Effects of Vet TRIIP Yoga Program on Pain and Stress among Veteran Participants
Yoga is a mind and body practice with a 5,000-year history in ancient Indian philosophy (Feuerstein, 2012). The benefits of yoga for both physical and mental health have been supported by research; regular yoga practice yields benefits for pain and stress (e.g., Ross et al., 2010).

Veterans face several risk factors for long-term mental health problems and reintegration to civilian life including posttraumatic stress disorder (PTSD), depression, chronic pain, mild traumatic brain injury (TBI), and other conditions which affect their quality of life and families (Lapiz-Bluhm & Peterson, 2014). A qualitative study exploring yoga in Veterans with PTSD symptoms indicated that they found benefits of yoga for mental stillness, body awareness, and social connection (Cushing et al., 2018). Interestingly, the Veterans identified barriers to the practice as being socially unacceptable, especially for men, and physically unchallenging (Cushing et al., 2018).

With the purpose of honoring and empowering Veterans to create healthy, happy and productive civilian lives, Vet TRIIP (Veterans Team Recovery Integrative Immersion Process) Program provides a short-term multi-modality complementary integrative immersion program for veterans with PTSD and related symptoms (http://www.vettriip.org/). The services provided through Vet TRIIP are emotional freedom technique (EFT), aromatherapy, clothes-on therapeutic massage, qigong, Reiki, chiropractic care, meditation, reflexology, and acupuncture in a two-hour session, as well as yoga, the focus of this specific study.

Veterans attended weekly yoga sessions held on Wednesdays at 11 am-1pm, and at the end they complete a survey at the end of the yoga session asking them to rate their pain and stress at the start of session (Pain-In and Stress-In) and after the yoga session (Pain-Out and Stress-Out) using a Likert scale (1-10, with 1 as least pain and 10 as most pain). For this analysis, data from Veterans (N=92) who attended yoga sessions from January – June 2019 (Number of sessions = 305) were analyzed for differences in pain and stress scores before and after the yoga session. The mean Pain-In score was 4 (SD =1.9) while Pain-Out score was 2.3 (SD=1.6). The mean Stress-In score was 3.3 (SD=2.2) while mean Stress-Out score was 1.3 (SD=1.5). At some sessions, Veterans shared that the yoga improved their physical mobility ("I could move my leg more") and increased their socialization (“If not for these sessions, I would not go out of the house”). The data show that the Vet TRIIP yoga program has been beneficial for Veterans; attendance of yoga sessions reduced their pain and stress levels. Yoga also improved their physical function and socialization. This program should be supported to allow more offerings to increase Veteran participation.
Triple Negative Breast Cancer Inhibition by Isothiocyanates from Cruciferous Vegetables

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It is estimated that 41,760 women will die of breast cancer in 2019 in the United States, of which approximately 50% may be from Triple-negative breast cancer (TNBC), which lacks receptors for hormones estrogen and progesterone, and HER2 receptor. TNBC poses a unique challenge to current breast cancer treatments as it lacks these targets and has higher recurrence and metastatic rates. Only toxic chemotherapies are the current choice of treatment for TNBC, therefore, we explored new compounds with less toxicity to treat TNBC using in vitro cell culture models. We hypothesized that chemicals derived from cruciferous vegetables, such as cabbage, broccoli, brussels sprouts, cauliflower etc., will kill cancer cells by binding to the cysteine residues of physiologically important non-genomic protein targets. Organic compounds in crucifers have long been suspected to have anti-cancer activity. The drugs being tested in our study were Phenyl isothiocyanate (PITC), Benzyl isothiocyanate (BITC), and Sulforaphane (SFN), which are found in Cruciferous vegetables of the Brassicaceae family (commonly known as the cabbage family). In fact increased consumption of such vegetables have been shown to reduce the risk of developing breast cancer. The anticancer properties of these compounds were tested using cultures of highly aggressive triple negative breast cancer cells, MDA-MB-231. We measured the half maximal inhibitory concentration (IC50) of these compounds in inhibiting the cell viability of MDA-MB-231 cells using Cell Counting Kit 8 (CCK8) assay. Measurement of IC50 values of these three compounds after 24h of treatment, suggested that PITC (IC50: 7.5µM) is much more effective in reducing the cell viability of MDA-MB-231 cells, followed by BITC (IC50: 26 µM) and then SFN (IC50: 54 µM). SFN is required about 7 x higher dose than PITC to achieve the same degree of inhibition of cell viability. Growth inhibition is further confirmed by measuring proliferation markers like pAkt and cell cycle inhibitors like p21 and p27 by Western blotting techniques. Our research is being continued to compare the effects of these drugs on normal cells (MCF 10 A) and TNBC cells (MDA-MB-231, HCC1937 and BT20) to assess the efficacy of isothiocyanates as anti-cancer drugs in the pre-clinical setting.
Maternal-Infant Stress Reactivity and Physiological Attunement in Prenatally Opioid-Exposed Newborns

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The quality of early primary maternal-infant dyad relationships is critical to subsequent childhood development. These relationships are supported by the reciprocal behavioral responses within the dyad, known as physiological attunement. Evidence shows that prenatal opioid exposure is an early life stressor for infants, possibly causing emotional, behavioral, and cognitive dysregulation, as well as a disruption of maternal-infant physiologic attunement. While researchers have examined physiological attunement in term and preterm infants, little is known about the impact of prenatal opioid exposure on physiological attunement. Therefore, the purpose of this study is to gain a better understanding of the impact of prenatal opioid exposure on maternal-infant stress reactivity and recovery, and physiological attunement. Pregnant or early postpartum women (N=220) and infants (N=220) shortly following birth are being enrolled in this study. When infants are approximately six months old, mother-infant dyads are assessed for stress reactivity, recovery, and physiological attunement using an established behavioral experiment—the Still Face Paradigm (SFP). This experiment consists of three stages labeled play, still face, and recovery. Each stage is approximately two minutes long, in which physiological reactivity (heart rate variability, respiratory sinus arrhythmia, and salivary biomarkers) is non-invasively recorded at baseline, during each phase of the experiment, and following completion of the SFP. Concurrently observational data is being recorded and coded for maternal-infant interaction patterns. Following the experiment, mothers are asked to respond to a series of self-report instruments where they indicate their past and present physiological states, including childhood trauma, perceived stress, and anxiety. Presently, 43 mother-infant dyads have completed all data collection. Further data collection and analyses are ongoing. The findings of this investigation may provide a better understanding of the impact of prenatal opioid use on early mother-infant interactions. The knowledge gained from this study may lead to the development and implementation of interventions to support the early maternal-infant relationship and improve stress response within this vulnerable population.
Involvement of RNA Binding Proteins Musashi1 and SERBP1 in Glioblastoma Development and Treatment

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Glioblastoma (GBM) treatment has not seen major improvements in decades with an average patient survival of 15 months. Despite all genomic efforts led by the TCGA, recent therapeutic strategies based on identified drivers and genomic alterations have been disappointing. To create new routes for therapy, it is necessary to continue mapping new pathways contributing to gliomagenesis. In this regard, there is growing evidence that RNA binding proteins (RBPs) are major contributors to expression alterations affecting genes in signaling pathways and biological processes critical to GBM growth and response to therapy. RBPs regulate gene expression via RNA processing, mRNA decay and transport and translation and are differentially expressed in tumors at significantly higher levels than other gene families. Importantly, distinct from previous therapeutic strategies that focused on a single proteins or pathways, RBP targeting provides the opportunity of interfering with several cancer pathways at once.

We have established the stem cell regulator Musashi1 (Msi1) as a critical player in GBM and medulloblastoma and as a marker of clinical outcome and response to therapy. To define Msi1 main routes in tumorigenesis, we conducted a comprehensive genomic and functional analysis where we mapped Msi1 target genes, evaluated its effect on expression, defined genes with high expression correlation in GBM and evaluated its impact on tumor growth and cancer phenotypes. Our results showed that DNA replication/repair and cell cycle/division are the processes affected by Msi1 the most. In our model, Msi1 regulates directly and indirectly the expression of a network of genes, promoting cell cycle progression and DNA replication. We propose Msi1 as a therapeutic target and we are working on identifying inhibitors of this RBP.

We identified SERBP1 (Serpine1 mRNA binding protein 1) as a new oncogenic factor in GBM. SERBP1 is a member of the RG/RGG family of RNA binding proteins, which are known for their involvement in neurological and neuromuscular diseases and cancer. As its name suggests, SERBP1 regulates the expression of Serpine1 (PAI-1), a member of the serine protease inhibitor family that is often highly expressed in tumors and implicated in tumor growth and metastasis. In respect to GBM, our study indicates that SERBP1 uses two main routes to contribute to tumorigenesis. It promotes “stemness” by repressing genes involved in neuronal differentiation and enhances the expression of genes driving alternative metabolic pathways often used by cancer cells. Therefore, SERBP1 influences two critical processes that are currently top priority in targeted therapy. Our project will not only deliver new information on molecular mechanisms implicated in these processes but also an inhibitor to be potentially used in the treatment of GBM and other malignancies affected by SERBP1.

SERBP1 is difficult to study because the beginning of the protein structure is disordered. In order to investigate the structure of SERBP1, we require a shorter fragment which is structurally stable. Using PCR based cloning, we produced a plasmid containing only the ordered part of the protein. We will perform assays using this plasmid to compare the full and shortened lengths of SERBP1 to determine whether the shortened fragment behaves differently than the full protein and whether they interact with the same RNA binding motifs. The plasmid containing the shortened fragment of SERBP1 will also help us discover the function of the disordered section of our protein of interest.
Alcohol Detection and Contingency Management for Alcohol Impaired Drivers

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Alcohol impaired driving is among the most frequently committed offenses in the U.S., with Texas having about 1,000 deaths per year due to alcohol-related crashes. The challenge in reducing alcohol driving offense, crashes, and deaths is the frequent incidence of pathological alcohol use, Alcohol Use Disorder, leading to unregulated and uncontrolled drinking and adverse consequences such as alcohol impaired driving crashes. Those with Alcohol Use Disorder often continue the use of alcohol despite the legal and/or social consequences, which in turn may contribute to recidivism of alcohol impaired driving. The aim of our study, therefore, is to develop an efficient and cost-effective intervention to reduce alcohol use and subsequent recidivism of alcohol impaired driving. Our approach uses contingency management, a principle in which one is rewarded for performance of a goal behavior, in this case abstinence from alcohol use. Detection of drinking relies on the SCRAM monitor, an ankle bracelet that detects the level of alcohol in one’s sweat. In weekly visits, SCRAM monitor data is processed, and $50 vouchers are paid for successfully avoiding alcohol use. Abstinence rates of success are compared against a non-contingent control group, and outcome monitoring extends out to 12-months after the 8-week intervention period. Predictors of alcohol abstinence are selected from measures of the Theory of Planned behavior collected across the intervention period. Successful demonstration of recidivism reductions by this intervention delivered in an academic medical center would provide the evidence basis for future work on dissemination and implementation of SCRAM-informed contingency management delivered in pretrial and probation settings.
The Role of Heat Shock Protein 12.6 in Lifespan and Health-span of C. elegans
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Previous research has shown that as an organism ages, protein homeostasis becomes less effective leading to the accumulation of harmful aggregates linked to many neurodegenerative diseases, such as Parkinson’s and Alzheimer’s disease. Molecular chaperones such as heat shock proteins (HSPs) surround misfolded proteins and prevent them from aggregating. Inversely, long-lived organisms such as the Heterocephalus glaber (naked mole rat) have been found to have an elevated level of HSPs. Elevated levels of HSPs provides greater resistance to stressors that normally activates protein homeostasis pathways to provide resistance to heat, reactive oxygen species, and starvation. The purpose of my current research is to investigate the role of the small HSP, Hsp-12.6 under stress conditions in the model organism Caenorhabditis elegans. Lifespan analysis was used to compare the longevity of wild type (N2) to worms that overexpress HSP-12.6 in a muscle specific manner (myo-3p::hsp-12.6::gfp) and with worms that lack HSP-12.6 due to a genetic knockout.

Lifespan analysis revealed that under moderate heat stress (25 C), HSP-12.6 overexpressing C. elegans live significantly longer than the control group (p<0.0001). In contrast, the HSP-12.6 knockout animals lived significantly shorter than control (p=0.0187). Under normal heat conditions (20 C), the overexpression or knockout of HSP-12.6 yields no significant difference in lifespan. We conclude that HSP-12.6 overexpression in muscle significantly improves lifespan at 25 C while the knockout shows evidence of the opposite effect, supporting the evidence that small heat shock chaperones play an important role in protein homeostasis under moderately stressful conditions.

Previous research shows that the activation of transcription factor DAF-16, through daf-2 mutation, disrupts the insulin/insulin-like signaling pathway extending lifespan and health-span by protecting C. elegans from nutritional stress. Studies have also showed that long-lived daf-2 mutants show higher hsp-12.6 transcription. When we reduced the expression of daf-16 using RNA interference to disrupt the insulin-like signaling pathway Lifespan analysis showed a significant decrease in lifespan in both control (p=0.015) and HSP-12.6 muscle specific overexpressor (p<0.0001) groups when daf-16 was knocked down. Overexpression of HSP-12.6 did not influence the sensitivity to nutritional stress through daf-16 down-regulation when compared to control animals under the same conditions. Further experiments will investigate the role of DAF-16 on hsp-12.6 mutant animals. Additionally, the lab intends to investigate muscle specific impacts via mobility assays, and HSP-12.6 expression with imaging experiments utilizing the commercially available GFP reporters.
Ewings sarcoma: NMR investigations of the major fusion protein EWS-FLI1

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Intrinsically disordered proteins are a class of proteins that do not have a fully defined shape or ordered structure, but still carry out a function. Ewing sarcoma (EwS), caused by a balanced chromosomal translocation commonly at the t(11;22)(q12;q24) location, is a malignant bone tumor predominantly found in children and adolescents. EwS may be caused by multiple different chromosome translocation combinations, each dependent on the location of the translocation, but for this project, we focused on the major translocation EWS-FLI1. Due to the unique nature of intrinsically disordered proteins, conventional structural methods such as X-ray crystallography and cryo-electron microscopy can not be used to solve their structure. Alternative methods, such as nuclear magnetic resonance (NMR), must be used to determine their relative structure. The goal for this project was to create a sample of highly concentrated protein to investigate by NMR spectroscopy. Due to the difficulty of expressing the full protein formed from the fusion EWS-FLI1, the protein was further broken down into sections: Serine 194-421 and Serine 218-445. These were chosen to include the functional portions of both the EWS and FLI1 parent proteins, and because they are shorter protein lengths for improved expression. Each section was inserted into vectors containing the solubility tags (maltose binding protein or glutathione S-transferase), or a His$_6$ tag, ultimately resulting in 6 constructs. Methods such as polymerase chain reaction, gel electrophoresis, polyacrylamide gel electrophoresis, and DNA sequencing, were all used to create and confirm the validity of each construct. Results from the polyacrylamide gel electrophoresis showed that predominantly all of the expressed protein were insoluble. Further testing demonstrated that when the target protein was expressed at 16°C, they were found to be more soluble than at 37°C. To create the NMR sample, EWS-FLI1 218-445 was chosen because of its favorable expression in combination with the His$_6$ tag/vector as the target protein. A colony transformed with that vector/construct combination was grown in M9 medium and purified using a BiologicLP system with Immobilized Metal Affinity Chromatography (IMAC) column purification method. Throughout the entire purification process, polyacrylamide gel electrophoresis was used to test to see if the target protein was present. We observed that the soluble fraction of the target protein, EWS-FLI1 218-445 with the histidine tag, would show signs of degradation throughout the process, eventually leading to the majority of the protein being lost to degradation. This was confirmed by the appearance of similar length bands appearing during different stages of the purification, and as a result, unlikely lost due to human error. For the insoluble fraction recovered from the purification, during high pH buffer exchange to the low pH buffer, the protein would constantly precipitate, making it unstable in low pH environments needed for NMR spectroscopy. We observed that the construct EWS-FLI1 218-445, even with a solubility tag such as histidine, the soluble fraction of the target protein was still extremely prone to degradation and a different approach must be used during purification. For the insoluble fraction, a new method must also be developed to prepare the protein for the low pH environment as the protein precipitated during buffer exchange, thus making it unusable for
NMR spectroscopy. Future efforts will focus on altering the expression and purification strategy to improve recovery of soluble protein.
Effects of Gestational Diabetes and Metformin Exposure on Mouse Offspring Social Behaviors

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Rates of gestational diabetes mellitus (GDM) have increased in recent decades, and an epidemiological association of GDM with an increased risk of autism was discovered. In light of this, reports that the anti-diabetic drug metformin may control GDM better than the “gold-standard” insulin raises the exciting possibility that its use might also curb autism. Yet use of metformin in pregnancy is still new, and it is readily transported across the placenta, so concerns were raised about potential long-term adverse effects on offspring. In this study, mice with pharmacologically induced GDM (by streptozotocin (STZ)), or high fat-high sucrose (HFHS) diet-induced GDM and their respective controls were treated with metformin (=200 mg/kg/day) in drinking water throughout pregnancy. Overall the STZ treated dams had fewer litters born than dams from the other groups. Mouse offspring were tested for social interaction and social novelty preference in three chamber choice tests when they were 7-8 weeks old. To increase scientific rigor and reproducibility all behavior data was collected by students trained to measure a specific behavior, and who were unaware of the treatment groups. In a prior published study, our lab observed that males exposed during gestation to metformin engaged in less social interaction than the vehicle control group. In this study we examined preference for social interaction and social novelty through social sniffing of stranger mice, with time spent sniffing an empty cage or known mouse at opposite end of the arena subtracted from the stranger sniffing time value. No differences in male social interaction or preference were evident among treatment groups. For males, the mean ± SEM preferences were: control 63.2 ± 7.5 sec, metformin 39±12.1 sec, STZ 53.3  ± 23.1 sec, and metformin 58.6 ± 14.5 sec (N = 4-14). Female offspring had similar results. Likewise males and females exposed during gestation to HFHS diet ± metformin also exhibited no differences between groups by measure of sniffing time. The reason for this outcome was that small sample sizes in critical STZ and HFHS control groups, due to loss of pregnancies and neonatal pups, did not provide critical data for detecting differences among treatment groups. By contrast metformin appeared to increase the fertility of the mice in the STZ and HFHS diet groups, and was reported in prior studies in fish to be an endocrine disrupter. A follow up study is under way to obtain larger numbers for those groups with low sample sizes. The offspring mice were also tested for repetitive behavior via a marble-burying test, and there were no differences among treatment groups or sexes in this restrictive-repetitive behavioral index, which averaged 5.6 ± 1.2 for male and 5.9 ± 1.8 for female offspring (N = 4 – 17). Metformin-exposed male offspring were more dominant than controls (nonparametric p = 0.04, N = 5), but offspring from GDM pregnancies did not exhibit this effect. While data collection is still underway, these preliminary findings indicate that despite prior findings of adverse effects of gestational metformin exposure on mouse offspring from non-GDM pregnancies on these behaviors, here metformin exposure had no obvious adverse effects on offspring from GDM pregnancies. Metformin enters the placenta via organic cation transporters and targets fetal adenosine monophosphate-activated protein kinase (AMPK) in mitochondria, resulting in metabolic responses which primarily help to control GDM. Under conditions of GDM, we predict any potential adverse impacts of metformin on fetal development to be dissipated through further research into the underlying mechanisms at work in this process.
Breast cancer is the most common cancer in American women with an estimated 268,600 new cases; causing an expected 41,760 women to die from BCa in 2019. The majority of breast cancer (70%) is estrogen receptor positive and these tumors initially respond to estrogen receptor-targeted therapy, however, acquired therapy resistance limit the utility of estrogen receptor-targeted therapy using aromatase inhibitors and antiestrogens. Mutations of estrogen receptor are now recognized as an important mechanism of therapy resistance, and approximately 39% of patients treated with anti estrogen therapy will acquire estrogen receptor mutations. Current therapies are less effective in targeting mutant estrogen receptor. Therefore, development of new inhibitors that target mutant estrogen receptor is clinically important. Vadlamudi lab recently reported the development of a small organic molecule, estrogen receptor coregulator binding modulator (ERX-11), that uniquely interacts with estrogen receptor and blocks the interaction of selective oncogenic coregulators with estrogen receptor. New analogues of ERX11 were designed to target mutant estrogen receptor. In this study, I characterized utility of ERX-245 in targeting mutant estrogen receptor. I have used estrogen receptor wild type and mutant positive MCF7 and ZR75 cells. In MTT based cell viability assays, ERX-245 significantly reduced the cell viability of both wild type and mutant cells with an IC50 of 500 nM. In long-term colony formation assays, ERX-245 significantly reduced the colony formation ability of both estrogen receptor wild type and mutant cells. Boyden chamber assays results indicated that ERX-245 blocks the invasion potential of estrogen receptor mutant cells. Collectively, these results suggest that ERX analogue ERX-245 has potential to therapeutically target mutant estrogen receptor. Future studies including further biochemical characterization of ERX-245 interactions with mutant estrogen receptor and testing its efficacy using xenograft tumors is needed further clinical translation.
Human individuals with autism spectrum disorder (ASD) imitate observed behavior less frequently when compared to age-matched peers. This deficit is most abundantly observed among developing children. These deficiencies subsequently deter learning and cognitive development in children. As ASD is considered a human specific condition, this deficit lacks preclinical assessment tools, such as a mouse model based assay. Recent findings show that typically developed mice can exhibit contagious itch behavior while viewing a scratching demonstrator mouse, as opposed to an ambulating demonstrator mouse; whether autism mice models imitate a demonstrator’s behavior remains unknown. However, the findings of the recent research are highly debated. Here, we show that itch imitation can be measured as a new behavioral phenotype in the mouse model for fragile X syndrome (FXS)- Fmr1KO mice - the most common monogenetic cause of ASD, with 46% of males affected displaying ASD. Fragile x syndrome is a genetic defect in the fragile x mental retardation 1 gene that disables the production of fmrp, a protein needed in the brain for normal synapse development. Identifying this phenotype in the mouse model of FXS enables a measurement for imitative deficits. In doing so, treatments against imitative shortfalls of ASD can be further analyzed with a preclinical model.
HPV/Cervical Cancer Health Disparities Among the South Texas Hispanic Population

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The human papillomavirus (HPV) is a group of more than 200 viruses, 40 of which are related to sexual contact. Almost all sexually active people are infected with a type of HPV in their life, but the immune system can usually control the infection. Although most of these viruses do not cause cancer, it is known to cause cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers. The HPV vaccines provide near 100% effectiveness against cervical cancers, which are all virtually caused by the virus meaning cervical cancer can be essentially eradicated; however, there is a significant lack of HPV vaccinations and cervical cancer screenings among the South Texas Hispanic population. The South Texas community is home to 4.96 million individuals, with the majority being Hispanic and of a lower socio-economic level. This study aims to collect qualitative and quantitative data to investigate the possible links (health literacy levels, Hispanic culture, and language) that discourage HPV vaccinations and cervical cancer screenings among the Hispanic population in the South Texas community. With 224 surveys already conducted in the under-represented population, most participants report there was difficulty navigating scientific knowledge and expected Hispanic cultural norms. Suggestions for promoting education throughout the local community include involving multi-generational education, including males in cervical cancer prevention education, providing incentives to the community to participate in educational programs, and beginning prevention education at an earlier age. The researchers intend to gather more data and work with community health workers to create a new intergenerational family-oriented educational strategy for the Hispanic population.
Caspase-2 Is Expressed in the Osteoblast Lineage and Affects Osteoblast Function

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Osteoporosis is a silent disease leading to painful fractures that increase morbidity and mortality with aging. Osteoporotic fractures have a higher prevalence as compared to the combination of heart attack, breast cancer, and stroke. Additionally, one in three women and one in five men will sustain osteoporotic fractures in their lifetime. With more than 2 million osteoporosis-based fractures every year, the societal burden of osteoporosis includes acute and rehabilitative medical costs of more than $20 billion in the United States alone, ranking it as one of the highest health care costs for older individuals. Hence, an understanding of the molecular mechanisms underlying osteoporosis and the subsequent development of novel therapies is imperative.

Caspase-2 is a cysteine protease involved in mitochondrial oxidative stress-induced apoptosis. Loss of caspase-2 results in premature aging, including a shortened maximum lifespan, impaired hair re-growth, reduced body fat content and, importantly, age-related osteoporosis. We have previously shown that loss of caspase-2 results in decreased bone mass due to an increase in the number of osteoclasts (bone resorbing cells) and an increase in osteoclast function. However, caspase-2 expression and function in other bone cell types were not delineated. The purpose of this study is to

We performed immunohistochemistry of bone sections from WT mice and Casp2 null mice for caspase-2; we also stained for caspase-2 in isolated mesenchymal stem cells using immunofluorescence. Quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) of whole bone samples from WT and Casp2 null mice was performed for RANKL.

We found that caspase-2 is expressed in bone marrow cells, osteoblasts, and lining cells in femur and tibia at all ages tested. Specifically, caspase-2 is constitutively expressed in mesenchymal progenitor cells (also called skeletal stem cells) that differentiate into osteoblasts. Loss of caspase-2 in these cells resulted in decreased mineralization capacity after their differentiation into osteoblasts. qRT-PCR showed that RANKL expression was significantly increased in Casp2 null bones (P=0.02) as compared to WT bone (n=6).

Taken together, we posit that loss of caspase-2 may result in altered skeletal stem cell differentiation and osteoblast function leading to decreased bone formation and increased bone resorption. Importantly, altered RANKL expression by osteoblasts will also lead to increased osteoclast differentiation. Our data highlights critical functional roles for caspase-2 in both osteoclasts and osteoblasts and identify caspase-2 as a novel target for combating osteoporosis.
Effect of YAP/TEAD on the Hippo pathway in Breast Cancer

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Breast cancer is quite common, more there are more than 200,000 cases in the U.S. per year, and it can occur in women and rarely in men. Furthermore, the early and later stages of breast cancer are quite different from one another. This research is to see the main differences within the different stages of breast cancer and how when they are being treated the drugs being used can vary. It concentrates on how estrogen and its nuclear receptor ERα are critical for breast cancer development through binding at distal enhancers. The immediate goal is to characterize component and architectural changes in ERα enhancers during the phenotypic transitions of breast cancers upon hormone therapy and to understand how these alterations result in the dysfunctional activation of ERα enhancers in hormone resistance.

The research being conducted is about YAP/TEAD which is a nuclear effector of the Hippo pathway, which is responsible for regulating organ size and tumorigenesis largely through a promoter-associated function. Their function as enhancer regulators remain poorly understood, which is something that in the lab we are working to further understand, through an in vivo proximity-dependent labeling technique known as BioID. We are able to identify YAP1 and TEAD4 protein as co-regulators of ERα on enhancers. The binding of YAP1/TEAD4 to ERα-bound enhancers is made larger in size upon E2 stimulation and is required for the induction of E2/ERα target genes and E2-induced oncogenic cell growth. Furthermore, their enhancer-binding is a prerequisite for enhancer activation marked by eRNA transcription and for the recruitment of the enhancer activation machinery component MED1, MED1 mediates induction of cell proliferation and migration and the genes associated with it in breast cancer, which is abrogated when used together with miR-191-inhibition. The binding of TEAD4 on active ERE-containing enhancers is independent of its DNA-binding behavior, and instead, occurs through protein-tethering trans-binding. The data reveal a non-canonical function of YAP1 and TEAD4 as ERα cofactors in regulating cancer growth, highlighting the potential of YAP/TEAD as possible actionable drug targets for ERα+ breast cancer.
Exercise Modulation On VEGF-A And Implications On Tumor Grade

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BACKGROUND: The progressive growth of a tumor results in an inability of normal tissue blood vessels to oxygenate and provide sufficient nutritional support to tumor cells. Consequently, hypoxia-inducible factor-1 (HIF-1) triggers the release of vascular endothelial growth factor (VEGF) to bind the tumor receptors to the surface of normal endothelial cells, forcing angiogenesis. The VEGF family comprises of five members: VEGF-A, placenta growth factor (PGF), VEGF-B, VEGF-C and VEGF-D. The latter following VEGF-A range in characteristics from maintenance of newly formed blood vessels to protection of neurons. VEGF-A is important for the formation of blood vessels, such as during development or in pathological conditions. These new blood vessels can be unbalanced, causing underdeveloped, structurally chaotic systems that have unstable speed, random direction of blood flow, and high vascular resistance. Antiangiogenic intervention has never proved to be effective. PURPOSE: Preliminary data shows a link between exercise and a retardation of tumor growth, decreased hypoxia, and the development of longer, more structured, VEGF-spawned vessels. Outcomes from this study could provide evidence to support non-pharmacological interventions to support cancer patients. The purpose of this study is to determine the role of exercise in either inhibiting or promoting VEGF-A concentration using the TRAMP model. METHODS: The transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse, developed by prostate-specific expression of SV40 large T antigen using the rat probasin promoter, is used in this study. Thirty TRAMP mice were randomized into either a control or exercise group. The exercise group had unlimited, unforced access to an electronically monitored running wheel. At weeks 4, 8, and 12, three mice were sacrificed from each group with the last 6 of each group sacrificed at week 20. Distance ran, tumor grade, and VEGF-A were recorded. Blood samples taken during euthanasia were analyzed using a mouse VEGF-A ELISA (ThermoFisher®). RESULTS: Exercising mice ran 14.31 ± 1.8 km/day on average, and exercise had a 60% beneficial effect on tumor grade with only 6 of the 15 mice having high grade tumors. Exercise (20.26±14.61pg/mL) significantly lowered VEGF-A concentrations compared to the control group (44.04±28.33 pg/mL) (p=0.02). CONCLUSION: Although this study highlights the anticarcinogenic efficacy of exercise versus nonexercise, an expanded sample size is necessary to insure sound data. Reducing study duration in transgenic mice will sharpen results as 20 week old mice had a tumor so large that it impaired mobility. This lab focused on VEGF-A, so future studies will isolate and analyze the remaining four isoforms. There are no known negative side effects to exercise, so it provides a safe alternative to pharmacological treatments while raising quality of life and lowering fatigue. Likewise, translational applications of exercise from bench to bedside remain unchallenged.
Identifying novel therapeutic targets for Glioblastoma

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Glioblastomas (GBM) are aggressive tumors that account for 45.6% of primary malignant brain tumors. The median survival rate of patients with GBM is approximately 15 months. The standard treatment for GBM consists of surgery followed by radiation and chemotherapy. Glioma stem cells (GSCs) play a central role in GBM development and contribute to tumor initiation, progression, and treatment resistance. Eradication of GSCs is critical for the development of efficient therapeutic strategies, and several strategies of targeting GSCs are currently being developed. A potential therapeutic strategy for GBM would be to use forced differentiation and apoptosis of GSCs. Understanding the molecular pathways that sustain GSCs are urgently needed and could elucidate novel therapeutic targets for GBM. Nuclear receptors (NRs) are a family of 48 transcriptional factors that regulate gene expression programs under the influence of natural occurring small molecules such as steroids, bile acids, and metabolites. Most of the tissues in the body, including brain, express multiple types of NRs and play essential roles in normal physiology and disease. Several studies demonstrated that NRs play important roles in cancer development and progression specifically in hormone-dependent cancers such as breast and prostate cancers. However, little is known about the role of NRs in GBM. In this study, we utilized two patient derived primary glioma stem like cells (GBM-080409 and 040815) that were cultured in undifferentiated condition in serum free neurobasal medium. To induce the differentiation process, GSCs were cultured in the presence of 10% FBS in DMEM medium for 7 days. After the cells were cultured in stem cell and differentiated medium for one week, they were collected and subjected to RNA isolation followed by cDNA synthesis. Then, the 48 nuclear receptors were profiled using Real Time PCR (qRT-PCR) with gene specific primers and GAPDH was used as internal control. The results from the qRT-PCR revealed that the nuclear receptor NR1I1 (VDR; vitamin D receptor) is highly expressed in the differentiated cells compared to GSCs suggesting that NR1I1 is involved in differentiation of GSCs. Further, the nuclear receptor NR5A2 (LRH-1; liver receptor homolog-1) is highly expressed in stem cells compared to differentiated cells for both cell lines suggesting that NR5A2 is required for the maintenance of GSCs. Future studies are needed to address the mechanistic insights of NR1I1 and NR5A2 and test the efficacy of NR1I1 agonists and NR5A2 antagonists in GSCs. These studies suggest that NR1I1 and NR5A2 plays a vital role in GSCs may represent potential targets for the development of therapeutic intervention in GBM.