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The Challenges of Engaging Rural Black Women in Cancer Research: Which Recruitment Strategies Work Best?

PRESENTING AUTHOR: Lillian Nwigwe

CO-AUTHORS: Leslie Carnahan, Yamilé Molina

ABSTRACT:

BACKGROUND: Cancer survivorship research is not evenly allocated in the United States, the intersections of race, gender and rurality. This is due to limited participation of rural African American female survivors. The current study focuses on identifying which strategies are feasible and optimal for recruiting rural African American women in cancer research.

METHODS: We examined three potential recruitment sources across time: the Illinois Cancer State Registry (10/17); community-based agencies (05/16-09/18); e.g., hospitals, non-profit organizations); and, commercial phone lists (04/18-09/18). We tracked how many rural African American female survivors after each strategy was implemented.

RESULTS: Two of the 3 strategies were feasible: recruitment through community-based agencies and commercial phone lists. The cancer registry was not able to support study recruitment. We engaged 367 community-based agencies (36 government agencies, 84 health departments, 152 hospitals/clinics, 16 academic institutions, and 79 community/private sectors) and called 3,214 phone numbers, of which we successfully contacted a person 471 times. Six AAW participants enrolled when recruiting through community-based agencies only, and 4 AAW participants enrolled when we began to use commercial phone lists.

DISCUSSION: Our findings suggest there are barriers for researchers to recruit medically undeserved groups. Cancer registries should be given resources to be able to work with researchers. Researchers should also partner with organizations that serve predominately African American with shared responsibilities for recruitment, who can conduct focus groups within those participatory niches in rural settings to facilitate this process.
Determining the role of adjuvant radiotherapy in the management of meningiomas: A Surveillance, Epidemiology, and End Result (SEER) analysis

PRESENTING AUTHOR: Abhinav K. Reddy

CO-AUTHORS: Steven Denyer, Laura S. McGuire, Ankit I. Mehta

ABSTRACT:

OBJECTIVE: This study was to illustrate the demographic characteristics of meningiomas and observe the effect of adjuvant radiation therapy in patient survival using the Surveillance, Epidemiology, and End Result (SEER) database.

METHODS: SEER data was queried from 1973-2015 for benign, atypical, and anaplastic meningiomas using appropriate ICD-O3 codes. Patient demographics, tumor characteristics, and treatment choices were analyzed. The effects of treatment regimen were examined using a multivariate Cox proportional hazard model and Kaplan-Meier survival analysis.

RESULTS: A total of 57,998 patients were included in the analysis of demographic, tumor, and treatment characteristics of meningiomas. Of this population, cases of unspecified WHO tumor grade were excluded in the multivariate analysis, resulting in a total of 12,931 patients for examining outcomes between treatment paradigms. In benign meningiomas, gross-total resection (HR 0.289, p=0.013) imparted a significant cause-specific survival benefit over no treatment. In anaplastic meningiomas, adjuvant radiotherapy imparted a significant survival benefit in both subtotal (HR 0.089, p=0.018) and gross-total resection (HR 0.162, p=0.002) patients compared to those who were treated with only gross-total resection. In atypical tumors, gross-total resection with radiotherapy did not significantly change hazard risk (HR 1.353, p=0.628) compared to gross-total resection. Similarly, it was found that adjuvant radiation did not significantly benefit survival after a subtotal resection (HR 1.440, p=0.644).

CONCLUSION: The results of this study demonstrate that the role of adjuvant radiotherapy, especially after resection of atypical meningiomas, remains somewhat unclear. Thus, prospective randomized clinical studies based on these results is warranted to provide clear information on the effects of adjuvant radiation in meningioma treatment.

LAYPERSON ABSTRACT:

OBJECTIVE: This study was performed to describe characteristics of patients with meningiomas, a type of tumor which arises from the outer envelope that covers the brain and spine, while seeing the effect of different treatment options, especially radiation therapy, on patient survival using a national cancer database.

METHODS: Meningioma patients from 1973-2015 were selected from the cancer database, and their demographic characteristics, tumor characteristics, and treatment choices were analyzed. The effects of treatment choice (surgical removal, chemotherapy, radiation, or a combination of treatments) on patient survival were also examined.

RESULTS: A total of 57,998 patients were analyzed for describing patient, tumor, and treatment characteristics for meningiomas. From this group, a subset of 12,931 patients for whom WHO tumor grade (a measure of how invasive a tumor is) was reported were used to see the effects of different treatment choices on survival. In the benign group of tumors, complete surgical removal of the tumor had the most benefit in survival. In the most malignant group of tumors, radiation was helpful after a surgical attempt to remove the tumor. In the intermediately malignant group of tumors, however, radiation was not found to be helpful after a surgical attempt to remove the tumor.

CONCLUSION: This study shows that there is an unclear benefit of radiation after a surgical attempt to remove meningiomas of intermediate malignancy. Thus, further clinical studies must be conducted to determine whether or not to radiate patients with these meningiomas after surgery.
Assessing the Quality of Life Differences among Rural Cancer Survivors Based on Their Marital Status

PRESENTING AUTHOR: Shaila Strayhorn
POSTER LOCATION: 3

ABSTRACT:

BACKGROUND: Married cancer survivors have a higher cancer survival rate and experience less metastatic cancer diagnoses compared to unmarried cancer survivors. In addition to this, married cancer survivors often experience less anxiety and depression compared to unmarried survivors. While previous studies suggest that the marital status of cancer survivors is associated with specific health outcomes such as their quality of life (QOL), it is unknown whether an association exist specifically among rural cancer survivors. The purpose of this study is to quantify the magnitude of relationships between the marital status and QOL domains among rural survivors.

METHODS: Study participants were obtained from the Illinois Cancer Assessment Study. Social well-being and functional well-being were assessed through the Functional Assessment of Cancer Therapy-General (FACT-G) Questionnaire. Both physical and mental health were assessed using the Short Form Health Survey (SF-12). All analyses were conducted with SAS, version 9.4.

RESULTS: Of the 139 rural cancer survivors with complete data, 70% (n=97) were categorized as married. Using linear regression analyses, the crude models displayed positive association between married rural cancer survivors and both their social well-being ($\beta = 2.28$, $p=0.02$) and physical health ($\beta = 4.67$, $p=0.03$). The socioeconomic variables (i.e. education and income) also displayed the strongest impact on the relationship between marital status and QOL based on the change in the magnitude of association.

CONCLUSION: The findings of this study indicate that married rural cancer survivors experience improvements in two of the four QOL domains compared to unmarried rural cancer survivors. It was also revealed that socioeconomic variables may potentially confound or mediate the relationship between marital status and QOL. The next phase of this study is to conduct a mediation analysis to examine the potential factors that lie in the casual pathway between marital status and QOL.
**Gemcitabine Primes Pancreatic Cancer Cells for Immune Checkpoint Inhibition**

**PRESENTING AUTHOR:** Daniel Principe

**CO-AUTHORS:** Matthew Narbutis, Jonathan Rubin, Alex Park, Matthew J. Dorman, Navin Viswakarma, Sandeep Kumar, Hidayatullah G. Munshi, and Ajay Rana

**ABSTRACT:**
Pancreatic ductal adenocarcinoma (PDAC) remains remarkably lethal with a 5-year survival rate of 8%. As the majority of patients are diagnosed with metastatic disease and are not eligible for surgery, most are administered broad-spectrum chemotherapy. While chemotherapy marginally improves survival, nearly all tumors either have or develop some degree of drug resistance. Recent evidence suggests that these cytotoxic therapies may alter a variety of cell signaling events extending well beyond proliferation and apoptosis, including the processing and presentation of self-peptide. We therefore sought to determine whether standard of care chemotherapy agents had an observable effect on the immunogenicity of PDAC cells. We first incubated cell lines with several standard of care chemotherapy agents and evaluated surface proteins by flow cytometry. Interestingly, both Gemcitabine and Paclitaxel strongly enhanced surface expression HLA-A,B,C, PD-L1, PD-L2, and CTLA-4. We therefore used the Ptf1a-Cre x LSL-KRASG12D (KC) model of murine carcinogenesis, and administered a combination of Gemcitabine and a PD-1 neutralizing antibody (Anti-PD-1). While KC mice failed to respond, Gemcitabine/Anti-PD-1 led to the regression of established tumors in KC mice with TGFβ receptor 1 (TGFBR1) deficiency. We therefore used the Pdx1-Cre x LSL-KRASG12D x LSL-TP53R172H (KPC) model of advanced PDAC, and administered a combination of Gemcitabine, Anti-PD-1, and a TGFBR1-inhibitor. This combination led to a robust CD8-mediated immune response surpassing that observed with immunotherapy alone. Mice had a significant reduction in burden, as well as preservation of normal gland architecture. Combined, these observations suggest that anti-neoplastic agents e.g. Gemcitabine may prime tumor cells for immune checkpoint inhibition, and that the combination of Gemcitabine and dual agent immunotherapy warrants therapeutic consideration.

**LAYPERSON ABSTRACT:**
Pancreatic cancer has a very poor prognosis, and is generally resistant to chemotherapy. While immunotherapy has been a major breakthrough in the management of other cancers, this approach has yet to show clear efficacy in pancreatic cancer patients. In our recent work, we found that simultaneous inhibition of PD-L1/TGFβ signaling reduced tumor burden in mouse models of advanced pancreatic cancer by enhancing the anti-tumor immune response. As chemotherapy remains the backbone of pancreatic cancer treatment, we next examined whether chemotherapy drugs like Gemcitabine can be used together with combined PD-L1/TGFβ inhibition. Interestingly, Gemcitabine increased the ability of tumor cells to be recognized by immune cells. When Gemcitabine was added to combined PD-L1/TGFβ inhibition in mouse models, we an overwhelming immune response and the rapid regression of advanced disease. Combined, these observations suggest that chemotherapy e.g. Gemcitabine may ready tumor cells for select immunotherapies, and that this combination warrants clinical consideration.
WIRELESS, BATTERY-FREE, FLEXIBLE, MINIATURIZED DOSIMETERS MONITOR EXPOSURE TO SOLAR RADIATION

PRESENTING AUTHOR: Manish Patel

POSTER LOCATION: 5

CO-AUTHORS: Seung Yun Heo, Jeonghyun Kim, Philipp Gutruf, Anthony Banks, Pinghung Wei, Rafal Pielak, Guive Balooch, Yunzhou Shi, Hitoshi Araki, Derrick Rollo, Carey Gaede, Jean Won Kwak, Amnahir E. Peña-Alcántara, Kyu-Tae Lee, Yeojeong Yun, June K. Robinson, Shuai Xu, and John A. Rogers

ABSTRACT:

The most common human malignancy, skin cancer, is heavily influenced by ultraviolet radiation (UVR). Collectively, basal cell carcinoma and squamous cell carcinoma of the skin account for more than 5 million cases per year at a cost of $8.1 billion dollars yearly. In 2018, there will be an estimated 90,000 new cases of melanoma, a lethal form of skin cancer, causing 9000 deaths yearly in the U.S. In the U.S., 69% of youths and 34% of adults recall at least one sunburn in the last year. Moreover, skin cancer incidence is reaching epidemic proportions in the U.S. Currently, there is a critical need for technologies that can accurately measure and promote safe UV exposure at a personalized level in naturalistic environments. This is particularly relevant in high-risk groups including kidney transplant survivors who have a 65x increased risk of certain skin cancers, the 1 million melanoma survivors in the U.S. who have a 9-fold increased risk of developing a second melanoma, and rare photosensitizing skin conditions (e.g. oculocutaneous albinism and porphyria cutanea tarda).

The most relevant spectral ranges in the solar UV spectrum include UVB (280-315 nm), and UVA (315-400 nm). While both UVB and UVA are carcinogenic and contribute to skin aging, UVB is 1,000 times more erythrogenic with distinct biological effects to the skin compared to UVA irradiation suggesting the need for differentiation of irradiance across the UVR spectrum. Beyond UVB and UVA, recent work suggests that both visible and infrared (IR) radiation in sunlight can lead to oxidative stresses that potentiate UV injury, skin darkening, and skin redness. As a result, there is a heavy need to design a system capable of precise quantification and wavelength-specific at a personal level. Our device allows patients and consumers to track their sun exposure based on their daily activities, geographic locations, and time of day and correlate their exposure based on their skin tone and/or medical needs. Indirectly, the device may promote the usage of sun-protective behaviors such as improving sun-sunscreen use, locating areas of shade, and modifying lifestyles to stay indoors during peak UV intensity hours. These lifestyle changes can help prevent the development of carcinomas and prevent evident skin erythema drastically if utilized.
The Role of Hexokinase 2 in Breast Cancer Metastasis

PRESENTING AUTHOR: Catherine Blaha

POSTER LOCATION: 6

ABSTRACT:

One hallmark of cancer cells is termed the “Warburg Effect,” a phenomenon where cancer cells exhibit accelerated glucose metabolism in the presence of oxygen. Hexokinase catalyzes the first committed step in glucose metabolism by phosphorylating glucose, thereby trapping it in the cell to be used in various downstream pathways. Previous research in our laboratory showed that while normal mammary gland cells do not express the hexokinase 2 (HK2) isoform, it is highly overexpressed in breast cancer cells, which is responsible for the accelerated glucose utilization in primary tumors. HK2 deletion inhibits the tumorigenicity of cancer cells in vitro and in vivo. As a result, HK2 appears to be a good potential target for therapeutic treatment of primary breast cancer tumors. However, metastasis accounts for the high mortality rate in breast cancer, which makes it important to elucidate the role of HK2 in breast cancer metastasis. The proposed study tests the innovative hypothesis that HK2 plays a role in breast cancer’s ability to metastasize. Systemic deletion of HK2 after tumor onset in a mouse model of breast cancer metastasis profoundly inhibited metastasis. In addition, we demonstrated a significantly higher level of HK2 protein in metastatic mammary tumor cell lines compared to a non-metastatic mammary tumor cell line. Mechanistically, the HK2 appears to drive metastasis through altered gene expression by stabilizing SNAIL, a pro-EMT transcription factor, as well as increased NAPDH production as. Overall, this study will provide a new potential therapeutic target for breast cancer metastasis.
Head and Neck Cancer in South Asian Diaspora Living in the US, 2004 – 2013

PRESENTING AUTHOR: Shaveta Khosla

POSTER LOCATION: 7

CO-AUTHORS: Caryn E Peterson

ABSTRACT:

BACKGROUND: Almost 58% of the global Head and Neck Cancer (HNC) cases occur in Asia, and a large proportion of these are from South Asia, mainly India and Pakistan. HNCs represent 30% of all cancers in males in India. However, not much is known about HNCs in this diaspora living in the US. The purpose of this study is to examine HNCs in South Asian males of Indian and Pakistani origin living in the US and compare them to nH-White (NHW) American males.

METHODS: Secondary data from National Cancer Database was used to analyze HNC cases from 2004 - 2013. The sites included oral cavity, oropharynx, non-oropharynx (nasopharynx and hypopharynx), and larynx. Salivary gland tumors were excluded. Bivariate and multivariate analyses were conducted to examine the association of HNC site with South Asian origin and other variables.

RESULTS: From 2004-2013, 887 South Asian males (of Indian and Pakistani origin) and 156927 NHW males were diagnosed with HNCs. South Asian males were more likely to have oral cancer (OC) (59% vs. 25%) but less likely to have oropharyngeal (OPC) (13% vs. 37%) and laryngeal cancer (14% vs. 29%; p<0.001 for all) and were also less likely to be HPV 16/18 positive. They were diagnosed at a younger age (Mean age=57.7±13 vs. 61±11; p<0.001) and were more likely to live in urban area (99% vs. 93%; p<0.001) and have higher area level median household income and educational attainment. They were also likely to be diagnosed at an earlier stage but had higher likelihood of invasive growth and were less likely to survive >5 years after diagnosis (21% vs. 27%; p=<0.001). South Asian males had 7 times higher odds of having OC (ORadj=7.1; 95% CI 5.7 – 8.7), and 5 times higher odds of having non-oropharyngeal cancer (ORadj=4.9; 95% CI 3.8 – 6.3), compared to OPC.

CONCLUSION: HNC in South Asian males in the US is more likely to be OC, whereas OPC is more common in NHW males. HPV 16/18 positive HNCs are less common in South Asians. Despite having higher area level socio-economic indicators, they may be prone to risk factors that increase likelihood of oral cancer. HNC risk factors and survival need further study in this population.
Comparing the dosimetric impact of dental implants of two different calculation algorithms in oropharyngeal IMRT treatment planning

PRESENTING AUTHOR: Rishi Neeranjun
POSTER LOCATION: 8

CO-AUTHORS: Dr. Chris Lominska, Rajeev Badkul

ABSTRACT:

PURPOSE/OBJECTIVES: Dental implants are extremely common in patients with head and neck cancer and result in metal artifacts on CT imaging that increase the difficulty of accurate dosimetric calculations. In our practice, we have noted more mucositis in the areas adjacent to dental implants and hypothesized that this may be due to incorrect dose calculation caused by electron back scatter from the metal implant. The purpose of this study was to retrospectively evaluate the dosimetric differences in the areas surrounding the implants using two calculation algorithms as well as tissue density override to correct for the metal artifacts.

MATERIALS/METHODS: Six patients with dental implants who were previously treated at our institution with radiation therapy for head and neck cancer were selected for this retrospective study. All patients were treated with 6 MV photons using intensity modulated radiation therapy (IMRT). Four upper and four lower molars were contoured as well as “donut” shaped rings around the teeth of sizes 3mm, 4mm, and 5mm. New IMRT plans were generated with identical beam geometry and monitor units using the uncorrected reference and corrected CT data set. The molars were all assigned an electron density with a Hounsfield Unit (HU) of 6000 and dose calculation was done in Eclipse using the Analytical Anisotropic Algorithm (AAA). The contours and uncorrected data set were then transferred to iPlan RT and a new treatment plan was generated using two Novalis 6X MV beams with 90 and 270 degree gantry angles. For the iPlan software the molars were assigned an HU of 3071 and dose calculation was performed using a Monte Carlo simulation algorithm. Using a Wilcox Rank-Sum test, the maximum dose, Dmax, was collected and compared between the three rings of the original plan and the corrected plans from both treatment planning softwares. P-values of <0.05 were considered significant and statistical testing was performed using RStudio and R 3.3.2.

RESULTS: There were statistically significant increases in Dmax when comparing the iPlan corrected data to the original data (p=0.0012) as well as when comparing the Dmax between the 3mm and 4mm rings of the corrected iPlan and original data (p=0.0253 and p=0.0333, respectively). The average hot spot (Dmax) increase of the iPlan data was 25.7 cGY when adjusting for the increased HU value of the dental fillings. There were no significant differences in Dmax when comparing the Eclipse corrected data to the original data.

CONCLUSIONS: In this retrospective study, adjusting the HU value of the molars to better simulate the actual electron density of an amalgam filling resulted in statistically significant increases in Dmax when the dose was calculated using iPlan’s Monte Carlo simulation. This suggests that using iPlan’s Monte Carlo dose calculation algorithm instead of Eclipse’s AAA can more accurately predict mucosal toxicity associated with dental implants. A further study would be to measure the degree of mucosal toxicity in patients to correlate it with the finding that Dmax decreases after the 4mm ring and to see if using a wax lining in the gums of 4mm thickness would help prevent mucositis in the areas of these dental implants.
Accurate Classification of Thyroid Carcinoma Subtypes using Mid-Infrared Spectroscopic Imaging

PRESENTING AUTHOR: David Martinez Marin

CO-AUTHORS: Hari Sreedhar, Vishal K. Varma, Caterina Eloy, Manual Sobrinho-Simões, André Kajdacsy-Balla, Michael J. Walsh

ABSTRACT:

Thyroid carcinomas are the most prevalent of endocrine organ malignancies, consisting of primarily papillary and follicular carcinomas. The diagnosis of follicular variant of papillary carcinoma (FVPCA) remains a clinically challenging diagnosis given its morphological mimicry of follicular thyroid carcinoma (FTCA), leading to improper and potentially excessive treatment. Fourier Transform Infrared (FT-IR) spectroscopic imaging has emerged as a potentially powerful clinical adjunct technique, capable of providing label-free imaging by deriving chemical information (i.e. nucleic acids, lipids, peptides) from tissue biopsies. Spectral data collected can then be mined, allowing for disease classification. In this study we demonstrate FT-IR imaging coupled with multivariate analysis, can be used to discern between FVPCA and FTCA disease subtypes and potentially assist to reduce inter-observer variability encountered in the FVPCA diagnoses.

Twenty formalin-fixed paraffin-embedded tissue samples from thyroid lobectomies or thyroidectomies were acquired from the University of Illinois at Chicago Biorepository. Serial sections of ten tissue samples from patients diagnosed with FVPCA and ten patients diagnosed with FTCA were collected for H&E staining and FT-IR imaging. Disease state verification and regions of interest (ROI), both gross and refined, were identified from H&E images and identified on the corresponding IR images. Chemical data collected from ROIs was then processed using multivariate analysis (i.e. PCA-LDA & Bayesian).

Using patients’ averaged ROI spectra as individual data points, clear disease state separation between FVPCA and FTCA was achieved using PCA-LDA, with only one patient being misclassified, suggesting the presence of unique spectral differences from averaged tissue spectra of both disease subtypes. Gross ROIs were probed at the pixel level using a Naïve Bayesian classifier, but its performance was not significantly better than mere chance. Using refined ROIs selecting individual cells, another Bayesian classifier was built and showed it to be able to successfully segregate both disease subtypes.

In this study, we demonstrate FT-IR imaging together with the appropriate classification methods can discern between thyroid carcinoma subtypes FVPCA and FTCA. FT-IR imaging holds much promise in aiding clinicians to address some of the challenges encountered when diagnosing these thyroid carcinoma subtypes, but care must be taken to judiciously select tissue sample features.
ABSTRACT:

BACKGROUND: The strength of associations between pre-diagnosis self-reported health (SRH) and mortality differ by medical condition, with a moderately strong association reported among cancer patients. Less is known about the impact of SRH on survival among patients diagnosed with multiple myeloma (MM). We aimed to evaluate pre-diagnosis SRH in relation to survival in a cohort of older MM patients.

METHODS: We analyzed a prospective cohort from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) database of patients 65 years and older diagnosed with first primary MM. Survey responses to a single general health question (asking patients to self-report their health as excellent, very good, good, fair, or poor) were used to determine pre-diagnosis SRH, grouped as high (excellent/very good/good) or low (fair/poor). We used multivariable Cox proportional hazards models to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between SRH and risks of all-cause and cancer-specific mortality.

RESULTS: Of 521 MM patients with pre-diagnosis SRH data, the mean (SD) age at diagnosis was 76.8 (6.1) years with 60% of patients identifying as white, 18% as black, and 32% reporting low SRH. Compared to patients reporting high SRH, patients reporting low SRH were older, had lower education levels, more comorbidities, and lower Veterans-RAND 12 physical health and mental health component summary scores. In multivariable analyses, MM patients with low SRH had a 28% increased risk of all-cause mortality (HR=1.28, 95% CI=1.00, 1.64) and a non-statistically significant 19% increased risk of cancer-specific mortality (HR=1.19, 95% CI=0.87, 1.61) compared to MM patients reporting high SRH.

CONCLUSIONS: Our findings suggest that lower SRH is highly prevalent among MM patients prior to diagnosis and is associated with modestly increased all-cause mortality. At a minimum, low SRH deserves clinical attention to determine how older MM patients’ quality of life may be compromised. The mechanism by which SRH affects mortality in MM should be further assessed and efforts should be made to identify whether any of the underlying mechanisms linking SRH and mortality in MM are mutable.
Depressive symptoms, mental health-related quality of life, and survival among older patients with multiple myeloma

PRESENTING AUTHOR: Ali Alobaidi

POSTER LOCATION: 11


ABSTRACT:

BACKGROUND: Few studies have evaluated the impacts of depressive symptoms and mental health on patients diagnosed with multiple myeloma (MM). The aim of this study was to examine associations between depressive symptoms and poor mental health-related quality of life in relation to survival in a cohort of older MM patients.

METHODS: We conducted an analysis using a prospective cohort from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) of patients aged 65 years and older diagnosed with first primary MM between 1998 and 2014. Subjects were required to have completed at least 1 pre-diagnosis survey and depressive symptoms were determined based on positive responses to at least 1 of 3 depression screening questions. Veterans-RAND-12 mental component scores (MCS) were also analyzed to evaluate mental health-related quality of life. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between pre-diagnosis depressive symptoms and risks of all-cause and cancer-specific mortality. Secondary analyses examined mortality risks in relation to pre-diagnosis MCS.

RESULTS: Of 522 multiple myeloma patients, the mean (SD) age at diagnosis was 76.9 (6.1) years and 158 (30%) self-reported positive depressive symptoms. Patients with depressive symptoms had a higher number of comorbid conditions and nearly all (84%) scored below the median MCS. Pre-diagnosis depressive symptoms were not associated with all-cause (HR 1.01, 95% CI: 0.79-1.29) or cancer-specific mortality (HR 0.94, 95% CI: 0.69-1.28). Myeloma patients scoring in the second MCS tertile (versus the highest tertile) had a modestly increased risk of all-cause (HR 1.19, 95% CI 0.91-1.55) and cancer-specific mortality (HR 1.17, 95% CI 0.86-1.60), but these estimates were not statistically significant.

CONCLUSION: Pre-diagnosis depressive symptoms and lower mental health-related quality of life are not associated with survival for MM. Nevertheless, the considerably high prevalence of depressive symptoms and poor mental health status among older patients with multiple myeloma deserves clinical attention.
A Knowledge Translation Approach to Support the Implementation of a Cancer Research Fellowship for Students with Disabilities

PRESENTING AUTHOR: Ryan McGraw

POSTER LOCATION: 12

CO-AUTHORS: Jasmine Brown, MS, OTR/L, Hannah Gin, MS, OTR, Vera Kaelin, MSc, Caniece Leggett, MS, OTR/L, Amy Roder McArthur, MS, OTR/L, Ryan McGraw, MS, Shoma Webster MS, OTR/L, Megan Win, MS, OTR/L, Alexa Wohlfort, MA, MSW, Susan Magasi, PhD

ABSTRACT:

BACKGROUND: Researchers with disabilities are historically underrepresented within Science, Technology, Engineering, and Mathematics (STEM). Students with disabilities experience barriers to STEM education, including: limited access to disability-related supports and accommodations, lack of disabled role models, low expectations, and limited exposure to pre-requisite classes. Pipeline education and mentoring programs have been effective in promoting STEM education in other underrepresented groups, such as racial and ethnic minorities. To date, no cancer research pipeline programs have been developed for students with disabilities. To address this gap, a team within the UI Cancer Center and UIC's College of Applied Health Sciences is creating a comprehensive Cancer Research Fellowship for Students with Disabilities. Successful implementation of the fellowship will require contributions from multiple stakeholders, including: faculty mentors, funders, and champions in the cancer research community. The Knowledge to Action (KTA) process is a translational strategy to support the implementation of evidence-informed innovations in education and clinical practice.

METHODS: A Knowledge Translation (KT) Collaborative—comprised of doctoral students in occupational therapy, disability studies, and rehabilitation science; disability community partners; and a team of mentors—engaged in stages of the KTA process to support implementation of the fellowship. Specifically, the KT Collaborative conducted a rapid review of the research literature to identify barriers and facilitators to STEM education and professional engagement among students with disabilities. Then in collaboration with a professional filmmaker, the KT Collaborative created a short evidence-informed film to support implementation of the fellowship. Capitalizing on the emotionally evocative aspects of film can be an effective way to communicate evidence-based information to diverse stakeholders in the YouTube era.

RESULTS: Based on the findings from the rapid review, the KT Collaborative identified several barriers to students with disabilities’ participation in higher education and STEM in particular. Common barriers included: negative attitudes towards disability, lack of knowledge about disability and potential accommodations. Thus the KT Collaborative determined that counteracting these attitudes would be the primary focus of the film with a secondary emphasis on the potential benefits of inclusion of students with disabilities in a Cancer Research Fellowship. In consultation with key informants, the KT Collaborative strove to strike a tone for the video that was honest but optimistic while avoiding prevailing tropes of people with disabilities as either burdensome and needy or triumphantly heroic. The video, as a knowledge product, will serve as a springboard for conversation in both mentor training and fellowship promotional activities.

CONCLUSION: A systematic application of the KTA Framework can help support the implementation of innovative clinical and educational programming. The KT collaborative model brings together people with disabilities and advanced graduate students as co-learners and co-creators of knowledge products. This is innovative approach ensures that diverse perspectives are integrated throughout the process.
Hepatocyte-derived osteopontin drives the development of hepatocellular carcinoma

PRESENTING AUTHOR: Romain Desert

CO-AUTHORS: Xiaodong Ge, Ioana Abraham-Enachescu, Chuck Blajszczak, Yu Chen, Xiaochen Sun, Anna P Koh, Grace Guzman, Yujin Hoshida and Natalia Nieto

ABSTRACT:

Osteopontin (OPN) expression correlates with tumor progression and metastasis in a wide variety of cancer including hepatocellular carcinoma (HCC); yet, the mechanisms by which hepatocyte-derived OPN contribute to HCC remain unclear. To investigate the role of OPN in HCC, we analyzed OPN mRNA and protein expression in cirrhosis, HCC and matched non-tumor liver tissues and used a mouse model of HCC with genetic manipulation of the Opn gene. In human normal liver, OPN expression was modest; however, it increased in pre-HCC cirrhosis and dysplasia and was much higher in well-established HCC. HCC expressing strong OPN mRNA expression were associated with poor outcomes. In patients with early cirrhosis, OPN was involved in a correlation network dividing patients into OPN-high and OPN-low. Patients with OPN-high had increased HCC incidence and expressed signatures of extracellular matrix remodeling, AKT and MYC activation and loss of function of P53. More, OPN expression in the non-tumor liver tissue of HCC was associated with novo carcinogenesis after surgical resection. Then we injected diethylnitrosamine in WT, Opn global knockout (Opn-/-) and transgenic mice overexpressing Opn in hepatocytes in either WT (OpnHep Tg) or global Opn null background (Opn-/-Hep Tg) and sacrificed them after 12 months. While Opn-/- mice expressed reduced levels of alpha fetoprotein, OpnHep Tg mice showed increased HCCs numbers and size compared to Opn-/- or WT mice and more preneoplastic lesions. In conclusion, our results from human and mouse data strongly demonstrate an active role of hepatocyte-derived OPN in the onset and the progression of HCC.
**SNAP Benefit Amount, Negative Net Income, and Food Insecurity: A Regression Kink Analysis**

**PRESENTING AUTHOR:** Sabrina K. Young  
**POSTER LOCATION:** 14

**ABSTRACT:**

Food security is “[a]ccess by all people at all times to enough food for an active, healthy life.” Food insecurity is low food security. Food security and food consumption are important factors in cancer prevention. Food insecurity is associated with lower dietary quality in adults and children, as well as with obesity. Separately, poor diet can lead to obesity and chronic disease, and obesity is associated with increased risk for a number of cancers.

Despite improvements in recent decades, food insecurity continues to be a major problem in the U.S. In 2017, more than 10 percent of the U.S. population experienced food insecurity. The Supplemental Nutrition Assistance Program (SNAP – formerly the Food Stamp Program) is a federal program provided by the U.S. Department of Agriculture and administered by states, with the goal of alleviating food insecurity in low-income households by providing funds to purchase food and beverages. It is the largest welfare program in the U.S. in terms of both participation and funding. Previous research on the causal effects of SNAP has found that SNAP reduces food insecurity, and higher real values of SNAP benefits reduce – but do not eliminate – the cyclic effect of SNAP benefits on caloric intake (the decrease in calories and eating at the end of the “SNAP month”).

This research expands upon the literature by estimating the impact of a SNAP dollar (i.e. a dose-response) on food insecurity. Using data from the Food Acquisition and Purchase Survey (FoodAPS; 2012-2013), I use a regression kink design (RKD), which is useful for assessing impacts of program design with a maximum or benefit – i.e., a “kink.” The RKD allows me to exploit SNAP’s benefit design based on net income, calculated as gross income less predesignated household deductions (e.g. shelter costs). I use net income as an instrument for SNAP benefit amount to compare households who are arguably receiving less in SNAP benefits than they may require, since they have a negative net income, with those receiving lower benefit amounts. The RKD compares the slope on either side of the $0 net income threshold.

Preliminary findings suggest that among households receiving the maximum benefit, those with net income further into the negative have reduced food security – that is, the maximum does a better job closer to $0 net income. Findings from this study provide insight into the effects of benefit level on household food insecurity and have the potential to inform decisions to better support low-income families in maintaining a sufficient, healthy diet for prevention of obesity and chronic disease including cancer.

**LAYPERSON ABSTRACT:**

Food security is “[a]ccess by all people at all times to enough food for an active, healthy life.” Food insecurity is low food security. Food security and food consumption are important factors in cancer prevention. Food insecurity is associated with lower dietary quality in adults and children, as well as with obesity. Separately, poor diet can lead to obesity and chronic disease, and obesity is associated with increased risk for a number of cancers. Therefore, a reduction in food insecurity may also reduce cancer risk.

Despite improvements in recent decades, food insecurity continues to be a major problem in the U.S. In 2017, more than 10 percent of the U.S. population experienced food insecurity. The Supplemental Nutrition Assistance Program (SNAP – formerly the Food Stamp Program) is a federal program provided by the U.S. Department of Agriculture and administered by states, with the goal of alleviating food insecurity in low-income households by providing funds to purchase food and beverages. It is the largest welfare program in the U.S. in terms of both participation and funding. Previous research on the causal effects of SNAP has found that SNAP reduces food insecurity, and higher real values of SNAP benefits reduce the cyclic effect of SNAP benefits on caloric intake (the decrease in calories and eating at the end of the “SNAP month”).

This research expands upon the literature by estimating the impact of a SNAP dollar (i.e. a dose-response) on food insecurity. Benefits are based on net income (gross income taking into account a set of household expenses such as housing costs), and my research uses this net income to compare households that receive the maximum benefit to those that receive lower benefit amounts using data from the Household Food Acquisition and Purchase Survey (FoodAPS; 2012-2013). My early findings suggest that the further a household moves into “the red” (negative net income), the more food insecure it becomes. This implies that the maximum SNAP benefit is insufficient in supporting the poorest of households. This study has the potential to inform decisions to better support low-income families in maintaining a sufficient, healthy diet for prevention of obesity and chronic disease including cancer.
Role of PAX2 in the development of fallopian tube derived high grade serous ovarian cancer

PRESENTING AUTHOR: Jose A. Colina
POSTER LOCATION: 15

CO-AUTHORS: Peter Varughese, Joanna E. Burdette

ABSTRACT:

Ovarian cancer is most lethal gynecological malignancy and the 5th leading cause of cancer deaths among women. The deadliest subtype of the disease is high grade serous ovarian cancer (HGSOC) with an average 5-year survival rate of 29%. The fallopian tube epithelium (FTE) gives rise to pre-cancerous secretory cell outgrowths (SCOUTs) which can go on to become HGSOC. PAX2 is a transcription factor that has been shown to be lost in HGSOC and in SCOUTs, indicating that loss of PAX2 is an early event in tumorigenesis. In the present study, we developed a PAX2shRNA Knockdown murine oviductal cell line (MOE) to model the phenomenon’s role in the development of SCOUTs and study how it potentiates the FTE for further transformation. Loss of PAX2 in MOE cells, regardless of level of PAX2 deficiency, lead to no significant cancer specific phenotypic changes including adhesion, migration, and proliferation; this observation is typical of a benign pre-curser legion. However, RNA sequencing of PAX2shRNA cells revealed a transcriptional overhaul that accurately captures the transcriptional dysregulation in key genes present in human SCOUTs as outlined by ning et al in recent publication. Furthermore, cross analysis of the RNAseq data of our newly created SCOUT model with RNAseq of estrogen stimulated MOE cells revealed remarkable overlap suggesting that loss of PAX2 regulates hormonal responses, a known pathway in gynecological tumorigenesis. Hormone responsiveness of these cells were investigated using ERE and PRE-luciferase assays which revealed higher basal hormone activity and sensitivity to hormone treatment. Our SCOUT model also showed increased Estrogen receptor, ligand independent induction of estrogen responsive genes, and increased sensitivity to estrogen mediated genotoxicity. This presents the possibility of a known subset of HGSOC precursor lesions having a predisposition for estrogen induced genotoxicity in the estrogen rich environment of the fallopian tube.
Deletion of Sorting Nexin 27 Suppresses Proliferation in Highly Aggressive Breast Cancer MDA-MB-231 Cells in vitro and in vivo

PRESENTING AUTHOR: Jilei Zhang

POSTER LOCATION: 16

CO-AUTHORS: Jilei Zhang, Kendy Li, Yongguo Zhang, Rong Lu, Shaoping Wu, Jingrong Tang, Yinglin Xia, Jun Sun

ABSTRACT:

Sorting Nexin 27 (SNX27) belongs to the family of sortin nexins and possesses a unique binding domain at the C-terminus which mediates protein-protein interaction in intracellular trafficking, membrane remodeling, organelle motility, and tight junctions. However, its role in cancer development, especially in vivo, remains largely unknown. We have generated a stable SNX27-knockdown clone in a highly aggressive breast cancer cell line MDA-MB-231 using an inducible lentiviral shRNA system. The wound healing assay and MTT assay showed that SNX27 knockdown significantly decreased cell motility and proliferation. Colony formation in soft agar showed that the SNX27 knockdown cells formed significantly fewer and smaller colonies than the parental MDA-MB-231 cells. Western blots and immunostaining showed that SNX27 knockdown led to increased expression of E-cadherin and β-catenin proteins, which facilitate adhesion formation and reverse EMT. EMT is a cellular program that allows polarized, immotile epithelial cells to convert to motile mesenchymal cells, promoting carcinoma invasion. The expression levels of Vimentin, the transcription factor of EMT, and tight junction protein Claudin-5, were significantly diminished in the SNX27 knockdown cells. In a xenograft nude mouse model, we found that knockdown of SNX27 significantly inhibited tumor growth. The tumors from mice with SNX27-KD cells showed less proliferation compared to tumors from mice injected with wildtype cells. The increase in E-cadherin and β-catenin and decrease in Vimentin and Claudin-5 were confirmed in tumors of mice injected with SNX27-KD cells. Our data have demonstrated that SNX27 plays a crucial role in tumor growth in vitro and in vivo.
ABSTRACT:

Notch signaling is activated by ligands Dll4 and Jag1 in the tumor microenvironment and promotes tumor angiogenesis and perfusion. Jag1 expression is associated with poor outcome in several cancers, particularly triple negative breast cancer (TNBC), and affects both tumor angiogenesis and metastasis. Previous approaches to blocking Notch signaling in tumors have targeted all Notch signaling or Dll4-Notch signaling, which cause toxicity. However, blockade of Jag1-Notch signaling remains an unexplored therapeutic opportunity.

Our lab has previously developed ligand-specific inhibitors of Notch signaling, called Notch decoys, which are comprised of Fc fusions to specific EGF-like repeats of the Notch1 extracellular domain and interfere with ligand activity. Jagged-specific Notch decoys inhibit angiogenesis in vitro and significantly impair tumor growth, tumor angiogenesis, and perfusion without apparent toxicity in mouse models of TNBC. However, our previous work administered Notch decoys via viral expression vectors, which preclude dosage control and limit clinical applicability.

We have developed a new generation of Notch decoys that contain fewer EGF-like repeats, show improved secretion characteristics, and can be purified as active proteins in clinically relevant quantities. One novel Notch decoy specifically blocks Jagged signaling in vitro and inhibits angiogenesis in sprouting assays, suggesting similar therapeutic action as previous decoys. This novel decoy inhibits TNBC cell attachment to or migration across endothelial monolayers, suggesting that it may also block key steps of metastatic progression.

Purified Notch decoys can now be used to test the therapeutic role of Jagged inhibition on tumor angiogenesis and metastasis, and establish dose-dependent efficacy and toxicity.
OBJECTIVE: Depressive symptoms and quality of life may adversely affect cancer treatment and survival in patients diagnosed with cancer. Co-morbid depression in older adults may contribute to lower initiation or adherence to treatment, leading to increased mortality. We evaluated the association between pre-cancer depressive symptoms and mortality in older patients diagnosed with non-Hodgkin lymphoma (NHL).

METHOD: A retrospective cohort study was conducted using the SEER-MHOS linked database. The study included adults ≥65 years diagnosed with first primary NHL between 1998 and 2014 that completed one survey within 5-years prior to diagnosis. Depressive symptoms were defined as a positive response to at least 1 of 3 depression screening questions and a mental health component summary score ≥42. We used multi-variable Cox-proportional hazards models to estimate risk of cancer-specific mortality in adults with baseline depressive symptoms relative to adults without depressive symptoms.

RESULT: In a cohort of 1,308 patients, 81% were non-Hispanic white and 51% were female with a mean age of 76 years. Prior to cancer diagnosis, 135 (10%) subjects reported depressive symptoms. Compared to patients without baseline depressive symptoms, patients with depressive symptoms reported lower education (less than high school: 39% vs. 25%, p <0.01), lower household income (less than $30,000: 81% vs. 62%, p<0.01) and had a higher number of co-morbidities (mean of 3 vs. 2, p<0.01). In multi-variable analyses, baseline depressive symptoms were not associated with cancer-specific mortality (HR 1.09, 95% 0.80-1.38, p=0.60).

CONCLUSION: Our findings provide little evidence to support the hypothesis that depressive symptoms adversely affect cancer-specific survival in older patients with NHL. However, the high prevalence of depressive symptoms among older lymphoma patients is consistent with that of other critically ill older adults and deserves clinical attention.
Cost-effectiveness of adherence and persistence interventions for adjuvant tamoxifen therapy

PRESENTING AUTHOR: Brian Talon

CO-AUTHORS: Alemseged Ayele Asfaw, Scott Wirth, Lisa Sharp and Daniel Touchette

ABSTRACT:

OBJECTIVE: Adjuvant tamoxifen therapy reduces the risk of breast cancer recurrence and mortality. Poor adherence and persistence to therapy adversely impact patient outcomes. This study evaluates the cost-effectiveness of adherence and persistence interventions for patients on adjuvant tamoxifen therapy as compared to usual care from a payer’s perspective.

METHODS: A five-state Markov model was developed to evaluate four hypothetical interventions. The Restart-Stopped intervention targets women who have discontinued tamoxifen and increases the proportion that restart therapy. The Never-Stop intervention targets all women on therapy and decreases discontinuation. The High-to-High intervention focuses on maintaining the current adherence level in women with high adherence (PDC ≥80%). The Low-to-High intervention focuses on women with low adherence, and increases the proportion who become highly adherent. Annual cycles and a five-year time horizon were used. Relative improvement in adherence or persistence was varied and the program cost was estimated for assessing incremental cost-effectiveness at a WTP of $100,000/QALY. Cost and benefits were compared at a 5% relative increase in adherence or decrease in discontinuation over the 5-year time horizon.

RESULTS: The Restart-Stopped was cost-effective at a per-patient per-year (PPPY) cost of $445 and saved 4 lives/1,000. The Never-Stop was cost-effective at $177 PPPY and saved 5 lives/1,000. The High-to-High was cost-effective at $290 PPPY and saved 6 lives/1,000. Lastly, the Low-to-High was cost-effective at $545 PPPY and saved 4 lives/1,000.

CONCLUSION: At a 5% effectiveness level, persistence interventions focusing on decreasing discontinuation and adherence interventions targeting patients with high-adherence resulted in more lives saved and met the willingness to pay threshold at a lower cost. Interventions targeting persistence have the greatest potential to improve life expectancy with greater cost-effectiveness.
Identification of xanthones from the mangosteen fruit that promote androgen receptor degradation.

PRESENTING AUTHOR: Mirielle Nauman
POSTER LOCATION: 20

CO-AUTHORS: Bhaskar Vemu and Jeremy Johnson

ABSTRACT:

The purpose of this study is to determine how isoprenylated xanthones disrupt androgen receptor function in prostate cancer cells. Xanthones are a class of chemical compounds isolated from the purple mangosteen fruit (Garcinia mangostana) native to Southeast Asia. α-Mangostin is the most common xanthone. Androgen receptor (AR) degradation represents an important strategy to overcome drug resistance to FDA approved anti-androgens used in prostate cancer.

METHODS: Two different prostate cancer cell lines, 22Rv1 and LNCaP, are used through-out these experiments. The cytotoxicity of α-mangostin after 24, 48, and 72 hours is evaluated through MTT assays. Prostate cancer cells are treated with α-mangostin for 24 hours and are lysed, and then the total protein content is isolated. Total AR, phosphorylation of the AR at Serine 81, and BiP proteins are analyzed through immunoblotting.

RESULTS: α-Mangostin has also been shown to interact with AR through a fluorescence polarization assay, suggesting there is a direct interaction between α-mangostin and the ligand binding domain of AR. Immunoblot data reveals a dose and time dependent decrease in AR, coupled with an increase in the chaperone protein BiP. Further analysis of post-translational modifications identified a reduction in phosphorylation of AR at Serine 81. Together, upregulation of BiP and inhibition of AR phosphorylation inhibit the nuclear translocation of AR. This leads to an inhibition of transcription of downstream genes that are necessary for cell growth and proliferation. Both upregulating BiP and inhibiting AR post-translational modifications inhibit the nuclear translocation of AR, thereby inhibiting the transcription of downstream genes that are necessary for cell growth and proliferation.

CONCLUSION: These results suggest that α-mangostin promotes AR degradation by inhibiting nuclear translocation, which could be effective in drug resistant prostate cancer cases.
Sorafenib is an FDA-approved drug currently available for the treatment of advanced, unresectable hepatocellular carcinoma (HCC). However, development of sorafenib-resistance in patients poses a major challenge to make this treatment successful long-term. There is thus an urgent need to explore the mechanisms underlying sorafenib-resistance and to develop strategies towards increasing sorafenib-sensitivity in HCC. Aberrant activation of Wnt/β-catenin signaling in HCC is suggested to maintain tumor initiating cells, drug-resistance, tumor progression, and metastasis. Combining β-catenin inhibitors with sorafenib might thus be an effective therapeutic strategy to target drug-resistant HCCs. To explore this, we used wnt/β-catenin pathway inhibitor XAV-939 (which promotes β-catenin degradation) in combination with sorafenib to study their effect on the apoptotic potential of HCC cell lines Huh7, Hep3B and HepG2. XAV-939 was demonstrated to effectively reduce the expression of β-catenin in Huh7 and Hep3B cells, which express wild-type β-catenin. Flow cytometric analysis of these cells pre-treated with XAV-939 followed by sorafenib treatment showed a significant increase in the apoptotic potential in a time dependent manner. Furthermore, these cells revealed increased mitochondrial depolarization which was accompanied by a parallel increase in cytosolic cytochrome c release and downregulation of pro-survival protein Mcl-1. These effects of XAV-939 were further validated following knockdown of endogenous β-catenin, which showed a potentiation of sorafenib effects with β-catenin knockdown. In HepG2 cells, which expresses truncated, degradation-resistant β-catenin resulting in deregulated β-catenin transcriptional activity, XAV-939 treatment was unable to show significant effect on sorafenib-mediated apoptosis. However, pre-treatment of HepG2 cells with iCRT, a potent inhibitor of β-catenin-responsive transcription was found to effectively increase sorafenib-mediated apoptosis. Taken together, these results indicated that inhibition of β-catenin axis by promoting its degradation (by XAV-939) or by antagonizing its transcriptional activity (by iCRT) could sensitize HCC cells towards sorafenib-induced apoptosis.
Regulation of megalin by vitamin D as the mechanism for differential levels of intra-prostatic androgens between African American and Caucasian men

PRESENTING AUTHOR: Jason Garcia

CO-AUTHORS: Zachary Richards, Larisa Nonn

ABSTRACT:

Prostate cancer (PCa) is a hormonally driven cancer and is currently the third most common cancer in the US. African American (AA) men are disproportionately at risk for both PCa and vitamin D (vitD) deficiency compared to white men. The numerous chemopreventative properties of vitD and epidemiological relationship of vitD status with PCa aggressiveness and mortality has led to the hypothesis that vitD deficiency is a biological contributor to the PCa disparity in AA men. Here we examine the mechanisms that regulate hormone import into the prostate to follow-up on unexpected relationships between serum and intraprostatic vitD metabolites in AA men that our lab recently reported. We also found that Megalin, a multiliganded endocytic membrane receptor encoded by the gene LRP2, is present on prostate epithelium and is regulated by vitD. Extra-renal activity of Megalin has not been well studied as the widely accepted Free Hormone Hypothesis assumes passive diffusion of circulating free hormones into tissues. However, the presence of megalin suggests that globulin bound hormones from the circulation, including 25D bound to vitamin D binding protein (DBP) and testosterone (T) bound to sex hormone binding globulin (SHBG), are imported into prostate in a regulated manner. Moreover, we found similar relationships between serum and intraprostatic testosterone metabolites, further supporting active megalin; AA men had higher levels of dihydrotestosterone (DHT) in prostate tissue compared to white men. Examination of megalin in vitro in primary human prostate cells and in tissue explants demonstrated that globulin-bound hormones are imported into the prostate and transcriptionally active. In vitro 25D deficiency increased expression of LRP2 in cells and tissue slices. 25D decreased LRP2 promoter activity in prostate cells. We also observed megalin-mediated internalization of DBP-bound 25D and SHBG-bound T into prostate cells. Ongoing studies are examining megalin-mediated import of estrogens, which are also implicated in carcinogenesis. In summary our findings support the presence of a negative feedback loop in which vitD deficiency increases hormone import into prostate epithelium via Megalin. Therefore the upregulation of megalin in the setting of vitamin D deficiency may facilitate increased import of circulating sex steroids into the prostate contributing to carcinogenesis in AA men.
Prostate cancer is a leading cause of death in men and deficiency in vitamin D (1,25D) is associated with increased risk of lethal prostate cancer. 1,25D is a pleotropic hormone that regulates calcium homeostasis and plays a role in processes such as differentiation, apoptosis and proliferation. Vitamin D receptor (VDR) expression is positively correlated with tumor differentiation, further indicating its role in differentiation, but its mechanism of action in the prostate is not well defined. Using human primary prostate epithelial (PrE) organoids as a model, the differentiative properties of vitamin D were examined and identified DKK3 as a potential target. Dickkopf-3 (DKK3) has recently emerged as a regulator of prostate epithelial proliferation and terminal differentiation that may act through the Wnt and/or TGFβ pathways. Because vitamin D is a known modulator of Wnt and TGFβ signaling in other cell types, we hypothesized it may mediate DKK3 in the prostate as a means to promote or maintain differentiation. To test this, PrE cells and prostate cell lines were grown as monolayers or organoids in the presence of low doses of 1,25D. Both conditions showed reduced DKK3 mRNA and DKK3 protein expression and secretion. ChIP-sequencing for VDR-bound-DNA revealed a peak near the DKK3 promoter, suggesting direct 1,25D-regulation over DKK3. PrE organoids grown in 1,25D conditioned media were strikingly larger than controls and showed earlier luminal cell populations via flow cytometry and whole-mount immunofluorescence, indicating increased differentiation. Addition of DKK3 to organoids attenuated these effects. 1,25D treatment altered Smad activity, consistent with findings of DKK3 as a regulator of TGFβ signaling. Taken together our data show that vitamin D inhibits DKK3 to regulate TGFβ signaling, which may explain the early expansion of intermediate cells towards a luminal phenotype and supports the role of vitamin D as a mediator of differentiation in prostate epithelium. Ongoing studies are focused further quantifying downstream consequences of DKK3 in both the TGFβ and Wnt pathways, which are required during prostate development and are both implicated in disease.
Latina Breast Cancer Patient Awareness in Financial Resources: Healthcare Providers’ Perspective

PRESENTING AUTHOR: Jocelyne Lemus

POSTER LOCATION: 25

CO-AUTHORS: Perla Chebli, Yamile Molina

ABSTRACT:

Little is known how existing financial assistance programs address these unique needs and Latinas' awareness of them. To address this gap, we conducted 10 semi-structured interviews with healthcare professionals to understand: 1) Latina patients’ unique economic needs; 2) availability of financial programs to address these needs; and, 3) Latinas' awareness of these programs. Staff from ALAS-Wings and the University of Illinois at Chicago used purposive sampling strategies to recruit 10 healthcare personnel familiar with financial aspects of cancer care for 60-minute semi-structured interviews. The average age of participants was 43.7 years, 80% identified as female, 50% identified as Latinx, and 50% had graduate degrees. The average number of years participants had engaged breast cancer patients in treatment and survivorship care was respectively 5.7 and 4.97. In terms of insurance status, 70% of personnel reported that most Latina patients they engaged were uninsured or uninsured. In terms of costs, healthcare professionals perceived that Latinas specifically struggled with non-medical costs (e.g., transportation, living utilities), for which there was economic support from a few foundations (Pink Fund, Patient Advocate Foundation, American Cancer Society). However, healthcare professionals did not believe Latinas were aware of financial programs due to shame/embarrassment and language barriers. Healthcare professionals perceived that these barriers and the prioritization of surviving resulted in delays in seeking financial supports. Our findings highlight the importance of healthcare professionals that are able to explain the availability of resources to Latina breast cancer patients in linguistically and culturally astute strategies immediately following diagnosis and throughout treatment. This resources will help increase Latinas’ awareness and utilization of resources for non-medical and other costs.
Prostate cancer is the leading cancer diagnosis in men and is the second most likely cause of cancer-related mortality in men. One function of the prostate is to produce citrate for the seminal fluid. To accomplish this, the prostate epithelium has a unique cellular metabolism that focuses its substrates on citrate production at the cost of energy efficiency. During prostate cancer initiation, citrate becomes increasingly more oxidized and the brake on oxidative phosphorylation is gradually lost facilitating energy production. Epidemiological and experimental evidence is mounting supporting vitamin D’s role in mitigating prostate cancer progression/aggression. Here we suggest a novel mitochondrial redox modifying mechanism of vitamin D in prostate epithelial cells. Vitamin D is activated in the mitochondria of target tissues by a P450 enzyme, CYP27B1, which hydroxylates the pro-hormone, 25(OH)D to genomically active 1,25(OH)2D. 1,25(OH)2D enters the nucleus and after binding the vitamin D receptor to regulate gene transcription. In addition to the genomic mechanism, though, we hypothesize that local metabolism of 25D in the mitochondria results in a redox-mediated mechanism that contributes to prostate epithelial cell health and function. To address this hypothesis, we examined mitochondrial metabolism in primary prostate-derived epithelial cells after 1 hour and 16 hour treatment with 25D. 25D induced an increase in oxidative respiration at 1 hour followed by a decrease at 16 hours. Concurrently, we observed an increase in ATP production in response to the 1 hour 25D treatment. Extended treatment with 25D suppressed ATP production in addition to the changes in oxidative respiration, supporting normal prostate epithelial cell function which favors citrate production over ATP. In this context, sufficient vitamin D levels do not just regulate transcription but also maintain the overall health and function of the mitochondrial.
What mediates the racial/ethnic disparity in psychosocial stress among breast cancer patients?

PRESENTING AUTHOR: Carola Sánchez-Díaz

CO-AUTHORS: Garth Rauscher, Yamilé Molina,

ABSTRACT:

BACKGROUND: Prior studies have observed greater levels of psychosocial stress (PSS) among non-Latina (nL) Black and Latina women when compared to nL-White patients after a breast cancer diagnosis. The absence of adequate social support among cancer patients has been associated with greater PSS. We aimed to determine the role of socioeconomic status (SES) and unmet support in the racial disparity in PSS among BC patients.

METHODS: For 989 recently diagnosed BC patients aged 30-79, income, education and tract level disadvantage and affluence were summed to create a standardized socioeconomic status (SES) score. Three measures of PSS related to loneliness, perceived stress, and psychological consequences of a breast cancer diagnosis were defined based on previously validated scales. Five domains of unmet social support needs (emotional, spiritual, informational, financial, and practical) were defined from interviews. We conducted path models in M-Plus to estimate the extent to which disparities in PSS were mediated by SES and unmet needs.

RESULTS: Black and Latina patients reported greater PSS compared to white patients, and greater unmet needs (p=0.001 for all domains). Virtually all of the disparity in PSS could be explained by SES. A substantial portion of the mediating influence of SES was further transmitted by unmet financial and practical needs among black patients and by unmet emotional needs for Latina patients.

CONCLUSIONS: SES appears to be a “root” cause of the racial/ethnic disparities in PSS. The role of unmet social support needs differs between Black-White and Latina-White disparities.
Metformin Reduces Pancreatic Lesion Frequency and Size in EK Lean and Obese mice via mTOR Inhibition and Autophagy

PRESENTING AUTHOR: Karla Castellanos

POSTER LOCATION: 28

CO-AUTHORS: Jessica I Bauer-Segura, Ashley M Rodriguez, Giamila Fantuzzi, Paul Grippo

ABSTRACT:

Risk factors of pancreatic cancer (PC) development include diabetes and obesity, though it is unclear if diabetes is a cause or consequence of PC. A prolonged state of obesity can lead to diabetes and both may synergistically increase risk of PC incidence. The antidiabetic drug, Metformin (MET), has exhibited antitumor activity and may improve PC outcomes. The present study assessed the effectiveness of MET to inhibit the frequency and size of pancreatic neoplasms in EL-KRAS B6 (EK) mice by inhibiting mTOR and activating autophagy.

Wild type and EK mice were placed on: Chow, Chow+ MET, High Fat Diet (HFD), HFD + MET after weaning and remained on diet until 6 months of age. Glucose tolerance and body weight were not affected by the addition of MET, though EK mice developed ~40% less cystic papillary neoplasms or CPNs on MET when compared to controls. Significantly fewer cysts were detected in the pancreas of HFD+ MET group (11/mouse) than in the HFD group (20/mouse). EK HFD+ MET had significantly lower pancreas and liver to body weight ratios compared to EK HFD mice, as well as significantly lower occurrence of fibrosis and acinar-ductal metaplasia (ADM). Western blot data indicate; AMPK is significantly higher in all MET treated mice and autophagy is also dramatically increased in the EK Chow+MET and EK HFD+MET animals while mTOR is noticeably decreased.

Though MET did not alter weight or glucose metabolism, MET significantly inhibited the etiology of pancreatic neoplastic lesions in EK mice, suggesting that MET may abrogate pancreatic carcinogenesis via autophagy. Indeed, these findings may indirectly explain the association between PC and diabetes and supports that MET improves survival in diabetics with PC.
Reduced Caveolin-1 Expression Promotes Mitophagy in MDA 231 Cancer Cells Associated with Increase in Macrophage M1 Polarization

PRESENTING AUTHOR: Ying Jiang

CO-AUTHORS: Peter T. Toth, Sarah Krantz, Zhenlong Chen, Misuk Bae, Adriana Zimnicka, Jalees Rehman, Marcelo G. Bonini, Richard D. Minshall

ABSTRACT:

Due to their bacterial ancestry, mitochondria are highly immunogenic and mitochondrial damage triggers inflammatory responses. Mitophagy, the selective degradation of mitochondria by autophagy, removes damaged mitochondria and thereby inhibits inflammatory responses. Macrophages that have infiltrated into malignant tumors are predominantly M2-like (anti-inflammatory) and they facilitate resistance to chemotherapy by providing survival factors, promote the activation of anti-apoptotic programs, and inhibit immunity. M1-polarized (pro-inflammatory) macrophages on the other hand exhibit anti-tumor properties, and thus promotion of macrophage M1 polarization may be a promising strategy for cancer immunotherapy. In this study, we test the hypothesis that mitophagy is a pivotal determinant of macrophage M1 polarization and that caveolin-1 (Cav-1) expression in breast cancer cells negatively regulates mitophagy by inhibiting PINK1/Mitofusin2/Parkin signaling. We also determined whether mitochondria damaged by exposure to chemotherapeutic agents promote macrophage polarization towards the M1 state, and whether mitophagy-associated inhibition M1 polarization via clearance of defective mitochondria leads to drug resistance in breast cancer cells. In studies thus far, we observed that the expression of Cav-1, a cholesterol-enriched membrane-associated scaffolding protein, negatively regulates mitophagy by directly preventing Mitofusin 2 (Mfn2) from translocating to mitochondria. When Mfn2 translocation to mitochondria is inhibited by Cav-1, there is reduced mitochondrial recruitment of PINK and Parkin and less mitophagy. We also observed an increase in the production of typical M1 markers from macrophages co-cultured with MDA-MB-231 breast cancer cells pretreated with doxorubicin to induce mitochondrial damage. This novel observation provides a strategy to target tumor-associated macrophages (TAMs) as a means of combating cancer. TAMs are abundant in solid tumors and thus therapies targeting TAMs could overcome the low infiltration efficiency issue associated with T cell targeting immunotherapies. The findings of this research could significantly expand our understanding of therapeutic resistance and reveal critical targeting factors important in cancer immunotherapy.

LAYPERSON ABSTRACT:

Macrophages are first responders of the immune system; they recognize foreign invaders and activate other immune cells to eliminate the invaders. They are abundant in solid tumors, however, despite their presence in the tumor microenvironment, macrophages are not necessarily effective at killing cancer cells. We hypothesize that mitophagy, the selective packaging and expulsion of damaged mitochondria from cancer cells provides a fundamental role by enhancing cancer cell survival and inhibiting the tumoricidal function of nearby macrophages. Our preliminary studies demonstrate that caveolin-1 expression in cancer cells is a key negative regulator of mitophagy. In the most aggressive breast cancers, caveolin-1 expression is low and mitophagy is enhanced, which we hypothesize leads to reduced macrophage-dependent killing of cancer cells. We propose here increasing caveolin-1 expression in cancer cells or treating solid breast tumors with the cell-permeable caveolin-1 scaffolding domain peptide will reduce mitophagy and promote tumoricidal macrophage-mediated killing of breast cancer cells.
Social Capital is Associated With Misconceptions on Breast Cancer Among Latinas

PRESENTING AUTHOR: Kryztal Pena

ABSTRACT:

INTRODUCTION: Latinas have higher rates of late stage breast cancer diagnosis relative to non-Latina Whites. Cultural misconceptions about breast cancer (e.g., risk factors, non-medical options, survivability) contribute to non-adherence to screening guidelines and late stage breast cancer diagnosis. Little is known about how the social environment (e.g., # of people, amount of social support) contributes to Latinas’ cultural misconceptions. The size of Latinas’ social networks and how much support they receive about health may impact their cultural beliefs in one of two ways: social support can give accurate health information or can provide inaccurate health information. Our study examined the affect of social environment size and amount of support on cultural misconceptions about breast cancer.

METHODS: Our study includes 109 Chicago-based Latinas who are non-adherent to mammography guidelines. Previously validated survey measures used for this tool were women’s perceived health-related social capital and women’s cultural misconceptions about breast cancer (Cronbach’s alpha = 0.86-0.86). We conducted one multivariable linear regression model adjusting for socioeconomic characteristics (education, income, insurance).

RESULTS: Our sample was largely of Mexican descent (92%) and approximately half of them had less than a 9th grade education (58%), had an annual household income of <$10,000 (45%), and uninsured (57%). After adjusting for education, income, and insurance, the health-related perceived health-related social capital was negatively associated with cultural misconceptions about breast cancer, B = -0.20, p = .05.

DISCUSSION: Women who perceived a larger and more supportive social network for health concerns had fewer cultural misconceptions about breast cancer. Our results suggest larger more integrated environments in Chicago exchange more accurate information, resulting in fewer cultural misconceptions among individual women. To address the needs of socially isolated women, we should consider providing health information through public spaces (e.g. schools, churches) and encouraging health-related social networking among socially isolated women.

LAYPERSON ABSTRACT:

This study focused on Latinas because they get diagnosed with cancer at later stages compared to white women. They also have a lot of misconceptions which can be influenced by their culture; these misconceptions can be the reason they don't get mammograms annually.

Previous research has not looked at the amount of people Latinas interact with nor the amount of social support they receive from those individuals and its influence on their knowledge on breast cancer. The amount of people Latinas socialize with and the amount of support they receive from those people can either provide them with accurate health information or inaccurate health information. This study looked at the effect of the amount of people and support Latinas receive and its influence on their accuracy of health information related to breast cancer.

We started by recruiting women that had not gotten their mammograms within the past 2 years, who live in Chicago and were considered Latinas. We gave them a survey to identify how many people they consider themselves close to and see the knowledge they had on breast cancer. We found that majority of the women were Mexican, about half of them had less than a 9th grade education, made less than 10,000 and were uninsured. Overall it was found that the more people they talked to and the amount of support they received meant that Latinas had more knowledge on breast cancer.

Larger and more connected environments in Chicago exchange more accurate information which means there are less misconceptions among each woman. Its then important to get women who don’t talk to many people or receive very little support to find accurate health information through public places like churches, so it can encourage those women to talk to others about health topics.
Activin inhibition in PDAC associates with protection from cancer progression

PRESENTING AUTHOR: Georgina Mancinelli

POSTER LOCATION: 31

CO-AUTHORS: Carolina Torres Perales, Ron McKinney, Jessica Bauer, Nancy Krett, Sam Grimaldo, Paul J Grippo, Barbara Jung

ABSTRACT:

Novel therapeutic and prognostic/diagnostic targets for pancreatic cancer (PC) are urgently needed to improve patient survival. One unappreciated candidate is activin, a member of the TGFβ family. In PC patients, serum activin levels have been shown to be significantly higher and associated with cancer cell stemness and cachexia. Hence, we focused our efforts on activin ligand and examined its expression using in silico mining and a human PC TMA. Activin effects were tested in cultured cancer cells and PC mouse models. We hypothesized that activin enhances migratory functions, thus increasing metastasis in PC.

Oncomine database confirmed higher expression of activin in PC tissue compared to adjacent normal tissue which was confirmed in our TMAs, particularly in the stromal compartment. This expression pattern correlated significantly to higher mortality in PC patients. Human pancreatic stellate cells secrete 300-fold more activin than Panc-1 cancer cells via ELISA, as PC cells treated with activin showed a significant increase in migration. In KPCluc mice (pancreatic luciferase expression) treated for 3 months with an activin neutralizing antibody, there was no significant advantage in survival, though these mice had delayed metastasis.

Our data suggest that activin plays a role in cancer metastasis in PC patients. Blocking the ligand with a stable antibody in vivo, we can delay metastatic spread. Indeed, activin may serve as an attractive target for advanced stage PC treatment.
Synergistic Cytotoxic Effect of Busulfan and the PARP Inhibitor Veliparib in Myeloproliferative Neoplasms

PRESENTING AUTHOR: Natalie Rodriguez


ABSTRACT:

Patients with high-risk myeloproliferative neoplasms (MPNs), particularly with myelofibrosis (MF), can at this time only be cured with allogeneic hematopoietic stem cell transplantation (HSCT). Because MPNs and JAK2V617F-mutated cells show genomic instability, stalled replication forks, and baseline DNA double-strand breaks, DNA repair inhibition with poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors represents a potential novel therapy. Because the alkylating agent busulfan is integral in conditioning regimens for HSCT and leads to stalled replication forks through DNA strand cross-linking, we hypothesized that PARP inhibition with veliparib in combination with busulfan may lead to synergistic cytotoxicity in MPN cells. We first treated 2 MPN cell lines harboring the JAK2V617F mutation (SET2 and HEL) with veliparib at increasing concentrations and measured cell proliferation. SET2 and HEL cells were relatively sensitive to veliparib (IC50 of 11.3 μM and 74.2 μM, respectively). We next treated cells with increasing doses of busulfan in combination with 4 μM veliparib and found that the busulfan IC50 decreased from 27 μM to 4 μM in SET2 cells and from 45.1 μM to 28.1 μM in HEL cells. The mean combination index was .55 for SET2 cells and .40 for HEL cells. Combination treatment of SET2 cells caused G2M arrest in 53% of cells, compared with 30% with veliparib alone and 35% with busulfan alone. G2M arrest was associated with activation of the ATR-Chk1 pathway, as shown by an immunofluorescence assay for phosphorylated Chk1 (p-Chk1). We then tested in vivo the effect of combined low doses of busulfan and veliparib in a JAK2V617F MPN-AML xenotransplant model. Vehicle- and veliparib-treated mice had similar median survival of 39 and 40 days, respectively. Combination treatment increased median survival from 47 days (busulfan alone) to 50 days (P = .02). Finally, we tested the combined effect of busulfan and veliparib on CD34+ cells obtained from the bone marrow or peripheral blood of 5 patients with JAK2V617F-mutated and 2 patients with CALR-mutated MF. MF cells treated with the combination of veliparib and busulfan showed reduced colony formation compared with busulfan alone (87% versus 68%; P = .001). In contrast, treatment of normal CD34+ cells with veliparib did not affect colony growth. Here we show that in vivo confirmation that treatment with the PARP-1 inhibitor veliparib and busulfan results in synergistic cytotoxicity in MPN cells. Our data provide the rationale for testing novel pretransplantation conditioning regimens with combinations of PARP-1 inhibition and reduced doses of alkylators, such as busulfan and melphalan, for high-risk MPNs or MPN-derived acute myelogenous leukemia.

LAYPERSON ABSTRACT:

Patients with high-risk myeloproliferative neoplasms (MPNs), particularly with myelofibrosis (MF), can at this time only be cured with allogeneic hematopoietic stem cell transplantation (HSCT). Because MPNs and JAK2V617F-mutated cells show genomic instability, stalled replication forks, and baseline DNA double-strand breaks, DNA repair inhibition with poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors represents a potential novel therapy. Because the alkylating agent busulfan is integral in conditioning regimens for HSCT and leads to stalled replication forks through DNA strand cross-linking, we hypothesized that PARP inhibition with veliparib in combination with busulfan may lead to synergistic cytotoxicity in MPN cells. Here we show in vivo confirmation that treatment with the PARP-1 inhibitor veliparib and busulfan indeed results in synergistic cytotoxicity in MPN cells, with synergy observed in CD34+ Myelofibrosis cells but not normal CD34+ cells. Both JAK2+ and CALR+ MPN CD34+ cells are sensitive to PARP inhibition, suggesting that PARP inhibition may be a viable treatment for MPNs regardless of patient mutational status. Our data build on the current preclinical and clinical data and provide rationale for testing novel pretransplantation conditioning regimens with combinations of PARP-1 inhibition and reduced doses of alkylators, such as busulfan and melphalan. Furthermore, our data have wider implications for the treatment of high-risk MPNs and MPN-AML, with combination therapies including DNA repair inhibition meriting further investigation for the treatment of these patients.
ABSTRACT:

In previous work, our lab established that AMP-Activated Protein Kinase (AMPK) is required for NADPH homeostasis when solid tumors encounter energetic stress. Specifically, we showed that AMPK-mediated inhibition of fatty acid synthesis (FAS) and concomitant activation of fatty acid oxidation (FAO) conserves and produces NADPH to neutralize toxic reactive oxygen species (ROS). More recently, Pascual et al. showed that CD36, a trans-membrane protein that promotes uptake of long chain fatty acids (LCFA), is required for metastasis initiation. Importantly, this group demonstrated that CD36 is required for the pro-tumorigenic effect of a high fat diet (HFD). However, they suggest that CD36 and the resultant increase in FAO facilitate ATP production. Using breast adenocarcinoma cells and mouse embryonic fibroblasts, we have utilized over-expression and knockdown models to demonstrate that CD36 promotes ROS neutralization during glucose withdrawal and matrix detachment (in vitro models of energetic stress). Furthermore, similar to reports in skeletal and cardiac muscle, AMPK activation promotes membrane localization of CD36, presumably for LCFA uptake for FAO. Finally, preliminary results suggest that CD36 over-expression can partially rescue AMPK-deficient cells from energetic stress, suggesting a second mechanism by which CD36 promotes redox balance. Taken together, our data suggest that a high fat diet may drive tumorigenesis by promoting NADPH homeostasis in a cell-autonomous manner through CD36. Importantly, CD36-neutralizing antibodies block the pro-tumorigenic effect of a HFD, and combining this strategy with drugs that induce oxidative stress may synergize for cancer treatment.

LAYPERSON ABSTRACT:

Cancer researchers have focused much attention towards the early detection of tumors before cancer cells metastasize, that is spread to a secondary site. These efforts have been very successful in many cancers, championed in breast cancer, where nearly 99% of patients with localized cancer survive longer than five years. However, despite aggressive screening efforts, it is not possible to catch every cancer early, and as a result only 27% of breast cancer patients who are diagnosed with metastases at a secondary location survive for longer than five years. Our lab has been focused on determining how cancer cells survive the metabolically stressful process of metastasis. It is understood that as a tumor cell breaks off from its primary site and migrates to a secondary organ, it experiences high levels of oxidative stress. Indeed, the “antioxidants” commercially branded to improve health may actually increase the ability of a cancer cell to travel to distant organs. All cells have intrinsic antioxidant systems to maintain their health, and our lab previously demonstrated that the ability to burn fatty acids is one such pro-survival mechanism. More recently, another lab demonstrated that the ability of cancer cells to bring fatty acids into the cell is required for metastasis. Furthermore, mice fed a high fat diet have significantly more metastases than those on a regular diet. Taken together, we hypothesize that tumor cells increase the uptake of fatty acids to promote their survival by increasing antioxidants. Considering that nearly 40% of American adults are obese, determining the exact mechanism by which fatty-rich diets regulate metastasis is required to develop more targeted and effective therapies for these patients.
ABSTRACT:

Triple-Negative Breast Cancer (TNBC) accounts for 10-15% of all breast cancers and is characterized by a lack of estrogen receptor (ER), progesterone receptor (PR), and amplified HER2 expression. TNBC exhibits poor prognosis due to the development of chemoresistance and metastasis. Currently, no FDA-approved targeted therapies are available for TNBC and chemotherapy regimens combining two or three agents, such as Adriamycin + Cyclophosphamide (AC), remains the standard treatment. Conventional laboratory methods of studying chemotherapy have focused on analysis of short-term (24-72hr) tumor cell responses to single agents and single drug exposures. However, chemotherapies are rarely used as single agents and are given in repeated cycles of every 14-21 days in the clinical setting. Thus, in order to better simulate clinical treatment approaches, we describe a novel method of using Mafosfamide in combination with Adriamycin (AM) to conduct in vitro studies that recapitulate AC. Furthermore, we analyzed the biological effects of single agent and combination chemotherapies at different time points. We demonstrate that AM treatment exhibits biological effects that are distinct from those of single agent treatments, both short-term and long-term. Overall, this study establishes a new method of studying chemoresponse and chemoresistance in vitro, and also highlights the importance of modeling treatment based on clinical dosing schedules.
**Risk of venous thromboembolism associated with initiation of chemo-immunotherapy among older patients with non-Hodgkin lymphoma: differences by race and subtype**

PRESENTING AUTHOR: Chandler Coleman


ABSTRACT:

BACKGROUND: Non-Hodgkin lymphoma (NHL) and its treatment are associated with an increased incidence of venous thromboembolism (VTE). Our goal was to determine the risk of VTE associated with chemo-immunotherapy and examine differences by race/ethnicity and histologic subtype.

METHODS: We conducted a nested case-control study from within a retrospective cohort of 29,102 patients greater than 66 years of age with a histologically confirmed first primary NHL using, the Surveillance, Epidemiology and End Results (SEER) Medicare linked database. VTE cases were identified from health claims data and matched to up to ten controls on age, sex, race/ethnicity, and NHL subtype, using incidence density sampling. We determined relative risk of treatment-related VTE using multivariable conditional logistic regression models to calculate adjusted OR and 95% CI.

RESULTS: Among 2,592 cases and 18,518 matched controls, the median age was 78 years and most patients were female (56%), non-Hispanic white (96%) and diagnosed with diffuse large B-cell lymphoma (70%). Overall, any use of chemo-immunotherapy was associated with increased risk of VTE (OR 1.18, 95% CI 1.05, 1.33). The greatest risk was observed in patients receiving chemo-immunotherapy within the last 30 days (OR 2.80, 95% CI 1.56, 5.05) and this remained elevated through the first 90 days post-treatment. In stratified analyses, VTE risk did not appear to differ significantly by race/ethnicity, although increased VTE risk was most consistently observed in patients with indolent NHL subtypes (OR 2.04, 95% CI 1.62, 2.55).

CONCLUSIONS: The first 90 days following initiation of chemo-immunotherapy treatment presents the highest risk of VTE among any chemotherapy treatment for NHL. Thromboprophylaxis strategies in patients with NHL may be most critical during this period. Consideration should also be given to older patients with indolent forms of lymphoma when initiating aggressive systemic therapy versus observation only.
Endothelial cells maintain vascular homeostasis by regulating the permeability of plasma fluid and proteins. Excessive loss of serum protein results in hypo-proteinemia and increased mortality. Plasmalemmal Vesicle Associated Protein (PV-1) is a 60 kilo-dalton glycoprotein that forms diaphragms at the neck of caveolae and is present in fenestrations. Previous studies have indicated that PV-1 prevents leakage of serum proteins into fenestrated organs. Interestingly, endothelial cells derived from malignant tumors (i.e. pancreatic adenocarcinoma, hepatocellular carcinoma) showed profound upregulation in PV-1 expression, whereas PV-1 depletion via siRNA or antibody-mediated targeting was shown to reduce tumor growth. However, the mechanism underlying endothelial PV-1 regulation of tumor growth is not known. Here, we generated endothelial cell specific PV-1 knockout (PV-1ECKO) mice and revealed a novel role for PV-1 in maintenance of the adult mouse lung endothelial barrier. PV-1ECKO mice demonstrated significant weight gain and ascites. Blood serum analysis of PV-1ECKO mice revealed significantly reduced serum albumin and serum protein (p<0.01). Concordantly, PV-1ECKO mice demonstrated reduced arterial blood pressure (p<0.05). PV-1ECKO organs were edematous, as determined by increased Wet-to-Dry ratios in lung (p<0.05), heart (p<0.05), stomach (p<0.05), pancreas (p<0.05), and kidney (p<0.001) tissues compared to controls. Further, albumin transport was increased in PV-1ECKO mouse lungs (p<0.05). Surprisingly, fluid permeability was also increased in PV-1ECKO mouse lungs (p<0.05). These findings suggest that PV-1 contributes to homeostatic barrier function in continuous-type endothelium, restricting both protein and fluid transport into the endothelial cells. Future studies will address the fate of protein internalized in PV-1 deficient endothelial cells, which might have mechanistic implications for tumor growth.
**Quantifying intrinsic subtype admixture in luminal A breast cancer and its relationship to clinical outcomes**

**PRESENTING AUTHOR:** Neeraj Kumar  
**POSTER LOCATION:** 37

**CO-AUTHORS:** Dan Zhao, Amit Sethi, Peter Gann

**ABSTRACT:**

**BACKGROUND/OBJECTIVES:** PAM50 gene profiling assigns each cancer to a single intrinsic subtype. However, individual cancers vary in their adherence to a prototype, and some may exhibit expression patterns that indicate intra-tumor admixture of multiple subtypes. Our objective was to develop admixture metrics from PAM50 gene expression profiles in order to stratify Luminal A cases according to their degree of subtype admixture, and then relate such admixture to clinical and molecular variables.

**METHODS:** We re-constructed scaled, normalized PAM50 profiles for 1,980 cases (674 LumA) in the METABRIC cohort and for each case we computed its Mahalanobis (M-) distance from its assigned centroid and its M-distance from all other centroids. We used t-SNE plots to visualize overlaps in subtype clustering. With Normal-like cases excluded, Median Distance Criteria (MDC) classified a case as Pure if it was located within the 50th percentile of the LumA centroid and >50th percentile from any other centroid. Distance Ratio Criteria (DRC) was computed as the ratio of M-distances from the LumA centroid to the nearest non-assigned centroid; cases were grouped by DRC tertile. Pure and admixed LumA cases were compared on clinical, molecular and survival traits. TCGA LumA cases (n=509) were used for independent validation.

**RESULTS:** Compared to admixed cases in METABRIC, pure ones by MDC had younger age at diagnosis, smaller tumor size, lower grade and lower stage. Comparisons of the highest (T3, most admixed) to lowest tertile (T1) for DRC revealed even stronger associations. Admixed cases, by both metrics, were more likely to show HER2 gain, high proliferation by AURKA expression, higher PAM50 Risk of Recurrence scores, more frequent TP53 mutation, and less frequent mutation of PIK3CA and CBFB. Similar results were observed in the TCGA validation cohort. LumA-LumB confusion was predominant, but other combinations with LumA were also present. Degree of admixture was associated with overall survival in both cohorts, as was disease-free survival in TCGA, independent of age, grade and stage. (See table for adjusted hazard ratios).

**CONCLUSIONS:** Luminal A breast cancers subgrouped based on PAM50 subtype purity support the hypothesis that admixed cases have worse clinical features and survival. Future analyses will explore more extensive genomic metrics for admixture and their spatial significance within a single tumor.
Lung cancer screening initiative and identification of novel blood biomarker for early detection of lung cancer

PRESENTING AUTHOR: Adijan Kuckovic

POSTER LOCATION: 38

CO-AUTHORS: Joseph Berei, Austin Anderson, Sherya Deb, Kayya Sri Racherla, Edward Miliavski, Shylendra Sreenivasappa, Joseph Ross, Sandra Martell, Connie Vitali, William Schulz, and Neelu Puri

ABSTRACT:

Lung cancer is generally asymptomatic at early-stages, and only 7%-10% of patients are detected at early-stages. Winnebago County has a 14% higher mortality rate for lung cancer when compared to the national rate; hence, to improve early detection of lung cancer in the Winnebago County, we implemented low-dose computed tomography (LDCT) screening. Currently, LDCT is used to detect lung cancer at early-stages, and the Center for Disease Control (CDC) has proposed new guidelines for early screening of lung cancer in individuals between 55-80 years of age with a 30 pack/year smoking history (1 pack/day for at least 30 years). Using liquid biopsy, we can identify changes in methylation patterns in genes that are expressed in the plasma of lung cancer patients and these changes in methylation patterns can be used for early detection. Epidermal growth factor receptor (EGFR) is a gene shown to be expressed in lung cancer patients’ plasma in all stages and is correlated with poor prognosis and overall poor survival; hence, it can potentially be used as a biomarker for early detection.

Awareness of LDCT lung cancer screenings will lead to detection of NSCLC cases at early-stages. We hypothesize that EGFR is over-expressed in lung cancer and that the EGFR promoter methylation patterns may be a predictive biomarker for the early detection of lung cancer.

This project incorporates community activities including educating physicians and smokers on LDCT and the importance of early detection while screening potential lung cancer patients as well as collecting clinical blood samples from local hospitals. From the samples collected, plasma was separated from whole blood. Circulating and genomic DNA were extracted using MagMax Cell-free DNA Isolation kit and QIAamp DNA Blood Mini Kit. These DNA samples were then bisulfite converted using an EZ DNA Methylation-Gold kit. MethPrimer software was used to identify CpG-rich islands in the promoter region of EGFR to design degenerate primers. Converted DNA samples were amplified using PCR, and sent for Next Generation Sequencing (NGS). The results were analyzed using bioinformatics to determine percent methylation at specific CpG sites identified in the EGFR promoter region after NGS.

1,116 LDCT screenings occurred in Winnebago County. Lung cancer was diagnosed in 19 patients, out of which 11 patients (57.8%) were early-stage patients. We detected that 45.4% of patients screened had nodules present compared to 24.2% of patients in the National Lung Cancer Screening Trial. We observed that 1.70% of patients referred for LDCT screening were diagnosed with lung cancer, compared to 0.87% of patients in the National Lung Cancer Screening Trial. This may be due to the higher incidence of smoking in Winnebago County (18%) compared to the nation (15.5%). Our screening study had 96.3% false positives, which is comparable (96.4%) to the results obtained in the National Lung Cancer Screening Trial. Using NGS, methylation in the promoter region of EGFR was studied using degenerate EGFR primers. In the promoter region of EGFR, our analysis showed that there are regions of hypermethylation (68-99%) in three CpG islands (Sequence 1: -1,017 to -1,207 bases distal to the reading frame ATG of EGFR). However, there was hypomethylation (6-21%) at four CpG island (Sequence 2: -621 to -334 bases proximal to the reading frame ATG). In the plasma of control patients, we observed the same trend with hypermethylation in (56%-99%) in three CpG islands in sequence 1. Also, there was hypomethylation (6%-29%) in four CpG islands further downstream in sequence 2. Further studies and more patient samples need to be analyzed to achieve statistical significance.

Currently in the Winnebago County area we have been able to successfully detect early-stage lung cancer and potentially save 11 patients in the community. Percent methylation in the plasma of NSCLC patients compared to the plasma of control patients demonstrates an average difference (3 CpG sites) of 18% in percent methylation for sequence 1 and an average difference (4 CpG sites) of 20% in sequence 2.
**Characterization of a novel human topoisomerase II beta mutant**

PRESENTING AUTHOR: Hannah Miles  
POSTER LOCATION: 39

CO-AUTHORS: Matthew Gilbertson, Amanda M. Johnson, Lokha Ranjani A. Boopathy, John L. Nitiss, Karin C. Nitiss

**ABSTRACT:**

Type II topoisomerases are critical enzymes in DNA metabolism. These enzymes carry out a transient DNA breakage by forming a 5' phosphotyrosyl linkage between the enzyme and DNA. The Top2beta isoform is required for cell division, while the Top2alpha isoform is crucial for the development of the nervous system and is required for hormone-mediated transcription. Ju et al. recently described a de novo mutation of Top2beta (His63Tyr) in a patient with severe developmental delay. However, the report failed to present evidence that the His63Tyr mutation was specifically involved in the disease process. We investigated the potential role of the His63Tyr as a disease-causing mutation by ectopically expressing the mutant protein in a model system and carrying out biochemical analyses of purified Top2beta carrying the His63Tyr mutation. We hypothesized that this mutation causes misfunctioning of Top2beta rather than simply eliminating Top2 activity. We assessed the cellular consequences of the His63Tyr mutant enzyme by the use of yeast models. The mutant enzyme was expressed and purified to characterize its activity. Since His63 is conserved in both human and yeast Top2, we also created the orthologous mutants in the human Top2alpha isoform (His42Tyr) and the yeast Top2 (His20Tyr) via site-directed mutagenesis. We found that the expression of any of the three mutant enzymes - (Top2alpha) His42Tyr, (Top2beta) His63Tyr, and (yeast) His20Tyr - could not complement a deficiency of yeast Top2. Expression of the Top2beta mutant enzyme led to elevated rates of recombination and increased sensitivity to the Top2 targeting drug etoposide, suggesting that the enzyme could generate enzyme-mediated DNA damage. The purified Top2beta mutant enzyme was catalytically active and exhibited elevated single strand DNA cleavage compared to the wild type enzyme. A Top2beta variant completely lacking the ATPase domain was constructed and this truncated variant generated high levels of DNA cleavage in vitro and required homologous recombination for yeast cell viability. The Top2alpha His42Tyr mutant enzyme caused very poor growth in yeast cells, suggesting that this mutation impairs cell growth by generating DNA damage. We suggest that the ATPase domain of Top2beta plays a critical role in regulating DNA cleavage by the enzyme and suggest that the dominant phenotype of Top2beta(His63Tyr) expression arises from generation of DNA damage, rather than loss-of-function of the enzyme. Additionally, the expression of the Top2alpha(His42Tyr) mutant in yeast cells was shown to be detrimental towards cell survival even in the presence of wildtype yeast Top2 enzyme.
EGFR TKI Resistance via Role of VEGFR2

PRESENTING AUTHOR: Shreya Deb

POSTER LOCATION: 40

CO-AUTHORS: Chike Osude, Leo Lin, Sanjana Singh, Joseph Berei, Ray Ortiz, Eva Drinka

ABSTRACT:

BACKGROUND: The treatment paradigm for late stage non-small cell lung carcinoma (NSCLC) has shifted toward molecular targeted therapy. Epidermal growth factor receptor (EGFR) is one of the most studied targets. Tyrosine kinase inhibitors (TKI) against EGFR have proven effective, however TKI resistance is common. The T790M mutation within EGFR kinase domain is the major mechanism of resistance and is seen in 50% of the cases with acquired EGFR TKI resistance. Vascular endothelial growth factor receptor (VEGFR-2) is a transmembrane bound RTK which binds to its ligand, VEGF-A165 (VEGF), and co-receptors, NP-1/NP2. VEGF/VEGFR-2 inducing angiogenesis in NSCLC through an autocrine feed-forward loop which may offer a novel perspective to study TKI resistance. VEGFR-2 expression is also enhanced in lung tumors.

HYPOTHESIS/AIMS: We hypothesize that an autocrine feed-forward mechanism leads to upregulation of VEGF-2, VEGF and NP-1 expression in TKI-resistant cell lines and NSCLC tumors, inducing angiogenesis and tumorigenicity which leads to NSCLC progression; thus, modulation of these proteins may help overcome TKI resistance.

STUDY DESIGN: H2170, H358, H3255 and H1975 NSCLC parental cells were obtained from ATCC. Erlotinib resistant cells were obtained by treating parental cells with increasing concentrations of erlotinib for H2170 and H358 cells only. DNA sequencing was performed to exclude T790M mutations. Quantitative real-time PCR was used on target genes coding for VEGF, VEGFR-2, NP-1. Immunofluorescence (IF) and Fluorescence-activated cell sorting (FACS) analysis were performed with antibodies against VEGFR-2 and NP-1. ELISA was used to quantify the amount of secreted VEGF. Viability of resistant cells was assessed after treatment with increasing concentrations of VEGF inhibitor or humanized monoclonal antibody (Avastin) in medium with or without erlotinib using a cell proliferation assay (MTT). Paraffin embedded tumor biopsy slides were immunohistochemically stained (IHC) with antibodies against VEGFR-2 and NP-1 and graded by a pathologist.

RESULTS: Through real-time PCR, we observed a 2.45-fold, 3.45-fold and 1.4-fold upregulation in gene expression of VEGF, VEGFR-2 and NP-1 in H2170ER and 3.59-fold, 3.34-fold and a 2.23-fold increase of VEGF, VEGFR-2 and NP-1 in H358ER cells compared to parental counterparts (H2170P and H358P). Immunoblotting results demonstrated there was a 3.63-fold and 2.77-fold increase in VEGF-2 and NP-1, respectively, protein expression of H2170ER cells compared to H2170P in the presence of Erlotinib. Immunoblotting results demonstrated there was a 5.27-fold and 2.12-fold increase in protein expression of VEGFR-2 and NP-1, respectively, in H358ER cells compared to H358P in the presence of Erlotinib. Furthermore, immunoblotting demonstrated there was an 8.26-fold and 4.13-fold increase in protein expression of VEGFR-2 and NP-1, respectively, in H1975 cells compared to H3255 in the presence of Erlotinib. Flow cytometry results demonstrated there was a 1.3 to 3.8-fold increase and IF results showed a 2.17 to 5.06 fold increase in cell surface expression of VEGFR-2 and NP-1 in H2170ER, H358ER and H1975 when compared to their parental counterparts. ELISA results demonstrated increased VEGF secretion between 24 and 48 hours. MTT assays showed that the VEGFR-2 inhibitor (ZM HCl 323-881) and Erlotinib lowered cell death to 9-57% compared to erlotinib alone (72-75%). MTT Assay after treatment with Avastin (monoclonal antibody against VEGFR) showed that it was not as effective as VEGFR-2 inhibitor since the combination of Avastin and Erlotinib decreased viability to 22%-85%. IHC data revealed a statistically significant result between length of survival in months and high/low VEGFR-2 tumor expression in late stage NSCLC patients. There was a median survival of 14 months in high VEGFR-2 expression group compared to 21 months in low expression (p<0.05).

CONCLUSION: This study indicates that angiogenic markers such as VEGF, VEGFR-2, and NP-1 may contribute to TKI resistance and inhibitors of these biomarkers may be an effective method to overcome resistance. Our results suggest up-regulation of VEGF/VEGFR-2 autocrine system may be an alternative signaling pathway that promotes proliferation, bypassing the inhibitory effect of erlotinib, leading to erlotinib resistance. IHC demonstrated that VEGFR-2 could be a prognostic biomarker in late stage NSCLC.
ABSTRACT:

PURPOSE: Effective communication is pivotal to timely cancer detection and treatment; however, for persons with limited English proficiency (EP), language may pose a considerable barrier to timely communication, access, and preventative measures in the US-based healthcare system. Historically, this is especially true in screening for the presence of Human Papilloma Virus (HPV), a sexually transmitted and preventable virus responsible for several forms of cervical cancer. This study aims to predict the likelihood of regular pap smears (RPS) by examining patient-related factors, such as EP, and cancer-specific information seeking behaviors (CISB). Specifically, we aim to disentangle behaviors and patient factors of patients living with a cancer diagnosis from other correlated factors among women undiagnosed with cervical cancer.

METHODS: Using weighted analysis, we conducted Chi-square and logistic regression on data collected from the 2018 Health Information National Trends Survey (HINTS) of the National Cancer Institute to conduct our analyses. RPS was determined by uptake of the last 3 years. EP was categorized as 'High', 'Medium', and 'low' based on responses (very well, well, not well, and not at all) to how well respondents spoke English.

RESULTS: Out of the 2,022 eligible women, the mean age was 48.73±0.69 years; with 187 (10.35%) reporting low to medium EP; 605 (26.72%) did not have an RPS and 293 (14.26%) were diagnosed with a type of cancer aside cervical cancer. Low EP women (LEPW) rated the doctor (67.69%) over the internet (26.28%) as their first point of contact for health information while high English proficient women (HEPW) rated the internet (78.45%) over the doctor (10.52%). About 82.31% of LEPW either strongly/somewhat agree that getting cancer information takes a lot of effort compared to 35.03% of HEPW. After adjusting for demographics and socioeconomic status (SES), odds of RPS was lower among LEPW (Adjusted odds ratio (aOR) = 0.85, 95% confidence interval [CI] = 0.83-0.86) compared to HEPW even after including cancer history and insurance status into the model (0.77, 0.75-0.79).

CONSIDERATIONS FOR IMMUNOTHERAPY: Our findings show that unlike HEPW, the LEPW are highly reliant on the doctor for health information hence, their exposure to immunotherapy communication may be limited by the clinician’s lack of knowledge. There is also a strong need to promote the visibility of reliable immunotherapy information on the internet since more HEPW will prefer the internet as their source of health information. Finally, the persistent association of EP with cancer prevention after adjusting for the above-mentioned characteristics, suggests that the language effect, in conjunction with SES and health characteristics, may act as a significant barrier to cancer communication and timely detection.

KEYWORDS: English proficiency; cancer information-seeking; regular pap smear, cervical cancer screening.

LAYPERSON ABSTRACT:

The United States of America (USA) is becoming more diverse, taking the first place among countries with the highest number of immigrants; yet linguistic diversity is lacking in the US healthcare system in that health providers may only speak English. This mismatch between health care providers and the changing US population creates a language barrier that has been shown to hinder appropriate access and utilization of preventive health care services. Namely, women with limited English proficiency may be greatly impacted as these women may have limited options for obtaining cancer-related information in their native languages. Historically, this is especially true in screening for the presence of Human Papilloma Virus (HPV), a sexually transmitted and preventable virus responsible for several forms of cervical cancer.

Our study reports evidence as to how women with different levels of English proficiency seek information related to their health. Specifically, we found that women with low English proficiency mostly rely on their doctor’s office for obtaining information about their health. Meanwhile, women who speak English comfortably report that they use the internet for their health information. This is problematic in seeking information related to cancer and cancer treatments. Unlike women with high English proficiency, women with limited English proficiency find it tiring and frustrating getting cancer-related information; they are also more likely to seek cancer-related information from cancer organizations as well.

Findings show that English proficiency levels may determine whether women receive appropriate screening for cervical cancer; however, other factors such as socioeconomic status, family history of cancer, and having health insurance all work together to influence their screening decision. Our results suggest that limited English proficient women's uptake of cancer recommendations is highly dependent of their doctor’s knowledge of the information. This is particularly problematic as new treatments, such as immunotherapy solutions, enter clinical trials or emerge on the market at a rapid pace. As the treatment options available to cancer patients are growing, it is now more important to provide up-to-date information on available treatment options to cancer patients rather than relying on the knowledge of an individual health care provider. There is also an urgent need to explore other less tiring sources of information where women with low English proficiency will be able to seek cancer-related information. Finally, priority should be given to promoting the visibility of reliable and high-quality cancer information, in particular to inform patients about immunotherapy options, on the internet since most highly proficient women use the internet as their source of health information.
ABSTRACT:

BACKGROUND: EMT is a vital process in the development of metastasis and occurs when epithelial cells lose their polarized structure by downregulation of adherens junction proteins, E-cadherin and Claudin1, located on the cell membrane. Cells which have undergone EMT have elongated spindle-like morphology due to upregulation of mesenchymal markers Vimentin and N-cadherin. EMT may be responsible for tyrosine kinase inhibitor (TKIs) resistance to epidermal growth factor receptor (EGFR) in patients with activated EGFR mutations. Our earlier studies indicate that the presence of T790M mutation may induce EMT in erlotinib resistant (ER) cells (H1975). When p120-catenin, a key EMT regulator, is no longer bound to membranous E-cadherin, a complex is formed with Kaiso factor, suppressing its transcription repressor activity and promoting oncogenesis. PRMT1, another key EMT inducer, is also overexpressed in non-small cell lung cancer (NSCLC). Cells undergoing EMT also acquire cancer stem-cell (CSC) like characteristics by expressing CSC markers ABCB1, BMI-1 and Oct-4.

HYPOTHESIS/AIM: We hypothesize that EGFR TKI resistant cells undergo EMT due to modulation of the p120-catenin/Kaiso factor pathways and PRMT1. Further downregulation/knockout of these EMT mediators may help overcome TKI resistance. The aim of this study is to investigate EMT and CSC like characteristics in wild type-EGFR and TKI resistant H358, H2170 and H1975cells. EMT and CSC like characteristics were also investigated in TKI resistant EGFR mutant H1975 cells (L858R and T790M mutation) and TKI sensitive EGFR mutant H3255 cells (L858R mutation).

STUDY DESIGN: To determine modulation of EMT biomarkers, immunoblotting (WB), qPCR and immunofluorescence (IF) were performed. Expression of ABCB1 and E-cadherin was measured using flow cytometry. In EGFR mutant cells, PRMT-1 was knocked down using siRNA or downregulated using an inhibitor, Furamidine, and examined/validated by immunoblotting or cell proliferation (MTT) assay. Knockout of p120-catenin was performed using CRISPR-Cas9 and verified using WB. Immunohistochemistry (IHC) was performed on 46 tumor sections.

RESULTS: PRMT1 and p120-catenin were upregulated 1.5 and 6.1-fold in H358ER cells, respectively. Other EMT regulators such as Snail, PRMT-5, Vimentin and Kaiso factor were also upregulated by 2.6 to 10.7-fold and E-cadherin and Claudin-1 were downregulated by 2.6 to 10-fold in H358ER cells, respectively. RhoA, a small GTPase downstream of p120-catenin and a negative EMT regulator, was also downregulated by 2.9-fold promoting EMT in these cells. Immunofluorescence (IF) studies showed that there was 95% colocalization of p120-catenin and Kaiso factor in H358ER cells whereas 70% colocalization was seen in H358 parental cells. In H358ER NSCLC cells with wild type EGFR, flow cytometry studies showed increased expression of CSC markers ABCB1 (1.12-fold), BMI-1 (1.2-fold) and Oct-4 (1.1-fold). Inhibition of PRMT1 by Furamidine increased erlotinib efficacy by 16.5% in H358ER and 21% in H2170ER cells. Knockout of p120-catenin by CRISPR-Cas9 increased erlotinib efficacy by 19% in H358ER cells. There was an increase to 54.7% in erlotinib's efficiency in p120-catenin knockout H358ER cells after treatment with Furamidine. IHC data revealed a statistically significant result between length of survival in months and high/low PRMT-1 and p120-catenin tumor expression in late stage NSCLC patients. There was a median survival of 23.4 months in high PRMT-1 expression group compared to 36.12 months in low expression (p=0.004). There was a median survival of 19.25 months in high p120-catenin expression group compared to 38.69 months in low expression (p=0.004). Preliminary results also indicated that PRMT-1 and p120-catenin expression is higher in smokers.

CONCLUSIONS/IMPLICATIONS: EMT maybe mediated through biomarkers such as PRMT1, which also upregulates other EMT regulators such as Snail, PRMT-5, Vimentin and Kaiso factor, and p120-catenin, which represses E-cadherin and Kaiso factor, thus activating EMT in TKI resistant cells. IHC demonstrated that PRMT-1 and p120-catenin could be prognostic biomarkers in late stage NSCLC.
ABSTRACT:

In understanding the role of biomarkers and environmental exposures on cancer outcomes, the question of statistical selection of important features can be challenging since the number of features are often large, and are often strongly inter-correlated among themselves. Feature selection has become an essential element of statistical modeling to yield parsimonious models while keeping high prediction accuracy. Features which are inter-correlated cause significant issues in feature selection and this is an active research area. In a study of cachexia in Non-Small Cell Lung Cancer (NSCLC), we, in particular, find that baseline level biomarkers are, in fact, strongly inter-correlated among themselves. For high-dimensional feature selection, a biostatistical method known as LASSO (Least Absolute Shrinkage and Selection Operator) has become strongly popular in the last decade and is available in many popular statistical software. This method, however, fails to select any of the biomarker features even though many of them have significant marginal (univariable) association with cachexia. We are developing a biostatistical feature selection method that promises to provide improved prediction errors by efficiently handling the collinearity problem through an iterative procedure of selecting features after clustering highly correlated features. The performance of this method is evaluated in an extensive set of simulation studies and in real data application.
ABSTRACT:

A comparative analysis was conducted; the microsatellite instability (MSI) is the state of genetic hypermutability that indicates from impaired DNA mismatch repair (MMR). MSI is the molecular fingerprint of the MMR system that distinguishes roughly 15% of colorectal cancers. MSI flourishes because of germline mutations in MMR genes. Also frequently from epigenetic silencing of the MLH1 gene in sporadic tumors, that happens in an environment of methylation of CpG islands in gene promoter regions. Likewise, recognizing inadequate MMR, portrays salient implications for patient management and will ameliorate patient outcomes.
Development of Locally Deliverable Polymeric Microspheres with Environmentally Specific Release for the Improvement of Cancer Therapy

PRESENTING AUTHOR: Karol Sokolowski

POSTER LOCATION: 45

CO-AUTHORS: Jason S. Buhrman, Richard A. Gemeinhart

ABSTRACT:

Although advancements in cancer therapy have improved patient outcomes, most therapies remain delivered via the traditional systemic route. A common caveat of systemic administration is the occurrence of dose-limiting toxicity, often resulting in cessation of therapy or decline in quality of life. Nanotechnology efforts to improve tolerability of systemic agents have suffered limited market viability due to problems such as rapid clearance, circulation instability, and low tumor site accumulation. While local delivery allows for overcoming the aforementioned hurdles, pre-set formulations and non-specific release pose alternate issues. To approach these challenges, we aimed to investigate our previously developed solid nanoparticles for delivery of protein-based therapy capable of addressing a tumor-specific profile and with selective release within the tumor environment due to elevated thrombin levels.

LAYPERSON ABSTRACT:

Although advancements in cancer therapy have improved patient outcomes, most therapies remain delivered via the traditional systemic route. A common caveat of systemic administration is the occurrence of dose-limiting toxicity, often resulting in cessation of therapy or decline in quality of life. Nanotechnology efforts to improve tolerability of systemic agents have suffered limited market viability due to problems such as rapid clearance, circulation instability, and low tumor site accumulation. While local delivery allows for overcoming the aforementioned hurdles, pre-set formulations and non-specific release pose alternate issues. To approach these challenges, we aimed to investigate our previously developed solid nanoparticles for delivery of protein-based therapy capable of addressing a tumor-specific profile and with selective release within the tumor environment due to elevated thrombin levels.

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Association Between Cadmium Air Exposure and Prostate Cancer at Diagnosis

PRESENTING AUTHOR: Vish Vijayakumar

POSTER LOCATION: 46

CO-AUTHORS: Jyotsna S. Jagai, Michael R. Abern and Andre Kajdacsy-Balla

ABSTRACT:

Studies have suggested that high levels of occupational exposure to cadmium (Cd) result in the occurrence of prostate cancer (PC) [1]. At levels of exposure which are more relevant to the general population, there is inconclusive evidence of an association between Cd and PC incidence [2]. In this study, we utilize a different approach to studying Cd and assess the relationship between ambient exposure to air Cd and the aggressiveness of PC at diagnosis. We collected outcome data from the Surveillance, Epidemiology, and End Results (SEER) for reported PC cases diagnosed from 2010 to 2014. PC stage at diagnosis was categorized as either metastatic or localized and either by high or low Gleason grade. Average county-level Cd exposure concentrations were calculated in the EPA's 2011 National Air Toxics Assessment. We calculated quintiles of Cd exposure concentration for ease of interpretation. Odds Ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression models. Analyses were adjusted for age at diagnosis, sociodemographic status, and overall air quality and were stratified by race. The study cohort consisted of 234,991 PC cases from 594 counties reported by SEER. Overall, higher levels of air Cd exposure were associated with an increased likelihood of a PC case of being metastatic and having high Gleason grade at diagnosis. The strongest associations were observed in medium-sized counties: those in areas with populations of 250,000 to 1 million people. These adjusted odd ratios for the 80th vs 20th percentile of Cd exposure were: (OR 1.25, CI 1.13 – 1.38) and (OR 1.39, CI 1.27 – 1.51) for metastatic vs localized cases and high vs low Gleason grade cases respectively. Further studies should be conducted to assess sources of Cd emissions like factories, smelters, and incinerators in these counties and confirm whether Cd causes PC to become more aggressive.
**Allosteric Regulation of Engineered Shp2 Tyrosine Phosphatase**

PRESENTING AUTHOR: Jordan Fauser

POSTER LOCATION: 47

CO-AUTHORS: Vincent Huyot, Jennifer Klomp, and Andrei Karginov

ABSTRACT:

Shp2 is a ubiquitously expressed protein tyrosine phosphatase. Increased Shp2 activity is associated with tumorigenesis, metastasis, and poor prognosis in many cancers. However, the exact role of Shp2 in signaling pathways is not well defined. Many studies evaluate the effect of long-term activation or depletion of Shp2, though these studies often come to conflicting conclusions. Investigating the immediate effect of Shp2 activation may aid in resolving the precise role. To accomplish this task, we have engineered allosterically regulated Shp2 proteins through the insertion of a Light Regulated (LightR) or Rapamycin Regulated (RapR) domain into the catalytic domain of Shp2. These tools provide temporal control of Shp2 activity allowing the elucidation of its role in various pathways. We have shown that the LightR and RapR-Shp2 activate known Shp2 pathways in a regulated manner. To further understand the mechanism of allosteric regulation, we performed molecular dynamic simulations to determine changes in the conformational dynamics of LightR-Shp2 induced by light. This analysis revealed that LightR destabilizes the catalytic domain in the dark. To optimize regulation of engineered Shp2, we evaluated different linkers connecting LightR domain to the catalytic domain of Shp2. Our in silico analysis correlated with biochemical results, identifying an optimal linker that enables efficient regulation of LightR-Shp2. These data demonstrate that allosterically regulated tools can be used to probe relevant pathways to elucidate the various roles of Shp2 as well as providing insight into the design of other regulated enzymes.
Modulation of VEGF pathway with optogenetic regulation of kinases

PRESENTING AUTHOR: Martin Brennan

POSTER LOCATION: 48

CO-AUTHORS: Mark Shaaya, Shahzeb Khan, and Andrei Karginov

ABSTRACT:

The initiation of angiogenesis and tip cell selection is a rapid and reversible process which can only be reproduced with limited control in vitro. Stimulation of angiogenesis with soluble factors such as VEGF results global response with slow temporal resolution. Optogenetic stimulation, with high spatial and temporal resolution, may allow VEGF signaling to be stimulated transiently in single cells. We aim to use our previously developed strategy for allosteric light regulation (LightR) of kinases, to probe the kinase nodes of the VEGF pathway. The LightR method uses the fungal photoreceptor Vivid (VVD), inserted in the catalytic domain of a constitutively active form of the kinase. In the dark, un-dimerized VVD disrupts kinase activity. Illumination with blue light, rescues catalytic function upon VVD dimerization. We have successfully applied the LightR method to control non-receptor Src family kinases and oncogenic B-Raf (V600E) which phosphorylate downstream targets when activated with light in cells. Activation of LightR Src in primary endothelial cells induces podosome formation and degradation of gelatin. Work is underway to apply the LightR method to the primary VEGF responder, VegfR2.

LAYPERSON ABSTRACT:

Angiogenesis is the growth of new blood vessels in response to need by the tissues. Some cancer treatment strategies try to prevent angiogenesis from supporting tumor growth. Angiogenesis at the cellular level, is initiated first by production of VEGF (vascular endothelial growth factor) by starving cells, signaling the need for more blood vessels. Endothelial cells detect VEGF when it contacts VegfR2 (VEGF Receptor 2) which activates signaling within the cell to begin proliferating and invading that begins the process of forming new blood vessels. Much of the signaling in the VEGF pathway is through protein kinases, that phosphorylate other proteins in the cell, altering the proteins function. For example, phosphorylation of a protein by a kinase may result in activating or deactivating it, or otherwise allowing it to perform its specific function. In this work we add a protein photoreceptor to kinases in the VEGF pathway which allows their activity to be controlled by light. The photoreceptor named VVD works by existing as a monomer in the dark, but upon exposure to blue light the monomers bind together to form dimers. By inserting a pair of these monomers in the proper site of a kinase we can disrupt structure of the protein making it unable to phosphorylate its targets. When exposed to blue light, the monomers dimerise which stabilize the native structure of the protein, restoring its activity. By using these light regulatable proteins in cells we can introduce a signal in one node of the signaling pathway and study how it propagates and influences the behaviour of the cell.

PRESENTING AUTHOR: Nnaemezie Ezeife

POSTER LOCATION: 49

ABSTRACT:

African American (AA) men have, by far, the highest incidence of prostate cancer (PCa): they are roughly 1.6 times more likely to develop PCa than whites and 2.6 times more likely than Asian Americans (Bradley, 2012). African American men have prostate-specific antigen (PSA) based screening for prostate cancer based off guidelines provided by the United States Preventive Services Task Force (USPSTF). The task force works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services and preventive medications (About the USPSTF. U.S. Preventive Services Task Force. February 2018). This research aims to prove that current USPSTF guidelines for PCa screening may not be inclusive or generalizable to address PCa disparities in AA men and hence the reason why AA men tend to have very high mortality and incidence rates. Through literature review, this research will analyze the factors such as access to knowledge, access to medical care and socioeconomic status which are responsible for the USPSTF guidelines not addressing PCa disparities in AA men. Additionally, this research will suggest policy recommendations that should potentially reduce PCa mortality rates in AA men.
Development of Selective Covalent Estrogen Receptor Degraders (SCERDs) as Novel Therapeutics for the Treatment of Resistant Breast Cancers

PRESENTING AUTHOR: Carlo I. Rosales
CO-AUTHORS: Rui Xiong, Gregory R. J. Thatcher

ABSTRACT:
Breast cancer is the second leading cause of cancer related deaths in American women. Activation of estrogen receptor alpha (ERα) is the primary proliferative mechanism of breast cancer cells, making it a logical target for therapy. ER ligands with antiestrogenic activity, such as the selective estrogen receptor modulator, tamoxifen, and selective estrogen receptor degrader, fulvestrant, have proven clinically successful as treatments for breast cancer; however, resistance in up to 50% of patients provides a therapeutic challenge. Once resistant, breast cancer cells become endocrine-independent. Thus, there is an unmet, urgent need for novel therapy.

Irreversible inhibition is an attractive approach because inhibition is reliant on the rate of protein turnover rather than competition at the binding site. However, there exists an aversion to covalent inhibitors in drug design due to perceived safety concerns regarding irreversible modification of off-target proteins. These off-target modifications can be attenuated by reducing the reactivity of the covalent warhead. Using a relatively poor electrophile decreases the intrinsic promiscuity, thereby reducing off-target effects. Only within the binding pocket and with sufficient propinquity to the electrophilic residue is covalent attachment achievable.

C530 of ER is a non-catalytic cysteine not found in the other hormone receptors (HRs). By targeting this non-conserved residue, high specificity towards ER over other HRs should be attainable. Our lab has also synthesized a series of benzothiophene-containing, high affinity ER ligands. By attaching a covalent warhead to these compounds, the reactive group can be anchored and correctly positioned relative to C530. Using this combination of high affinity cores and finely tuned electrophilic moieties, selective covalent estrogen receptor degraders (SCERDs) can be designed and have the potential to overcome resistance in breast cancer.
The Potential for Circulating Extracellular Vesicle microRNAs to Predict Prostate Cancer Aggressiveness

PRESENTING AUTHOR: Morgan Zenner

CO-AUTHORS: Dr. Michael Abern, Dr. Klara Valyi-Nagy, Dr. Gayatry Mohapatra, Ruben Sauer, and Dr. Larisa Nonn

ABSTRACT:

INTRODUCTION AND OBJECTIVE: Prostate cancer remains one of the most common cancer diagnoses among men worldwide, and the risk stratification system between indolent and aggressive disease continues to evolve. Radical prostatectomy surgery (RP) is a common curative treatment option, but incontinence and erectile dysfunction are frequent side effects of the procedure. As 30-40% of low-grade patients are upgraded to higher grade at RP, many patients choose RP treatment even though they harbor indolent disease. We have previously established a serum microRNA signature that predicts prostate cancer aggressiveness in order to further stratify patients and potentially help guide treatment decisions. Our current goals are to 1) validate the serum microRNA signature in a larger cohort and 2) determine if this prognostic signature is further enriched in circulating serum exosomes. Our hypothesis is that circulating exosomes harbor an enriched microRNA prognostic signature due to selective secretion from the prostate.

METHODS: Serum and serum exosomes are currently being collected from a cohort of 200 prostate cancer patients pre-RP from the University of Illinois Hospital (UIH) and the Jesse Brown VA Medical Center in order to validate the serum microRNA signature. Both sample types have been collected from 150 patients thus far. In addition, human primary prostate tissue slices and cells from RP surgery are in vitro models being used to examine the exosomal microRNAs released directly from the prostate. Small RNAs from prostate tissue, cells, and exosomes have been sequenced by next generation sequencing and will be validated using the nanoString platform.

RESULTS: We have assessed the presence and stability of circulating exosomal microRNAs in male serum in order to determine the potential for this test to be successfully brought to the clinic. We found that microRNAs from the prognostic signature are present in serum exosomes and that they are stable at 4°C, -20°C, and -80°C for up to one week. We have also detected microRNAs in exosomes from primary prostate cells and human prostate tissue slices.

CONCLUSIONS: We have discovered that serum exosomes harbor some prognostic microRNAs and may serve as a noninvasive biomarker for prostate cancer. In addition, primary prostate tissue and cells release exosomes which may enter circulation or have effects on the tumor microenvironment. We are currently working to validate the serum prognostic microRNA signature and examine the potential role of these exosomal microRNAs in prostate cancer progression.
Melanoma is a rapidly progressing skin cancer and the sixth most common cancer among women. Skin self-examination (SSE) was associated with reduced incidence of advanced melanoma. Because women start receiving mammograms at 40 years old, when melanoma often initially presents, there is an opportunity to raise SSE awareness in an at-risk population. A convenience sample of women having mammograms at the Lynn Sage Breast Center of Northwestern Medicine/Prentice Women’s Hospital were block randomized to a two-arm intervention to complete baseline and follow-up surveys to assess SSE performance. Both groups received an instructional brochure, and group one also received a 1-week reminder to perform SSE. Performance of SSE between groups was compared using chi-squared analysis. At 1-month, 384 (91.4% retention) women completed the survey, 356 (92.7%) read the brochure and 311 (80.9%) performed SSE. Of those who performed SSE, 54 (14%) found a concerning mole. At 3-months, 346 (82.4% retention) women completed the survey and 280 (80.9%) women performed SSE. The number of women who performed SSE did not differ between groups at 1 month or 3 months. This study demonstrated the effectiveness of delivering SSE education to women already engaging in health promotion by receiving mammograms. These findings suggest that combining SSE education with mammography screening can serve as a low burden and low-cost method to promote the early detection of melanoma.
Capturing Small Molecule Exchange Driving Primary Metastasis of Ovarian Cancer

PRESENTING AUTHOR: Katherine E. Zink

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ABSTRACT:

High grade serous ovarian cancer (HGSOC) is the fifth leading cause of cancer death among women, and its fatality is closely linked to the difficulty in detecting symptoms of early stages. We have developed a novel method to visualize small molecule chemical gradients via imaging mass spectrometry of the primary metastasis of HGSOC. This method requires very little biological material and detects not only molecules relevant to HGSOC but can also localize their tissue or cell of origin. Excitingly, we believe this innovative visualization of exchanged molecules can be modified to other coculture systems to answer a range of biological queries. We have identified that the release of norepinephrine from the ovary is induced in the presence of tumorigenic fallopian tube epithelial (FTE) cells and not healthy FTE or other cell types. Norepinephrine was validated by tandem mass spectrometry and retention time matching with an authentic standard and has previously been implicated in ovarian cancer development. Currently, efforts are focusing on elucidating the signals from the FTE that are inducing the production of NE from the ovary. We have begun to identify the FTE signal responsible for NE release, called factor X, by doing bioactivity guided fractionation of conditioned FTE media to examine whether the ovary response is mediated by small molecules, lipids, or proteins. Interestingly, it appears that the release of NE from the ovary is likely protein-mediated and further proteomics studies will be conducted to identify the nature of protein factor X.

LAYPERSON ABSTRACT:

High grade serous ovarian cancer (HGSOC) begins with tumorigenesis in the fallopian tube and later migrates to the ovary, where tumors grow larger and spread aggressively. We are aiming to understand the chemical communication between these organ structures in terms of the small molecules that are exchanged to promote this migration step. Because incubation in the ovary is a dangerous phase in HGSOC, if we can understand how to prevent the exchange of metastasis-inducing molecules, we can achieve a small step toward prevention of this step in the disease.
Utilizing Protein Signatures from Heterogeneous Cell Populations in a Murine Model for Diagnosis of Ovarian Cancer

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ABSTRACT:

Ovarian cancer is a severe gynecological disease and is currently the fifth leading cause of cancer-related deaths among women. This disease is typically diagnosed in its later stages, once tumor metastasis has occurred, due to the fact that there are no routine screens that are clinically available. Due to a stagnation of development in ovarian cancer diagnostics, the medical field is in significant need of tools to better detect ovarian cancer. Recent evidence suggests that DNA sourced from ovarian cancer tumor cells has been found in Pap smear samples, which are sourced from the cervix. This would imply that these cells migrate from their tumors of origin in the fallopian tube and/or ovaries and that it is feasible to detect these cells using a sensitive analytical technique, such as mass spectrometry (MS). We hypothesize that cells sourced from the local microenvironment of female reproductive tracts can be used to diagnose ovarian cancer in its early stages through the development of MS methods. Female athymic nude mice were obtained (N=5) and given intraperitoneal injections of OVCAR-8-RFP to initiate tumor growth. Samples containing heterogeneous cell populations were obtained weekly from mice via vaginal lavage and spectral fingerprints were collected using MALDI-TOF MS. Samples obtained throughout the study were found to have specific peaks increase over time that appeared to dominate the protein fingerprint in terms of intensity. We believe this technique has promise in its ability to differentiate between healthy and disease states based on cell populations taken from a local environment. With further validation of our model system and advancement in our statistical analyses, we believe this method has the potential to be translatable to a human model and that we are moving closer to a clinically viable diagnostic tool for ovarian cancer.

LAYPERSON ABSTRACT:

Ovarian cancer is currently the fifth leading cause of cancer-related deaths among women with an estimated 22,530 newly diagnosed cases and 13,980 deaths expected in 2019. There are no routine screening methods for this disease so ovarian cancer typically isn’t diagnosed until it has spread throughout the body. In an attempt to diagnose ovarian cancer in stages I and II, where tumors are contained to the reproductive organs and there are more treatment options, we plan to repurpose the Pap smear, a common screening tool for cervical cancer. Recent studies have shown that DNA from ovarian cancer tumor cells have been found in Pap smears, which would imply that these cells move from the ovaries to the cervix and that we could detect them using a sensitive technique such as mass spectrometry (MS).

We hypothesize that samples taken from the female reproductive tract can be used to diagnose early-stage ovarian cancer using MS. Female mice were injected with OVCAR-8-RFP cells, a human ovarian cancer cell line, to allow for tumor formation. Vaginal lavages, similar to a Pap smear, were obtained on a weekly bases and mass spectra focusing on protein detection was collected using mass spectrometry. We found proteins that increased and decreased in abundance throughout tumor progression. We believe that this method has promise in the ability to differentiate between healthy and cancerous states based on samples taken directly from the reproductive system. With further studies into our model and statistical analysis, we feel this method can be translated to humans and that we are moving closer to a clinically viable tool for the diagnosis of ovarian cancer.
Development of Novel Cell-permeable Gα12-αSNAP Binding Domain Peptide and Small Molecules for Inhibiting Microvascular Thrombosis associated with Cancer and Cancer Treatment

PRESENTING AUTHOR: Misuk Bae

CO-AUTHORS: Misuk Bae, Hyun Lee, Laura J. Bloem, Kiira Ratia, Xiaoping Du, and Richard D. Minshall

ABSTRACT:

RATIONALE: Microvascular thrombosis and disseminated intravascular coagulation occurrence is increased by cancer as well as cancer treatment. Signals originating from the tumor microenvironment as well as radiation or chemotherapeutic regimens (e.g., thalidomide analogs and some tyrosine kinase inhibitors) promote vascular inflammation, activation of the coagulation cascade, and increased thrombotic risk. Interestingly, elevated plasma level of von Willebrand factor (vWF), the glue to which platelets adhere to form a clot, is associated with reduced survival and poor outcome in cancer patients. Previously, we demonstrated that sterically stabilized simple micelles (SSM) containing cell-permeable myristoylated αSNAP binding domain (Myr-SBD) peptide based on the unique N-terminal Gα12 sequence that binds to αSNAP, inhibits vWF secretion. Here, we report direct binding characteristics of Myr-SBD to purified αSNAP as a first step toward identification of novel small molecule anti-thrombotic therapeutics that target Gα12/αSNAP interaction and prevent clotting in cancer patients.

METHODS: Codon-optimized human αSNAP was cloned into a bacterial expression vector pGEX-4T-1 with thrombin-cleavable GST-tag. GST-αSNAP protein was purified by glutathione affinity chromatography followed by size exclusion chromatography. Protein purification was confirmed by Coomassie blue staining and western blot. Protein folding was assessed by fluorescence thermal shift assay of melting point. Myr-SBD was synthesized in the RRC Protein Research Core. Binding of Myr-SBD to purified αSNAP was evaluated by surface plasmon resonance (SPR) analysis using Biacore T200 using CM5 sensor chips. Naked SBD peptide was also examined to assess the effect of myristoylation on peptide binding to αSNAP. The structural complex of αSNAP/SBD was predicted using blind- and data-driven docking predictions using AutoDock4.2.6 and HADDOCK2.2, respectively.

RESULTS: The melting curves of GST-αSNAP (> 90% purity confirmed by SDS-PAGE) indicated a melting point Tm = 57 ± 0.5 °C, suggesting the E. coli expressed protein exhibited significant tertiary structure. Binding of Myr-SBD to SBD was immobilized GST-αSNAP showed equilibrium dissociation constants (KD) of 9.6 ± 0.2 μM and 12.9 ± 0.5 μM, respectively. Myr-SBD had a significantly higher calculated Rmax (maximum binding capacity for analyte) compared to SBD (91% vs 14%), indicating higher binding affinity to αSNAP. The docking approach used to make inference about αSNAP/SBD structure identified a potential interaction between Arg1 of SBD and Glu139 of αSNAP by H-bond. The blind docking and data-driven docking of the αSNAP/SBD cluster with the lowest binding free energy was Binding E = -1.55 Kcal/mol and Ki = 73.21 mM vs HADDOCK score = -65.8 ± 3.6 and RMSD = 0.8 ± 0.5, respectively, implying that peptide ligand binding to protein αSNAP occurs without energy consumption.

CONCLUSION AND FUTURE DIRECTION: Our studies demonstrate that Myr-SBD peptide directly binds to αSNAP with approximately 10 μM affinity suggesting feasibility for development of in vitro screening assay for identifying small molecular inhibitors of microvascular thrombosis associated with cancer or cancer treatment. In future studies, Myr-SBD and small molecule lead compounds targeting Gα12/αSNAP binding will be developed as novel antithrombotic therapeutics for inhibiting vWF secretion in cancer.

ACKNOWLEDGEMENT: This work was supported by the Chicago Biomedical Consortium with support from the Searle Funds at The Chicago Community Trust (RDM, MB), NIH MPI R01 HL125356 (RDM, XD), and American Heart Association 19POST34420012 (MB).

LAYPERSON ABSTRACT:

Cancer patients are at increased risk of developing blood clots that can lead to heart attack, stroke, or organ failure. The inflammation associated with the cancer per se as well as cancer treatment (i.e., radiation therapy and some chemotherapeutic regimens) increase von Willebrand factor (vWF) secretion from endothelial cells (vWF is the glue that platelets adhere to form a clot). Recently, we discovered the signaling pathway in endothelial cells that is required for vWF secretion and are now developing therapeutic interventions to prevent blood clots in patients with cancer. We are currently characterizing the binding between two key proteins involved in vWF secretion, Gα12 and αSNAP. Based on these data, we are developing high throughput screening assays for identifying and characterizing peptides and small molecules that can block the binding of endogenous Gα12 to αSNAP and thereby inhibit excess vWF secretion and prevent blood clots in cancer patients.

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ACKNOWLEDGEMENT: This work was supported by the Chicago Biomedical Consortium with support from the Searle Funds at The Chicago Community Trust (RDM, MB), NIH MPI R01 HL125356 (RDM, XD), and American Heart Association 19POST34420012 (MB).
Modulation of estrogen biosynthesis in estrogen receptor positive breast cancer cells by Humulus lupulus and its bioactive compounds

PRESENTING AUTHOR: Amanda Christine Maldonado

CO-AUTHORS: Atieh Hajirahimkhan, Shao-Nong Chen, Guido F. Pauli, Birgit M. Dietz, Judy L. Bolton*

ABSTRACT:

Obese menopausal women have a substantially higher risk of developing estrogen receptor positive (ER+) breast cancer. Higher estrogen levels in the fat tissue surrounding their mammary epithelium and systemic inflammation due to obesity may work synergistically in concert to develop enhance breast cancer risk. Many obese menopausal women have turned to botanical supplements, such as Humulus lupulus (hops), to seek relief from menopausal symptoms. Little is known about the biological effects that these botanicals may have in modulating key network pathways responsible for the proliferation of breast cancer tissue production of estradiol/estrone. Aromatase (CYP19A1) and aldo-keto reductase (AKR1C3) are two enzymes responsible for the key steps in the biosynthesis of 17-\(\beta\)-estradiol (E\(_2\)) in the breast tissue. As women are more exposed to estrogens, the risk for breast carcinogenesis increases. E\(_2\) can induce proliferation of mammary cells and mammary carcinogenesis through multiple pathways. Regulation of CYP19A1 and AKR1C3 may decrease E\(_2\) biosynthesis and thus the risk for breast carcinogenesis. This study expands on the in vitro effects of hops and its bioactive compounds xanthohumol (XH), 8-prenylnaringenin (8-PN), 6-prenylnaringenin (6-PN) in modulating these enzymes cell line?.in MCF-7:WS8 cells and MCF-7 cells overexpressing AKR1C3 (MCF-7:1C3). qRT-PCR was used to quantify changes in CYP19A1 and AKR1C3 transcription mRNA expression. Hops and its bioactive compounds 6-PN and XH significantly upregulated CYP19A1 and AKR1C3 while 8-PN has been previously shown to act as a potent inhibitor of CYP19A1 activity in a cell-free assay. In-cell Western analysis was used to confirm relative protein expression of AKR1C3 and CYP19A1. The mechanism of action for the increase in CYP19A1 and AKR1C3 expression by botanicals hops will be analyzed through luciferase activity. This study highlights the importance of elucidating the relative risk/benefit ratio effects that botanical supplements may have on women’s health. WHY is this important, One big picture sentence, did you only analyze hops than I would say hops instead of botanicals in the sentence before. Supported by NIH grant P50 AT00155 provided by ODS and NCCIH; and American Cancer Society grant PF-18-049-01-NEC.

LAYPERSON ABSTRACT:

Obese menopausal women have a substantially higher risk of developing breast cancer. Higher estrogen levels in the fat tissue surrounding their mammary tissue and systemic inflammation due to obesity may work in concert to enhance breast cancer risk. Many obese menopausal women have turned to botanical supplements, such as Humulus lupulus (hops), to seek relief from menopausal symptoms. Little is known about how these botanical supplements may affect the pathway responsible for the production of estrogens. Two enzymes, aromatase (CYP19A1) and aldo-keto reductase (AKR1C3), are responsible for the key steps in the biosynthesis of 17-\(\beta\)-estradiol (E\(_2\)) in the breast tissue. Downregulation of CYP19A1 and AKR1C3 may decrease E\(_2\) biosynthesis and thus the risk for breast carcinogenesis. This study expands on the in vitro effects of hops and its bioactive compounds xanthohumol (XH), 8-prenylnaringenin (8-PN), 6-prenylnaringenin (6-PN) in affecting these enzymes in two cell lines, MCF-7:WS8 cells and MCF-7 cells overexpressing AKR1C3 (MCF-7:1C3). qRT-PCR was used to evaluate changes in CYP19A1 and AKR1C3 mRNA expression. Hops and its bioactive compounds 6-PN and XH significantly upregulated CYP19A1 and AKR1C3 while 8-PN has been previously shown to act as a potent inhibitor of CYP19A1 activity in a cell-free assay. In-cell Western analysis was used to confirm relative protein expression of AKR1C3 and CYP19A1. The mechanism of action for the increase in CYP19A1 and AKR1C3 expression by hops will be analyzed. This study highlights the importance of clarifying the relative risk/benefit ratio of botanical supplements for women’s health. Supported by NIH grant P50 AT00155 provided by ODS and NCCIH; and American Cancer Society grant PF-18-049-01-NEC.
Vemurafenib (ZELBORAF®) targets PTK6 to inhibit prostate cancer growth

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ABSTRACT:

The intracellular protein tyrosine kinase 6 (PTK6) plays a role in promoting growth of several tumor types, such as breast and prostate cancers. Loss of PTEN, which is a common event in prostate cancers, leads to activation of PTK6 at the plasma membrane where it is involved in oncogenic signaling. Active PTK6 at the plasma membrane phosphorylates oncogenic targets and leads to enhanced migration, survival, and growth. No kinase inhibitors that target PTK6 are used in the clinic. Vemurafenib (PLX4032) is an FDA-approved small molecule inhibitor designed to inhibit BRAF V600E. It displays activity against a range of kinases but is most potent in inhibiting BRAF and PTK6 with IC50 of 130 nM. We hypothesized that Vemurafenib could be used to inhibit growth and migration of cancer cells that have active PTK6. Using saturation transfer difference NMR and molecular docking, we demonstrated that Vemurafenib is binding the active site of PTK6, preventing its activation. When PTK6 is activated at the membrane, it activates phosphorylates and activates FAK, EGFR, and ERK1/2. We demonstrate that this signaling could be blocked by Vemurafenib in a BRAF-independent manner. Vemurafenib also inhibits PTK6-mediated cell growth, migration, and invasion. Since, PTK6 plays an important role in several different solid tumors, we tested if Vemurafenib can inhibit PTK6 in cell lines derived from breast, prostate, and pancreatic cancer, and we found that PTK6 is inhibited by Vemurafenib in multiple cell lines. Vemurafenib is a potent inhibitor of both endogenous and ectopically expressed PTK6. In flank xenograft model, Vemurafenib reduces tumor burden. Tumors from animals treated with Vemurafenib show reduced proliferation, which is assessed by Ki67 staining, and increase in apoptosis shown by staining for cleaved caspase 3. These data suggest that Vemurafenib can be further refined to develop new drugs that could target active PTK6 and be used in combination therapies.