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Development of an Oncolytic Adenovirus to Treat Metastatic Colorectal Cancer

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OBJECTIVES/GOALS: Colorectal cancer (CRC) is a leading cause of cancer mortality, and many patients will develop metastatic disease at some point during their treatment course. Conventional therapies such as surgery, chemotherapy, and radiation are often of limited effectiveness in these advanced stages, which necessitates the development of novel therapies. METHODS/STUDY POPULATION: Our group has designed an oncolytic adenovirus backbone structure expressing the sodium iodide symporter (NIS) which can be used in conjunction with radioiodine to facilitate cancer imaging and therapy. Using multiple CRC cell lines, oncolytic adenoviruses with different fibers were tested in vitro to determine which of these modifications yielded the highest binding to the cancer cells. Additionally, multiple promoter structures are being tested to determine the impact on the replication and oncolytic effect of the virus. Furthermore, the potential of adenovirus-mediated NIS expression to facilitate PET/CT imaging and therapy with I-131 will be explored. RESULTS/ANTICIPATED RESULTS: The Ad5/3 chimeric fiber modification demonstrated the best binding in CRC cell lines. Additionally, tissue specific promoters are employed in oncolytic viruses to confer selective replication in cancer cells, while minimizing off target effects in nearby normal tissues. We have employed a Cox2 promoter, which has demonstrated an excellent oncolytic effect. In vitro NIS expression was shown in multiple CRC cell lines through immunostaining. Small animal PET/CT imaging demonstrated signal uptake in mice with subcutaneous CRC tumors after virus and radioiodine (I-124) administration. We anticipate that future studies employing radioactive iodine (I-131) in combination with our oncolytic virus will yield an augmented antitumor effect. DISCUSSION/SIGNIFICANCE: The NIS-expressing adenovirus has the ability to support radionuclide-based imaging and therapy for CRC. With additional pre-clinical testing, our adenovirus construct has the potential to bring NIS-based therapeutics to the bedside to positively impact CRC patient care outcomes.

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Eribulin Synergizes with STING Agonists by Enhancing Type 1 Interferon Expression and Improves Antitumor Efficacy as Combination Treatment

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OBJECTIVES/GOALS: Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks effective targeted treatment options. TNBC's greater degree of immunogenicity than other breast tumors makes immunotherapy a viable strategy. Strategies to improve the immunotherapy response includes targeting the cGAS-STING innate immune pathway with STING agonists. METHODS/STUDY POPULATION: We have previously shown in vitro that eribulin, a microtubule destabilizer currently used in the treatment of TNBC, functions as an indirect STING agonist because it promotes the release of mitochondrial DNA into the cytoplasm. Separately, eribulin also significantly enhances type I interferon expression induced by STING agonists measured by qRT-PCR through a second TBK1-dependent mechanism downstream of STING activation through detecting higher amounts of phosphorylated IRF-3 by western blot protein analysis. Mechanisms of eribulin-mediated interferon expression occur in immune and TNBC cells and are shared with other microtubule destabilizers but not with the microtubule stabilizing agent paclitaxel. RESULTS/ANTICIPATED RESULTS: We determine that the enhancement of type I interferon expression by eribulin is pharmacologically synergistic with multiple STING agonists. The significant enhancement by eribulin led us to evaluate the antitumor efficacy of eribulin in combination the STING agonist ADU-S100 in a challenging spontaneous mammary tumor model MMTV-PyVT. We show that the combination treatment significantly decreased tumor growth which allowed for longer survival compared to other groups. This is particularly interesting because of our previous studies showing that eribulin alone, but not paclitaxel, promotes the activation of CD4+ T-cells in the spleen and draining lymph nodes of BALB/c mice with 4T1 tumors through flow cytometric analysis. DISCUSSION/SIGNIFICANCE: These data contribute to accumulating evidence that there are important mechanistic differences between the microtubule targeted chemotherapeutics currently used in the treatment of TNBC and suggest that eribulin can act as an immune adjuvant in addition to its anti-mitotic effect.

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Etiology of Hepatocellular Carcinoma in the 27-County Rochester Epidemiology Project Catchment Area, 2010-2021

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OBJECTIVES/GOALS: The goal of this study is to examine the incidence, etiology, and outcomes of hepatocellular carcinoma (HCC) in a 27-county region in SE Minnesota and W Wisconsin between 2010 and 2021. A comparison of the first to second half of the period will be made to look for possible trends. METHODS/STUDY POPULATION: The Rochester Epidemiology Project (REP) is a database of patient records across SE Minnesota and W Wisconsin. Starting in 2010, the REP opened to a 27-county catchment area, which includes over 1.3 million patients with a population coverage of approximately 64%. This study will use the expanded REP data to collect data on patients 20 years of age and older with a new diagnosis of HCC between Jan 1, 2010 and Dec 31, 2021â€"an estimated 1000 cases. Patients with a record of less than one year of residence in the catchment area will be excluded. Data on etiology, comorbidities, and outcomes of HCC will be extracted from medical records and analyzed for risk factors and changes over time. RESULTS/ANTICIPATED RESULTS: We anticipate that the overall incidence of HCC in the REP geographic area has increased over the period of 2010 to 2021. We anticipate that the prevalence of hepatitis C virus infection in patients with HCC has between 2010 and 2021, due to the widespread use and accessibility of hepatitis C-specific antiviral treatment over the past decade. We anticipate that the prevalence of NAFLD in patients with HCC has increased between 2010 and 2021. We do not anticipate significant changes in treatment modality or survival outcomes over this period. DISCUSSION/SIGNIFICANCE: This study will provide a comprehensive update on the state, etiology, and outcomes of HCC in the area surrounding

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Rochester, MN. We will be able to track changes in risk factors over time and work to enhance screening protocols to target the most vulnerable populations.

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Evaluating defective Transcription Coupled-Nucleotide Excision Repair as a mechanism for sensorineural hearing loss in a zebrafish model of Cockayne Syndrome

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OBJECTIVES/GOALS: The characterization of the zebrafish as an animal model for Cockayne Syndrome may guide us towards role of Transcription-Coupled Nucleotide Excision Repair (TC-NER) defects in sensorineural hearing loss. METHODS/STUDY POPULATION: To examine our model, we have developed a zebrafish line with a 9+1 base-pair deletion in the ercc6 gene using TALENs. Mutation has since been confirmed by PCR and subsequent restriction digest with StuI. A series of assays evaluating hair cell morphology, structure and function, as well as ribbon synapse structure, will be used to analyze potential differences between the ercc6 mutant zebrafish line a their wild-type siblings. Additionally, electron microscopy will be used to assess differences in hair cell ultrastructure between the ercc6 mutant zebrafish line a their wild-type siblings. Finally, UVC exposure assays will be used to determine the role TC-NER plays in our novel zebrafish model, and evaluate its potential implications in sensorineural hearing loss. RESULTS/ANTICIPATED RESULTS: We anticipate that biallelic loss of function mutations in the zebrafish ercc6 gene will result in abnormalities in hair cell structure, mechanotransduction, or cell number. Additionally, we anticipate that hair cell ultrastructure and ribbon synapse structure will be impacted by loss of ercc6 expression. DISCUSSION/SIGNIFICANCE: Hearing loss mechanisms associated with defects in TC-NER are yet to be described. We believe our model will provide the tools for a faster and efficient way to carry out Cockayne Syndrome studies while laying the groundwork for the association between TC-NER and hearing loss.

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Ionizing radiation acoustic imaging (iRAI) for volumetric mapping the dose deep in the liver during radiation therapy

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OBJECTIVES/GOALS: The goal of this study was to develop a clinically applicable technique to increase the precision of in vivo dose monitoring during radiation therapy by mapping the dose deposition and resolving the temporal dose accumulation while the treatment is being delivered in real time. METHODS/STUDY POPULATION: Ironizing radiation acoustic imaging (iRAI) is a novel imaging concept with the potential to map the delivered radiation dose on anatomic structure in real time during external beam radiation therapy without interrupting the clinical workflow. The iRAI system consisted of a custom-designed two-dimensional (2D) matrix transducer array with integrated preamplifier array, driven by a clinic-ready ultrasound imaging platform. The feasibility of iRAI volumetric imaging in mapping dose delivery and real-time monitoring of temporal dose accumulation in a clinical treatment plan were investigated with a phantom, a rabbit model, and a cancer patient. RESULTS/ANTICIPATED RESULTS: The total dose deposition and temporal dose accumulation in 3D space of a clinical C-shape treatment plan in a targeted region were first imaged and optimized in a phantom. Then, semi-quantitative iRAI measurements were achieved in an in vivo rabbit model. Finally, for the first time, real-time visualization of radiation dose delivered deep in a patient with liver metastases was performed with a clinical linear accelerator. These studies demonstrate the potential of iRAI to monitor and quantify the radiation dose deposition during treatment. DISCUSSION/SIGNIFICANCE: Described here is the pioneering role of an iRAI system in mapping the 3D radiation dose deposition of a complex clinical radiotherapy treatment plan. iRAI offers a cost-effective and practical solution for real-time visualization of 3D radiation dose delivery, potentially leading to personalized radiotherapy with optimal efficacy and safety.

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Novel approach for tracking interdisciplinary research productivity using institutional databases

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OBJECTIVES/GOALS: This study proposes a pragmatic approach for tracking institutional changes in research teamwork and productivity in real time using common institutional electronic databases such as eCV and grant management systems. Dissemination of this approach could provide a standard metric for comparing teamwork productivity across different programs. METHODS/STUDY POPULATION: This study tracks research teamwork and productivity using commonly available institutional electronic databases such as eCV and grant management systems. We tested several definitions of interdisciplinary collaborations based on number of collaborations and their fields of discipline. Publication characteristics were compared by faculty seniority and appointment type using non-parametric Wilcoxon Rank Sum Test (p RESULTS/ANTICIPATED RESULTS: Interdisciplinary grants constitute 24% of all grants but the trend has significantly increased over the last five years. Tenure track faculty collaborated with more organizations (3.5, SD 2.5 vs 2.3, SD 1.1, p DISCUSSION/SIGNIFICANCE: This study provides empirical evidence of the benefits of interdisciplinary collaboration in research and identifies an important role that senior faculty may be playing in creating the culture of interdisciplinary teamwork. More research is needed to improve efficiency of interdisciplinary collaborations.

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