYLACETONATE TREATMENT ACCELERATES FRACTURE HEALING IN A MATURE RAT MODEL**

MENTOR: **SHELDON LIN, MD, ASSOCIATE PROFESSOR**
DEPARTMENT: **ORTHOPAEDICS**

PARTICIPATION DESCRIPTION:

As part of this study, I was involved in monitoring the health of the lab's BB Wistar rat colony, including treating the diabetic rats with a slow release insulin implant consisting of palmitic acid and bovine insulin when their blood glucose values exceeded 400 mg/dL. The animals used in this particular project were 26-weeks old and 52-weeks old diabetic-resistant BB Wistar rats. I participated in surgery, which involved intramedullary femur fixation and introducing a closed mid-diaphyseal fracture to the right femur of each rat. I then learned to examine fracture healing by using mechanical testing and histological techniques. Prior to testing the bones' torque to failure using a servohydraulics machine, I was responsible for resecting all surrounding tissue from the femora that may otherwise contribute confounding biomechanical properties. For histological outcomes, I worked with a graduate student to section slides of femora and stain the tissue, allowing us to identify cartilage and new bone.

INTRODUCTION:

As evidenced by multiple past studies, aging delays fracture healing in humans. Similar to these findings in humans, it has been proven that advanced age impairs femoral fracture healing in rats Meyer *et al.* demonstrated that young adult (6 weeks) rats require 4 weeks to regain normal biomechanics post-fracture, while adult (26 weeks) rats take up to 10 weeks to return to normal, and elderly (52 weeks) rats need over 6 months[2]. This diminished bone regeneration results from many age-related pathophysiological changes including various decreased gene expression, delayed cell differentiation, decreased angiogenesis, decreased periosteal formation, and hindered bone remodeling.

In post-fracture management, age correlates with hospital stay length and eventual mortality. Since the life expectancy of the US population is increasing, it is imperative to facilitate fracture healing through innovative science in the aging population. Insulin has been shown to enhance bone healing in animal studies[5-7], yet hypoglycemia is a potential risk unless the exogenous insulin is administered as a slow-release formula[7]. Insulin-mimetic bone healing adjuncts, such as Vanadyl acetylacetonate (VAC), are potentially superior options since the risk of hypoglycemia can be avoided[8]. Our lab previously showed that local intramedullary VAC treatment in young adult rats produces accelerated tissue mineralization and increased biomechanical strength in fractured femora.

OBJECTIVE:

This study evaluated the efficacy of local vanadyl acetylacetonate (VAC) on femoral fracture bone healing in elderly non-diabetic BB Wistar rats (52 weeks) compared to adult rats (26 weeks). We theorize that local administration of VAC enhances fracture healing in mature (26 week) rats and elderly (52 week) rats. To test this hypothesis, early and late parameters of fracture healing were assessed in a non-diabetic BB Wistar rat femoral fracture model using histomorphometry and mechanical testing.

METHODS:

Animal Model:

This study used 41 healthy, non-diabetic, male BB Wistar rats in two age groups, 26-weeks and 52-weeks old. Four of these rats were excluded due to improper fracture location.

Surgical Model:

General anesthesia was achieved by intraperitoneal injection of ketamine (60 mg/kg) and xylazine (8 mg/kg). The right leg of each rat was shaved, and the incision site was cleansed with 70% ethyl alcohol. A 1-cm medial parapatellar skin incision was made over the patella. The patella was dislocated laterally and the intercondylar notch of the distal femur was exposed. An entry hole was made with an 18-gauge needle and the femur was reamed with the same needle. 0.1 ml of either saline or 1.5 mg/kg VAC solution was injected into the intramedullary canal prior to Kirschner wire fixation. Following surgery, a closed mid-diaphyseal fracture was made to the right femur of each rat. Blood obtained from the tail vein was tested for blood glucose levels to monitor for signs of hypoglycemia on the day of surgery, the day following surgery, and the day of sacrifice.

Mechanical Testing

Bilateral femora were resected 4 weeks post-fracture and radiographs were taken to ensure Kirschner wire fixation was maintained throughout the study. The femora were prepared and mechanically tested to failure at a rate of 2°/s of torsion. The torsional testing was completed using a servohydraulics machine.

Histomorphometry

Fractured femora were resected at 7 days or 14 days post-fracture, and processed using standard decalcified histologic techniques. Fractured femora were fixed in formalin, decalcified using 15% EDTA, embedded in paraffin, sectioned into multiple slides and stained with either Masson's trichrome or safranin-orange. Masson's trichrome stain, used to assess new mineralized tissue, consists of Weigerts Iron Hematoxylin, biebrich scarlet and analine blue. Weigerts Iron Hematoxylin is a general nuclear stain, biebrich scarlet stains cytoplasm and muscle, and analine blue stains for collagen. The tissue corresponding to bone appears blue, while cartilage appears red. Safranin-orange was used to assess cartilage formation, which appears pink-red.

Images were then taken at 2.5x magnification and outcome parameters were quantified using Image-Pro Plus computer software. New mineralized tissue and cartilage area were normalized to callus area and expressed as the percent area. Two blinded independent reviewers performed the analysis to minimize inconsistencies between specimens.

SUMMARY:

Histological Evaluation:

Table 1: Histomorphometry at days 7 and 14 post-surgery of 26-weeks old rat model

	Day 7		Day 14	
	% Bone	% Cartilage	% Bone	% Cartilage
Saline control	15.3 +/- 3.5 (n=6)	1.7 +/- 0.8 (n=6)	15.5 +/- 4.0 (n=7)	7.1 +/- 4.3 (n=7)
1.5 mg/kg VAC	19.3 +/- 3.9 (n=7)	3.4 +/- 1.7* (n=7)	20.3 +/- 3.9* (n=8)	7.8 +/- 3.9 (n=8)

Histological analysis of sectioned femora revealed a 49% increase ($p = 0.048$) in cartilage formation 7 days post fracture and a 24% increase ($p = 0.03$) in new mineralized bone within the fracture callus at day 14, compared to saline controls. No difference in cartilage formation was observed between experimental and control group 14 days post-surgery The results suggest that local VAC treatment enhances chondrogenesis within the first 7 days post-fracture, which leads to enhanced mineralized tissue formation by day 14.

Mechanical Testing:

Mechanical testing demonstrated a 68% increase in maximum torque to failure in VAC-treated femora at 4 weeks post fracture.

The data for the 52-weeks old rat model is pending for both histological evaluation and mechanical testing.

CONCLUSION:

As the main objective of this study, this lab has been experimenting with various new treatments for fracture healing in rat models. Other studies have found that insulin or insulin-like growth factor-1 (IGF-1) treatment can enhance fracture healing. The current study using a single injection of local VAC complements these earlier studies, with significantly improved mechanical parameters post-fracture for 1.5 mg/kg local VAC treated animals, compared to saline controls. Our findings also suggest that VAC treatment may enhance fracture healing through a direct stimulatory effect on callus osteoblasts. In vitro, vanadium can stimulate cell proliferation and differentiation in rat osteosarcoma. However, these effects are inhibited at very high vanadium conecntrations. Similarly, Cortizo et al. found that vanadyl(IV)-ascorbate, a vanadium complex similar to VAC, increased Type 1 collagen production, osteoblastic cell proliferation, and mineralized nodule formation (Paglia). In vivo, oral organic vanadium treatment can advance diabetic bone mechanical and material properties. Local VAC acts as an effective agent to improve femoral fracture healing in mature adult rats (26 weeks old) compared to the control saline solution. We are still in the process of completing our study, but we hypothesize that the elderly rats (52 weeks old) will show similar results, Additionally, we are investigating whether VAC augments cell proliferation, growth factor production, and angiogenesis early in the bone healing process, providing the framework for new bone formation and enhanced biomechanical properties observed in this study.

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Cortizo AM, Molinuevo MS, Barrio DA, Bruzzone L. 2006. Osteogenic activity of vanadyl(IV)-ascorbate complex: evaluation of its mechanism of action. *Int J Biochem Cell Biol 38: 1171– 1180.*

Cortizo AM, Etcheverry SB. 1995. Vanadium derivatives act as growth factor—mimetic compounds upon differentiation and proliferation of osteoblast-like UMR106 cells. *Mol Cell Biochem 145: 97– 102.*

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PROJECT TITLE: **GREEN SYNTHESIS AND ELCTRO SPRAY ATMOSPHERIC PRESSURE IONIZATION MASS SPECTRAL STUDIES OF HYDRAZINOCURCUMIN: A POTENTIALLY IMPORTANT DERIVATIVE AS AN ANTI-CANCER AND ANTI-ANGIOGENESIS AGENT**

MENTORS: **BISHAMBAR DAYAL, PhD, ADJUNCT ASSOCIATE PROFESSOR**
MICHAEL LEA, PhD, PROFESSOR
DEPARTMENTS: **MEDICINE AND MICROBIOLOGY, BIOCHEMISTRY AND MOLECULAR BIOLOGY**

A facile microwave-induced synthesis of hydrazinocurcumin having Potent Antiproliferative HT 29 Colon Carcinoma Cell line specificity has been achieved. Microwave irradiation promoted intermolecular cycloaddition of curcuminoids in methanol (40 mgs, curcumin, demethoxycurcumin and bisdemethoxycurcumin) with 1 molar/hydrazine/ THF and triethylamine in the presence of catalytic amount of acetic acid was performed in the domestic microwave oven (MW). The reaction mixture after gentle stirring was carefully heated in the MW for 50 seconds at 5 seconds interval providing a major hydrazinocurcumin derivative in 80% yield. After evaporation of methanol under nitrogen the resultant mixture was resolved and analyzed via analytical and preparatory thin-layer chromatography (Aluminium backed pre-coateed SIL G/UV254 TLC plates in the solvent system: $CHCl_3$:CH_3OH (20:8 v/v). The major extremely polar hydrazinocurcumin and its analogs were only visible in iodine chamber providing hydrazinocurcumin (Rf=0.20), hydrazinodemethoxycurcumin (Rf=0.16) and hydrazinobisdemethoxycurcumin (Rf=0.14). The electrospray atmospheric pressure ionization (ES-API) mass spectra of the hydrazinocurcumin provided a major fragment ion at m/z 217 characteristic of this derivative and derived from the molecular ion at m/z=366 $[M+H]^+$. The parent curcumin metabolites were analyzed TLC solvent system ($CHCl_3$: CH_3OH, 19:1 (v/v) were visualized and detected only under UV light. Their (ES-API) mass spectra in the positive ion mode provided m/z 309 $[M+H]^+$, m/z 339 $[M+H]^+$ and m/z 369 $[M+H]^+$ and (ES-API) in (-ion mode) provided m/z 307, 337 and 367 respectively.

The reaction reported here was completed in 50 seconds in comparison to the literature reported which takes 24 hours for completion.

This facile methodology for synthesizing hydrazino curcumin derivatives will be extremely useful for studying their effect on the growth of various cell lines specificities as potent chemopreventive agents and inhibitors of endothelial cell proliferation.These studies will be also helpful in modulation of DNA methylation and gene expression changes (epigenetic alterations) in colorectal cancer cell lines.

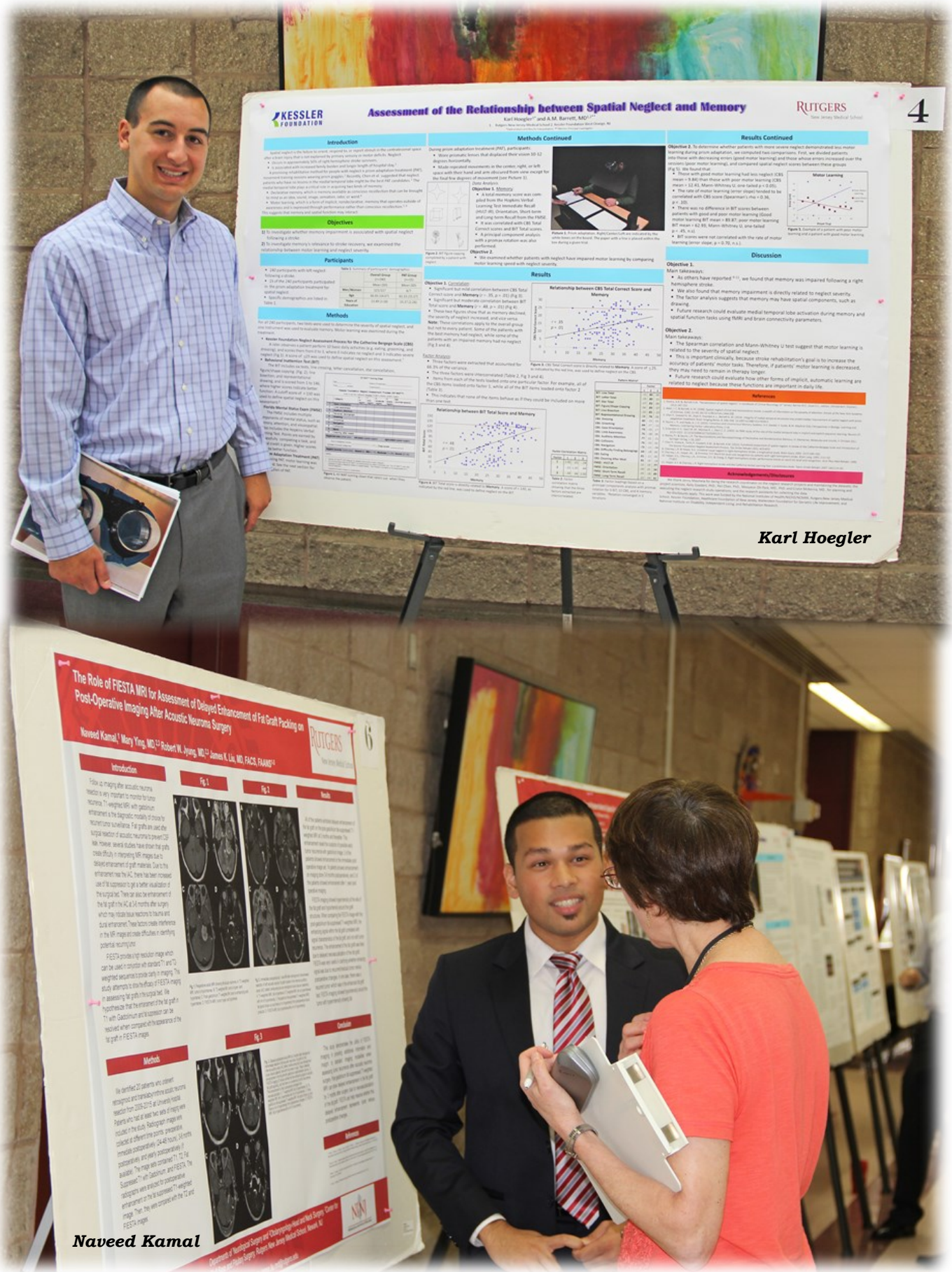
Rationale for Synthesizing Hydrazinocurcumin (HC):

Potential Synergistic anti-cancer effect of Hydrazinocurcumin:

The parental compound curcumin inhibits proliferation of HT29, colorectal colon cancer cells in a non-selective manner. We will investigate the cell line specificity of HC on different colon cancer cell lines and record anti-proliferative activity spectrum. Examination of the effect of HC on cell proliferation using MTT colorimetric assay has shown the most potent growth inhibitory activity against bovine aortic endothelial cells (BAECs) almost 30 -fold higher than that of curcumin. Furthermore, *in vivo* experimental angiogenesis assays have been performed suggesting that hydrazinocurcumin has the potential to become a anti-angiogenic drug as well.

It is therefore important to develop drugs for resistant cancer cells and complete killing of cancer cells should be a desirable goal.

Winners of the 2015 Poster Symposium Competition



Karl Hoegler

Naveed Kamal


0
Autoimmunity and Cancer: One gene linking two diseases
Betsy J. Barnes, Ph.D.
Associate Professor
Rutgers Biomedical and Health Sciences
July 23, 2015


Interferon Regulatory Fa
DNA-binding pro
Conserved DNA
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✓ Host defens
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apoptosis, cell
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Postoperative complications in Sialoadenectomy patients compared by racial demographics.
Anudeep Alberts, NERA III, Kristen A Echanique, BS, Emily Marchiano, BA, Meghan Crippen JB, Jean Andrews Eloy, MD
Department of Otolaryngology, Rutgers New Jersey Medical School, Newark, New Jersey
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Ethnic Variation in Presence and Location of Colorectal Screening Colonoscopies: A Retrospective Study in a Minority Population
Assessment of the Relationship between Spatial Neglect and Memory
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The Role of FIESTA MRI for Assessment of Delayed Enhancement of Fat Graft Packing on Post-Operative Imaging After Acoustic Neuroma Surgery
Ethnic Variation in Presence and Location of Colorectal Lesions Found in Screening Colonoscopies: A Retrospective Study in a Minority Screening Population
Neuromodulation as a Potential Treatment for Dysarthria
Dose Response Effect of Insulin on Posterolateral Spinal Fusion
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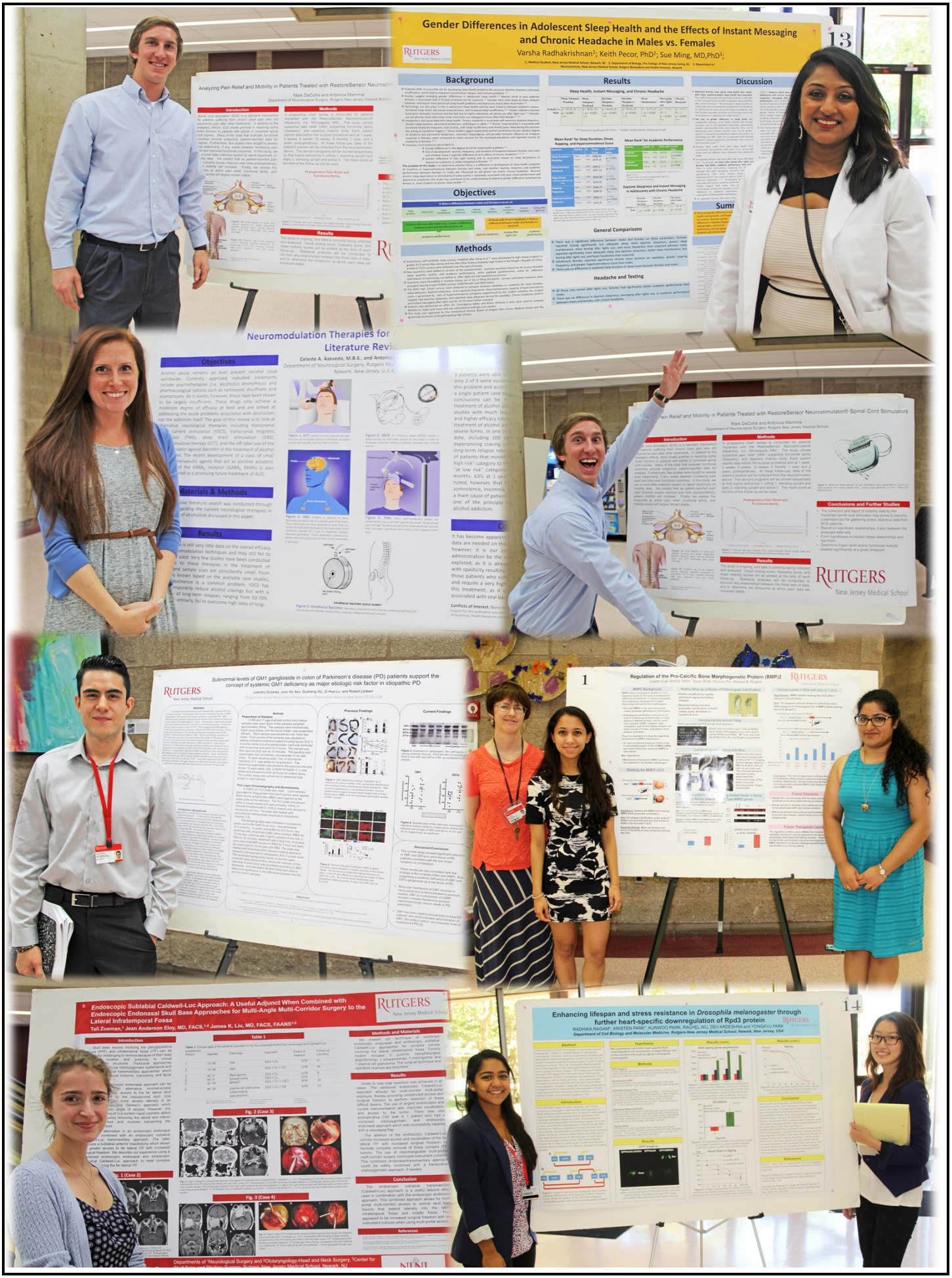
Intimate Partner Violence in Clinical Settings: Prevalence & Willingness to Receive Intervention
Amy Patel, BS; Ping-Hsin Chen, PhD
Department of Family Medicine, Rutgers – New Jersey Medical School
EXIT
Cloning and Purification of Bacterial cGAMP Phosphodiesterases


Gender Differences in Adolescent Sleep Health and the Effects of Instant Messaging and Chronic Headache in Males vs. Females
Varsha Radhakrishnan; Keith Pecor, PhD; Sue Ming, MD,PhD;
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Analyzing Pain Relief and Mobility in Patients Treated with RestoreSensor Neurostimulator® Spinal Cord Stimulators
Mark DeCotiis and Antonios Mammis
Department of Neurosurgical Surgery, Rutgers New Jersey Medical School
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Celeste A. Azevedo, M.B.S., and Antonio
Department of Neurological Surgery, Rutgers Ne
Newark, New Jersey, U.S.A.
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Subnormal levels of GM1 ganglioside in colon of Parkinson's disease (PD) patients support the concept of systemic GM1 deficiency as major etiologic risk factor in idiopathic PD
Leandro Gutierez, Joon Ho Seo, Gusheng Wu, Zi-Hua Lu, and Robert Ledeen
Rutgers New Jersey Medical School, Neuroscience Department, Newark, New Jersey 07103, USA
Regulation of the Pro-Calcific Bone Morphogenetic Protein (BMP)2
Lauren Cue, Annica Tekin, Tejan Shah, Youhua Zhu, Melissa B. Rogers
Endoscopic Sublabial Caldwell-Luc Approach: A Useful Adjunct When Combined with Endoscopic Endonasal Skull Base Approaches for Multi-Angle Multi-Corridor Surgery to the Lateral Infratemporal Fossa
Tali Zusman,1 Jean Anderson Eloy, MD, FACS,1-3 James K. Liu, MD, FACS, FAANS1-3
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Departments of 1Neurological Surgery and 2Otolaryngology-Head and Neck Surgery, 3Center for
NJMS
Enhancing lifespan and stress resistance in Drosophila melanogaster through further heart-specific downregulation of Rpd3 protein
RADHIKA RAGAM*, KRISTEN PARK*, KUNWOO PARK, RACHEL WU, DEVI ARDESHNA and YONGKYU PARK
Department of Cell Biology and Molecular Medicine, Rutgers-New Jersey Medical School, Newark, New Jersey, USA
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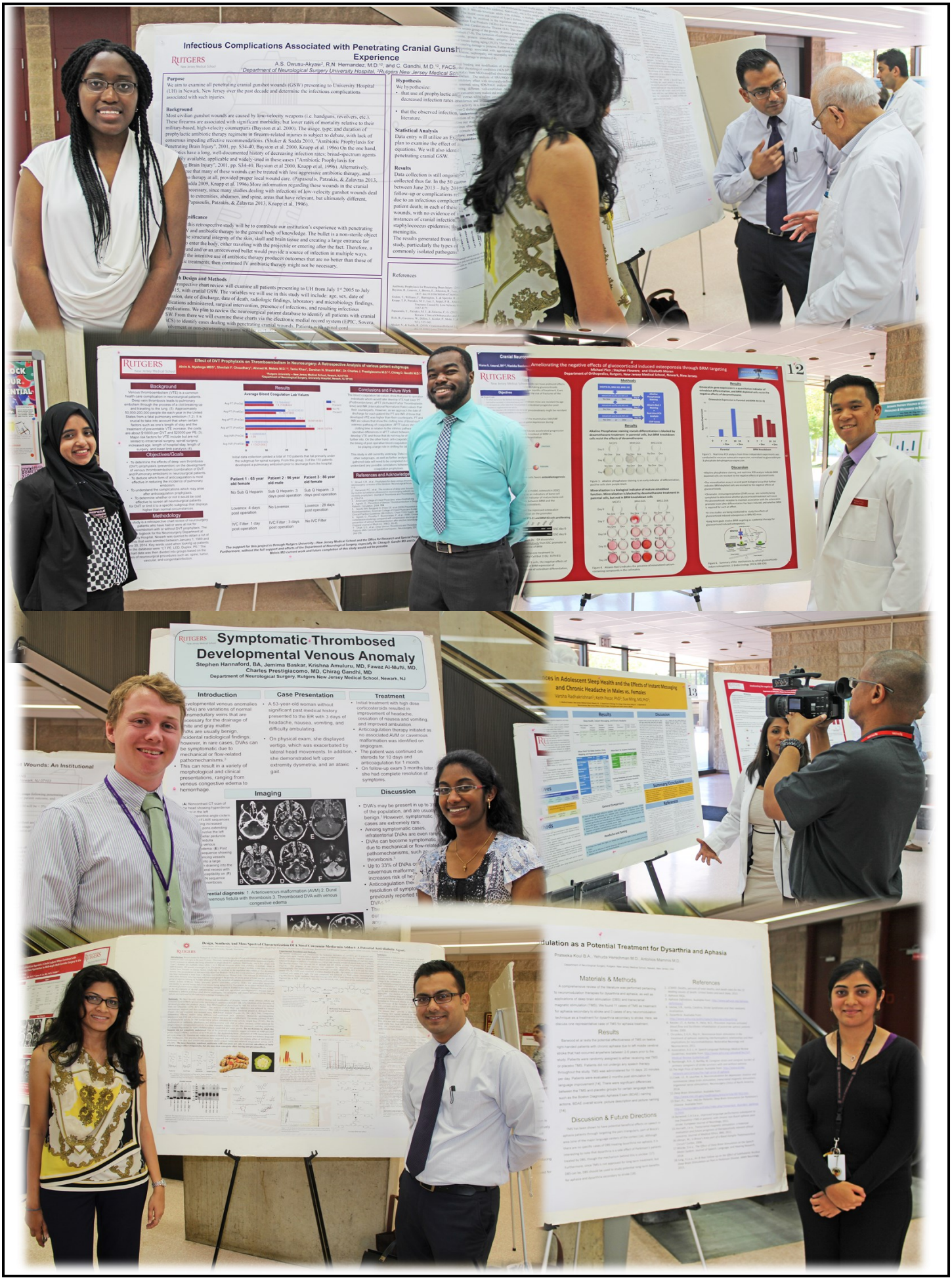
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Symptomatic Thrombosed Developmental Venous Anomaly
Stephen Hannaford, BA, Jemima Baskar, Krishna Amuluru, MD, Fawaz Al-Mufti, MD, Charles Prestigiacomo, MD, Chirag Gandhi, MD
Department of Neurological Surgery, Rutgers New Jersey Medical School, Newark, NJ
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Enhancing lifespan and stress resistance in Drosophila melanogaster through further heart-specific downregulation of Rpd3 protein
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Evidence of a role of the SWI/SNF complex, PU.1, and PRMT5 in 1,25(OH)2D3 regulation of cathelicidin antimicrobial peptide (CAMP) in lung epithelial cells
Kamil Lupicki, Ran Wei, Puneet Dhawan, and Sylvia Christakos
Cranial Neuropathies Secondary to Intracranial Aneurysms: A Case Series and Literature Review
UNIVERSITY HOSPITAL
Cervical Fracture Patients Receiving Spinal Fusions
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The Impact of Science and Medicin
Working together is imperative.
– Translational research which moves scientific research findin
lab, clinical, or population studies more quickly into medical
the population or community level.
– Growing demands for Population Health with the emergenc
also contributes to community based participatory and hea
research to name a few.
– Keep in mind that this work engages other types of researc
includes public health, social science, and others.
– The present and our future research seeks to engage the
patient at an unprecedented level.
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