**AUTOFLUORESCENCE LIFETIME FOR INTRAOPERATIVE REAL-TIME AUGMENTED REALITY OF BRAIN TUMORS AND NECROTIC LESIONS: THREE CASE STUDIES**

Alba Alfonso-Garcia, PhD¹, Julien Bec¹, Shamira Sridharan¹, Brad Hartl¹, Jakob Unger¹, Matthew Bobinski², Mirna Lechpammer³, Fady Girgis⁴, James Boggan⁴, Laura Marcu¹,⁴

¹Department of Biomedical Engineering, University of California, Davis, California
²Department of Radiology, University of California, Davis, California
³Department of Pathology and Laboratory Medicine, University of California, Davis, California
⁴Department of Neurological Surgery, University of California, Davis, California

Brain tumors and their margins are currently identified by surgeons based on visual and tactile subjective assessment with the guidance of pre-operative clinical images and histopathology of resected tissue. There is currently a lack of techniques for intraoperative and real-time detection of brain tumors and other lesions such as radiation-induced necrosis. To address that unmet need, we have integrated a fluorescence lifetime imaging (FLIm) instrument with a neurosurgical microscope that provides real-time augmented reality of brain tissues with fluorescence lifetime parameters that encode diagnostic information. With this approach, surgeons may navigate the surgical field of view to detect abnormal tissue areas. Here, we describe the functionality and safety features of the instrument and present three case studies where this approach was tested in patients undergoing craniotomy for the resection of brain tumors or radiation damage. The device uses a 355 nm pulsed laser beam to excite tissue autofluorescence that is time resolved in four spectral bands (390/40 nm, 470/28 nm, 542/50 nm, and 629/53 nm). While being compliant with the maximum permissible exposure of laser light, the FLIm device acquires and displays fluorescence results in 33 ms for an augmented reality experience when the results are integrated with the microscope video-feed. Fluorescence lifetime has the ability to distinguish between non-affected cortex, white matter, tumor and radiation-induced necrosis. In particular, necrotic brain tissue from two patients with effects of radiation therapy exhibited fluorescence that had 3 to 4 ns longer lifetimes and about 30% increase in optical redox ratio with respect to non-affected cortex. In addition, an oligodendroglioma resected from a third patient reported 1 to 2 ns shorter fluorescence lifetime and a mild decrease in optical redox ratio with respect to the surrounding white matter. These results encourage the use of FLIm as a label-free and non-invasive intraoperative tool for neurosurgical guidance presented through a real-time augmentation of the surgical field of view.

**COMPUTATIONAL MODELING AND MATERIAL DESIGN OF AN INTRACRANIAL TUMOR TREATMENT FIELD SYSTEM IN A RODENT**

Amir Goodarzi, MD, Noah Goshi, Erkin Şeker, Gene Gurkoff, Kiarash Shahlaie

**Introduction:** Glioblastoma multiforme (GBM) is a highly malignant brain tumor with a median survival of 15 months. Tumor treating fields (TTFields) are a novel treatment modality for GBM consisting of low intensity (1-2V/cm), alternating electrical fields that disrupt mitosis in cancer cells. The current extracranial system has several limitations including: large energy requirements (60V), field heterogeneity near the tumor, discontinuous therapy, and psychosocial burdens due to the device appearance and shaving of hair. We propose a new modality for generating TTFields using a miniaturized implanted intracranial system inside the brain to address the limitations of the extracranial device. Towards this goal, we present a computational modeling and material design study of intracranial electrodes coated with different insulators to analyze the electric field intensities achieved and the expected energy requirements.
Methods: COMSOL Multiphysics software was used to develop a spherical tumor inside the grey matter of a rat brain flanked by 0.2mm diameter tungsten electrodes insulated by an insulator. The electrodes are designed using a 10mm long wire that is folded in half, allowing for a completely insulated electrode tip and to increase surface area. Permittivity constants for glioma tumor, grey matter, tungsten electrodes, polyimide(dielectric=3), and BaTio3(dielectric=10000) were applied to each object. The electrostatic model was solved for the field intensity generated between a 3 by 3 electrode array configuration with the following parameters: alternating current, 50V potential difference, frequency 200 kHz.

Results: The polyimide insulated electrodes achieved 1V/cm field intensity within 0.05mm of the electrode array and did not achieve therapeutic fields within the tumor or the peritumoral tissue. The BaTio3 insulated electrodes achieved 5-7V/cm in 100% of the tumor and the peritumoral tissue.

Conclusion: Our computational model predicts that high dielectric insulating materials such as BaTio3 are superior to conventional insulating materials in achieving therapeutic TTFields using intracranial electrodes. These results suggest that an implanted rodent TTFields system is feasible, effective, and energy efficient.

REAL-TIME TISSUE CLASSIFICATION VIA FLUORESCENCE LIFETIME IMAGING (FLIm) AND DEEP LEARNING

Mark Marseden, PhD, Department of Biomedical Engineering, University of California, Davis

Inter-patient variability is one of the key limiting factors in the development of robust classification models for medical diagnosis. This work looks to address this issue within the context of fluorescence lifetime imaging (FLIm) data captured in a clinical setting, specifically in the delineation of tumor margins during surgery. Data acquired from studies in breast as well as head and neck cancer will be used to develop the proposed method. Deep machine learning techniques such as convolutional neural networks and transfer learning will be investigated as a means to accurately classify fluorescence decay data captured for healthy and cancerous tissue. A leave-one-out cross-validation (LOOCV) is performed across patients to comprehensively evaluate classifier performance and avoid model overfitting. Preliminary results were calculated for 8,989 FLIm measurements captured in vivo for n=9 head and neck cancer patients. A one-model-fits-all neural network classifier was trained on 6 FLIm signal parameters (average lifetime and intensity ratio for 3 spectral channels) resulting in an overall accuracy of 71%, an ROC-AUC of 0.77 and an average precision of 0.59. This project will seek to improve upon this performance through the development of an unsupervised transfer learning method to fine tune the trained classifier to the measurements acquired for each individual patient. This patient-specific refinement step must be performed in an unsupervised fashion in order to then generalize to unseen patients in future deployment. Other machine learning concepts such as multi-task learning will then be integrated in an attempt to further improve model performance and provide additional functionality.

EFFECT OF RACE/ETHNICITY ON LONG TERM CYTOPENIAS AND MAJOR INFECTIONS IN ADOLESCENT YOUNG ADULT BREAST CANCER SURVIVORS

CM Sauder1,2, M Goldfarb M4, Alicia A. Gingrich, MD2, Q Li3, T Wun1,3, THM Keegan1,3

1Comprehensive Cancer Center, University of California, Davis
2Department of Surgery, University of California, Davis
3Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California, Davis
4Center for Endocrine Tumors and Disorders John Wayne Cancer Institute, Santa Monica, CA

Background: Many Adolescent and Young Adult (AYA) Breast Cancer (BC) patients receive chemotherapy as part of their initial treatment. Long-term bone marrow suppression is a potential complication, but no studies have evaluated the impact of race/ethnicity on the development in AYA BC survivors.

Methods: Female patients ages 15-39 diagnosed with BC during 1996-2012 and surviving ≥ 2 years were obtained from the California Cancer Registry and linked to statewide hospitalization data. We estimated the
cumulative incidence of developing anemia, leukopenia, or major infection/sepsis (≥ 2 years after diagnosis), accounting for death as a competing risk, and examined the impact of race/ethnicity using multivariable Cox proportional hazards regression.

**Results:** Of 14,729 patients, 48.8% were non-Hispanic white, 8.3% non-Hispanic black, 25.5% Hispanic, and 16.5% Asian/Pacific Islander. At diagnosis, 95.5% had local or regional disease (27.7% stage I, 49.4% stage II), and were mostly treated with surgery (96.2%) and chemotherapy (74.3%). The 10-year cumulative incidence of anemia (16.8% vs 11.7%), leukopenia (4.6% vs 2.1%), and major infection/sepsis (13.2% vs 7.9%) was greater following initial treatment with chemotherapy (p<0.0001 for all vs no chemotherapy). In multivariable analyses controlling for sociodemographic factors, baseline comorbidities, treatment and stage, Blacks had the highest risk (vs. non-Hispanic whites) of medical late effects, including anemia [HR: 1.62, CI 1.41-1.86], leukopenia (HR: 1.53, CI 1.17-2.00), and major infection/sepsis (HR: 1.36, CI 1.16-1.60). Similarly, Hispanic and Asian/Pacific Islanders had a higher risk of developing anemia (HR: 1.16, CI 1.04-1.29; HR: 1.17, CI 1.03-1.33) and trended toward developing more leukopenia (HR: 1.24, CI 1.00-1.54; HR: 1.25, CI 0.98-1.61).

**Conclusions:** AYAs of Black, Hispanic, and Asian/Pacific Islander race/ethnicity are at an increased risk of anemia and leukopenia after chemotherapy compared with non-Hispanic Whites. With improvements in prognostic testing resulting in potential decreased chemotherapy usage, there may be a decrease in long-term late effects for these young cancer survivors.

**DISPARITIES IN THE OCCURRENCE OF LATE EFFECTS FOLLOWING TREATMENT AMONG ADOLESCENT AND YOUNG ADULT MELANOMA SURVIVORS**

Alicia A. Gingrich, MD1,2, M Goldfarb3, CA Sauder1,2, Q Li1, T Wun1,2, THM Keegan1,2

1 Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California, Davis
2 Comprehensive Cancer Center, University of California, Davis
3 Center for Endocrine Tumors and Disorders John Wayne Cancer Institute, Santa Monica, CA

**Background:** Melanoma is the third most common cancer in the adolescent and young adult (AYA) population and the incidence worldwide is increasing. However, no studies have addressed the occurrence of late effect medical conditions following melanoma treatment in these young survivors.

**Methods:** All patients ages 15-39 diagnosed with cutaneous melanoma from the 1996-2012 and surviving ≥ 2 years were obtained from the California Cancer Registry and linked to statewide hospitalization data. The influence of age at diagnosis, sex, race/ethnicity, neighborhood socioeconomic status (SES), and health insurance on the development of late effects by system was evaluated using multivariable Cox proportional hazards regression models.

**Results:** Of 8,524 patients, 35.6% were male, 83.1% non-Hispanic white, 82.1% had private health insurance, 60.3% were considered high SES, and 70.7% had no documented co-morbidities at diagnosis. After controlling for competing factors, males had an increased risk of developing late effects across all systems, including cardiac [HR:2.13, 95%CI 1.87-2.42], neurologic (HR:2.24, CI 1.92-2.63), lymphedema (HR:2.22, CI 1.89-2.62), bleeding events (HR:2.35, CI 2.00-2.77), major infection/sepsis (HR:2.23, CI 1.95-2.56), and second cancers [HR:1.66, CI 1.47-1.89]. In addition, patients with public or no insurance (vs. private) had a greater risk of developing all studied late effects, including lymphedema (HR:2.48, CI 2.04-3.01), respiratory illness (HR:2.21, CI 1.85-2.64) renal dysfunction (HR:2.31, CI 1.90-2.81), and subsequent cancers (HR:1.82, CI 1.54-2.16). AYA patients residing in low SES neighborhoods had a similar increased risk of developing late effects. However, neither age nor race/ethnicity had an impact on the occurrence of late effects.

**Conclusion:** Of AYA melanoma survivors, males, those with public or no health insurance, and those living in low SES neighborhoods had a much greater likelihood of developing of late effects. Strategies to improve
surveillance and secondary prevention of these late effects is needed among AYA melanoma survivors, particularly for this demographic.

IDENTIFICATION AND CHARACTERIZATION OF AN INTRA-TUMORAL MICROBIOME IN SOFT TISSUE SARCOMAS BY ANATOMIC LOCATION AND TREATMENT STATUS: A PILOT STUDY

Ugur N. Basmaci¹, Louis B. Jones², Shuai Chen³, Cordelia Dunai⁴, Alicia A. Gingrich⁵, Sean J. Judge⁵, Jonathan A. Eisen⁶, Robert J. Canter⁷

¹UC Davis School of Medicine, Sacramento, CA
²Department of Orthopedic Surgery, UC Davis Health, Sacramento, CA
³Division of Biostatistics, Department of Public Health Sciences, UC Davis School of Medicine, Sacramento, CA
⁴Department of Dermatology, UC Davis School of Medicine, Sacramento, CA
⁵Department of Surgery, UC Davis Health, Sacramento, CA
⁶Department of Medical Microbiology and Immunology, UC Davis School of Medicine, Sacramento, CA
⁷Division of Surgical Oncology, Department of Surgery, UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: The gut microbiome has received a significant amount of attention in the area of immunoncology with the discovery that a microbiome that is sub-optimally diverse and unstable (termed dysbiosis) may play a key role in the development of various types of cancers. Previous studies have also demonstrated an association between specific taxa of gut commensal microbes and patient responses to different cancer treatment modalities, including immunotherapy. Furthermore, it has been shown that tissues such as the breast and pancreas harbor a microbiome as well, and that the intra-tumoral microbiome of these organs differ from that of their corresponding healthy states. However, the question of whether there exists an intra-tumoral microbiome in soft tissue sarcomas (STS), a putatively “sterile” tissue, has not been explored previously. Given recent successes in bridging microbiome research with cancer treatment outcomes, as well as in identifying distinct mechanisms of microbiome modulation of the immune response within the tumor microenvironment, there is now an exciting window of opportunity for progress in our understanding of STS and potential STS-microbiome interactions.

Methods: We employed 16S sequencing to identify microbiome-specific genetic signatures in four treated (post-radiotherapy) STS patient samples, specifically examining abundance and diversity of microbial species against a background of reagent-only negative controls. All sequencing was performed at the Microbiome Core on banked tissue specimens that were obtained from the UC Davis Comprehensive Cancer Center Biorepository.

Results: The most abundant genera across all four patient samples (in descending order) were Bacillus, Anaerobacillus, Escherichia-Shigella, Enterococcus, Parabacteroides, Blautia, and Ralstonia. All samples individually demonstrated appreciable diversity in the genera present. The genera Bacillus, Anaerobacillus, Escherichia-Shigella demonstrated consistently high relative abundances in three of the samples; in one sample, the genera Enterococcus, Parabacteroides, Blautia were noted to be the most abundant.

Conclusion: For the first time to our knowledge, our preliminary data support the existence of a diverse intra-tumoral microbiome in treated STS. We further plan to examine a larger and more diverse STS sample cohort to identify variations in the STS intra-tumoral microbiome based on anatomic site and treatment type/status.

INCREASING RATES OF COLORECTAL CANCER (CRC) AMONG YOUNG PEOPLE IN CALIFORNIA

Ani Movsisyan, MS¹, Cyllene R. Morris¹, Arti Parikh-Patel¹, Kenneth W. Kizer

¹CalCARES Program, Institute for Population Health Improvement, UC Davis Health
²School of Medicine and Betty Irene Moore School of Nursing, University of California, Davis and CalCARES Program, Institute for Population Health Improvement, UC Davis Health
Background: Colorectal cancer (CRC) incidence among persons older than 50 years old has decreased in California and nationally, but incidence rates have increased among persons younger than 50. Previous studies present incidence rates among younger persons using a wide age group of 20-49 years. Incidence rates for such a wide age group do not provide enough detail about risk among specific segments of the population, nor allow for tailored recommendations about CRC screening among young adults.

Purpose: To identify CRC rates by 10-year age intervals (20-29, 30-39, and 40-49) to better understand incidence trends among younger persons.

Methods/Approach: We used SEER*Stat and Joinpoint software for people diagnosed from 1989 to 2015 identified in the California Cancer Registry. Year of diagnosis was grouped by three years (1989-1991, 1992-1994, etc.) for statistical analysis. Joinpoint trends in incidence were examined by age and race, and the average annual percentage change (AAPC) in rates was quantified by age group. Age was divided into 10-year intervals (20-29, 30-39, 40-49), and race was categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, and American Indian groups.

Results: Significant AAPC increases in CRC incidence rates were observed among the 20-29, 30-39, and 40-49 age groups in both Non-Hispanic White (3.5%, 3.2%, 1.9%) and Hispanic (3.5%, 2.7%, 1.4%) populations, respectively. Significant increases were observed among the 40-49 year old Asian/Pacific Islanders (1.0%) and American Indians (4.6%). No significant increases were seen in the 20-29 and 30-39 groups among Non-Hispanic Blacks and Asian/Pacific Islanders, although the number of CRC cases in these groups was quite small.

Conclusion: CRC is significantly increasing among several young age groups. Since there is no formal CRC screening recommendation for persons less than 50 years old and since evidence suggests that younger adults present with more advanced disease, these results may be useful for educating healthcare providers about CRC risk and suggest that CRC screening recommendations should be developed for this population. Continued surveillance of CRC incidence rates among young adults is warranted.

TARGETING THE DNA-BINDING DOMAIN OF THE ANDROGEN RECEPTOR IN IN VITRO MODELS OF CASTRATION RESISTANT PROSTATE CANCER

Elisabeth A. Messner*, Ruiwu Liu**, Paramita M. Ghosh†

*Graduate Group in Integrative Pathobiology, University of California, Davis
**†Department of Biochemistry and Molecular Medicine, University of California, Davis
†Department of Urology, University of California, Davis
*†VA Northern California Health Care System, Mather, CA

Background: Current standard of care treatment for castration resistant prostate cancer (CRPC) includes androgen receptor (AR) inhibition, focusing on direct or indirect inhibition of the ligand binding domain. This treatment is ineffective upon cellular production of AR splice variants that lack the ligand binding domain. Thus, we hypothesize a series of compounds targeted to the DNA-binding domain (DBD) of the AR will cause cell death by directly binding the AR to inhibit AR functional activity.

Methods: A series of compounds potentially targeting the DBD were constructed by Dr. Ruiwu Liu, Biochemistry and Mol. Med, UC Davis. MTT assays were performed to determine the inhibitory roles of a compounds targeted to the DBD of the AR. Flow cytometry double stain analysis indicated cell death activated by compound treatment. Immunoblot analysis, qRT-PCR, and the luciferase assay elucidated the degree of total AR functional inhibition. Immunofluorescence indicated localization of the AR post-DBD-inhibition, and the Drug Affinity Responsive Target Stability (DARTS) elucidated the potential binding of the compounds to the AR.

Results: C05 and C08 decrease 22Rv1 and CWR-R1 (which contain the spliced AR) cell viability to a greater extent than in C4 and C4-2 (which both contain the full-length AR). C14 and C15 more evenly decrease
viability across cell lines, but these compounds have a reduced effect on AR-negative PC3 cells. PSA protein expression levels do not appear to be widely affected by most compounds across cell lines. C08 and C15 significantly reduce PSA mRNA and PSA-luciferase expression compared to DMSO controls in both C4-2 and 22Rv1 cell lines. In C4-2 cells, TMPRSS2 and Nrdp1 mRNA is significantly reduced compared to the DMSO control. No tested compound alters AR localization in C4-2 or 22Rv1 cells. Enzalutamide can be used as a positive control using DARTS to test compound binding to the AR. C08 and C15 may directly bind AR.

**Conclusion:** Compounds C08 and C15 reduce *in vitro* cell viability not by blocking AR localization to the nucleus, but rather by reducing AR transcriptional activity by possibly physically interacting with the full-length AR and its splice variant. We continue to confirm the effects and specificity of these compounds. The outcome of this work may indicate alternative inhibition strategies to clinically overcome castration resistant prostate cancer.

INTERNALIZED \(^{131}\text{I}-\text{METAIODOBENZYLGUANIDINE SHOWS DIFFERENTIAL TRANSCRIPT EXPRESSION OUT TO 15 DAYS AFTER TARGETED RADIATION TREATMENT IN PATIENTS WITH HIGH-RISK NEUROBLASTOMA}

Angela C. Evans\(^1,2\), Tim Setzkorn\(^9\), Haley Segelke\(^2\), David A. Edmondson\(^3\), Jackson Swift\(^1\), Andrew Vaughan\(^1\), Katherine K. Matthey\(^4\), M. Meaghan Granger\(^5\), Araz Marachelian\(^6\), Daphne A. Haas-Kogan\(^7,8\), Steven G. DuBois\(^7\), Matthew A. Coleman\(^1,2\)

\(^1\)Department of Radiation Oncology, University of California Davis, School of Medicine, Davis, CA.
\(^2\)Lawrence Livermore National Laboratory, Livermore, CA
\(^3\)School of Health Sciences, Purdue University, West Lafayette, IN
\(^4\)Department of Pediatrics, University of California San Francisco School of Medicine, San Francisco CA.
\(^5\)Cook Children’s Hospital, Fort Worth, TX.
\(^6\)Children’s Hospital Los Angeles, Los Angeles, CA
\(^7\)Department of Pediatrics, Dana Farber Cancer Institute, Boston, MA
\(^8\)Brigham and Women’s Hospital, Boston, MA
\(^9\)Technical University of Munich, School of Medicine, Germany

\(^{131}\text{I}-\text{metaiodobenzylguanidine (}\(^{131}\text{I-mIBG)}\text{ is a targeted radiation therapy for neuroblastoma. We have previously predicted internalized dose associated with early }^{131}\text{I-mIBG exposure 72 hours after treatment. We now expand these studies to identify gene expression differences associated with }^{131}\text{I-mIBG exposure 15 days after treatment. Total RNA was isolated from 16 patients before and after }^{131}\text{I-mIBG treatment in peripheral blood. We found that some transcripts predictive of early exposure returned to baseline levels by day 15, however, selected transcripts continued to fluctuate. At 72 hours, 13 of the 17 selected pathway-specific transcripts were differentially expressed. Up-regulated transcripts at early exposure compared to untreated controls include CDKN1A, FDXR, BAX, and DDB2. Transcripts CDKN1A (p<0.000001), FDXR (p<0.000001), and DDB2 (p<0.000001) showed the highest up-regulation at 72 hours post-\(^{131}\text{I-mIBG} exposure, with mean log\(_2\) fold changes of 2.93, 2.85, and 2.28, respectively. At 15 days post-\(^{131}\text{I-mIBG} treatment, 11 of the 17 selected transcripts were differentially expressed, with XPC, STAT5B, MDM2, and IGF1R displaying significant up-regulation at 72 hours and significant down-regulation at 15 days. Interestingly, transcripts BCL2 (p<0.0026), PRKDC (p<0.0015), POLH (p<0.0008), and SGK1 (p<0.0093) were not differentially expressed at 72 hours, but were significantly down-regulated at 15 days after \(^{131}\text{I-mIBG} exposure. These results suggest that transcript levels for DNA repair, apoptosis, and IR-induced cellular stress are still fluctuating by 15 days post-\(^{131}\text{I-mIBG} exposure. Our studies indicate that our biodosimetry gene expression panel is useful for identifying biomarkers for both early and late internalized \(^{131}\text{I} exposure in children, a vulnerable population that is usually absent from biodosimetry studies. Ongoing analyses will expand on these findings to identify biomarkers associated with dose estimates and susceptibility factors predictive of positive outcomes of treatment for children with high-risk neuroblastoma.\)
AUGMENTED REALITY VISUALIZATION FOR INTRAOPERATIVE GUIDANCE AND TUMOR
DELINEATION BASED ON FLUORESCENCE LIFETIME

Tianchen Sun, Department of Computer Science, University of California, Davis

Real-time visualization of imaging data constitutes a critical part of surgical workflow. Utilizing AR techniques with a conventional surgical navigation system can generate a mixed-reality surgical field of view to support the surgeon finding specific targets, avoiding areas of risk, and providing intraoperative orientation. We are currently developing an AR framework for clinical imaging and guidance using an optical see-through head-mounted display (OST-HMD) and fluorescence lifetime imaging (FLIm) instrumentation. This framework supports in vivo scanning of FLIm data and the real-time visualization of diagnostic information overlaid on the interrogated tissue area. We designed a calibration and registration procedure for a precise AR visualization overlay. We also aim to provide an intuitive and easily accessible user interface in the system. FLIm technology has demonstrated the capability to do in vivo tissue diagnosis. We also investigate into cancer diagnostic using FLIm and machine learning technology. Our team is developing a classifier with FLIm data and the registered histology findings to produce the probability distribution over classes of tissue types. The results can be visualized as simple color schemes representing the different classes tumor, adipose and fibrous tissue through augmented reality. With the high discriminative power of FLIm, our FLIm-AR concept has the potential for indicating tumor margins and assisting with tumor excision surgery.