Oncology Models Forum

2021 Annual Meeting

Agenda

DAY 1

DATE: Tuesday, March 30, 2021
TIME: 11:00 am – 4:30 pm EST
WebEx Link
PW: Tuesday1!

TIME	TITLE	SPEAKER
11:00 am	Welcome and Introduction	Joanna Watson, PhD NCI
Session 1: Application and Credentialing of Novel Technologies		
11:10 am – 11:30 am	*Preclinical models of metastatic gastric cancer reveal new principles of immune surveillance* **PI: Scott Lowe, PhD** **Sloan Kettering Institute**	Josef Leibold, PhD University of Tubingen
11:30 am – 11:50 am	*Rapid Interrogation of Cancer Variants using Base Editing Screens* **PI: Lukas Dow, PhD** **Weill Cornell Medicine**	Bianca Diaz Weill Cornell Medicine
11:50 am – 12:10 pm	*Partnering with patients to discover dependencies of rare tumors* **PI: Jesse S. Boehm, PhD** **Broad Institute**	Jesse S. Boehm, PhD Broad Institute
12:10 pm – 12:30 pm	*Multimodal Functional Imaging of Heterogeneity in Patient-Derived Models of Head and Neck Cancer* **PI: Mukund Seshadri, PhD** **Roswell Park Comprehensive Cancer Center**	Mukund Seshadri, PhD Roswell Park Comprehensive Cancer Center

Session 1: Flash Talks		
12:30 pm – 12:35 pm	*Occult polyclonality of preclinical pancreatic cancer models drives in vitro evolution* **PI: Anirban Maitra, MBBS** **MD Anderson Center**	Maria Monberg MD Anderson Center
12:35 pm – 12:40 pm	*Imaging studies in a preclinical model of pancreatic cystic neoplasia* **PI: Anirban Maitra, MBBS** **MD Anderson Center**	Sonja Woermann, PhD MD Anderson Center
12:40 pm – 12:45 pm	*Credentialing Patient-derived Organoid Models of Head and Neck Cancer* **PI: Mukund Seshadri, DDS, PhD** **Roswell Park Comprehensive Cancer Center**	Vincent Vui King Chong, PhD Roswell Park Comprehensive Cancer Center
12:45 pm – 12:50 pm	*Living tissue imaging-based dependency biosensors for gastroesophageal tumors* **PI: Jesse Boehm, PhD** **Broad Institute**	Mushriq Al-Jazrawe Broad Institute
12:50 pm – 12:55 pm	*A Novel Pre-Clinical Model to Further Understand Role of Immunity in Cervical Cancer* **PI: T.-C. Wu, MD, PhD** **Johns Hopkins University**	Talia Henkle, PhD Johns Hopkins University
12:55 pm – 1:15 pm	**BREAK** *(20 minutes)*	
Session 2: Models for Credentialing Cancer Biology and the Microenvironment		
1:15 pm – 1:35 pm	*Modeling K-Ras allelic variation in mice* **PI: Kevin Haigis, PhD** **Dana Farber Cancer Institute**	Kevin Haigis, PhD Dana Farber Cancer Institute
1:35 pm – 1:55 pm	*Highly penetrant and immunogenic mouse models of non-viral HCC that are suitable for evaluation of immune checkpoint inhibitors* **PI: Michael Karin, PhD** **University of California, San Diego**	Michael Karin, PhD University of California, San Diego

1:55 pm – 2:15 pm	*Interrogating cellular heterogeneity in liver regeneration and cancer* **PI: Hao Zhu, MD** **Children's Medical Center Research Institute at UT Southwestern**	Hao Zhu, MD Children's Medical Center Research Institute at UT Southwestern
2:15 pm – 2:35 pm	*Expansion of tumoroid models for precise treatment of the rectal cancer patient* **PI: Josh Smith, MD** **Memorial Sloan Kettering Cancer Center**	Brian Szeglin Memorial Sloan Kettering Cancer Center
Session 2: Flash Talks		
2:35 pm – 2:40 pm	*Modeling necrosis and the tumor microenvironment in glioblastoma to improve therapeutic targeting* **PI: Dan Brat, MD** **Northwestern University**	Steve Markwell, PhD Northwestern University
2:40 pm – 2:45 pm	*Improving hepatocellular carcinoma mouse modeling by understanding the malignant potential and biology of liver cell subpopulations* **PI: Hao Zhu, MD** **Children's Medical Center Research Institute at UT Southwestern**	Andrew Chung Children's Medical Center Research Institute at UT Southwestern
2:45 pm – 2:50 pm	*Modeling acute inflammation in Patient Derived Xenografts (PDX) of Chronic Myelomonocytic Leukemia (CMML)* **PI: Eric Padron, MD** **Moffitt Cancer Center**	Hannah Newman Moffitt Cancer Center
2:50 pm – 3:10 pm	**BREAK** *(20 minutes)*	
Session 3: Models for Predicting and Evaluating Therapies		
3:10 pm – 3:30 pm	*Development of combination regimens for myeloid malignancies in humanized mice* **Leighton Grimes, PhD, Cincinnati Children's Hospital** **Stephanie Helene, MD, Yale University**	Stephanie Helene, MD Yale University

3:30 pm – 3:50 pm	*Modeling necrosis and the tumor microenvironment in glioblastoma to improve therapeutic targeting* **PI: Daniel Brat, PhD** **Northwestern University**	Daniel Brat, PhD Northwestern University
3:50 pm – 4:10 pm	*Credentialling a genetically engineered clinically relevant mouse model of multiple myeloma* **PI: Marta Chesi, PhD** **Mayo Clinic**	Marta Chesi, PhD Mayo Clinic
4:10 pm – 4:30 pm	*Rescue of cognitive function following fractionated brain irradiation in a novel preclinical glioma model* **PI: Susanna Rosi, PhD and Nalin Gupta, MD** **University of California San Francisco**	Nalin Gupta, MD, PhD University of California San Francisco
4:30 pm	**Wrap-up**	

Preclinical models of metastatic gastric cancer reveal new principles of immune surveillance

Josef Leibold[1,2,6], Corina Amor[1,3,6], Kaloyan M. Tsanov[1,6], Yu-Jui Ho[1], Francisco J. Sánchez-Rivera[1], Judith Feucht[2], Timour Baslan[1], Hsuan-An Chen[1], Leah Zamechek[1], Sha Tian[1], John E. Wilkinson[4] and Scott W. Lowe[1,5]

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Gastric cancer is the third leading cause of cancer-associated death worldwide with more than 750000 patients dying from this disease each year. Gastric cancer thereby readily metastasizes to the liver, peritoneal cavity and lungs, which is the main cause of patient morbidity and mortality. While the genomic landscape of the disease is now well described, this has not yet translated into improved treatments. The standard-of-care remains cytotoxic chemotherapy and patients frequently suffer recurrence and/or tumor progression. A major impediment to the progress towards better therapies has been the relative lack of preclinical models that faithfully recapitulate the biology of late stage gastric cancer. We have developed a novel and flexible non-germline genetically engineered mouse model of gastric cancer via direct organ electroporation of genetic elements into adult tissue, known as electroporation-based genetically engineered mouse models (EPO-GEMMs). With this approach, we modelled all non-virus associated genetic subtypes of gastric cancer and the resulting tumors display many characteristics of the human disease including their metastatic, histopathological and transcriptional features as well as chromosomal (in)stability and therapeutic response. Using this newly developed platform we identified a critical role of natural killer (NK) cells in controlling metastatic spread of different gastric cancer subtypes. Moreover, we uncovered that T cells mediate immune surveillance of metastases in microsatellite instable (MSI) gastric cancer - a finding that could be corroborated by genetic analysis of metastases in gastric cancer patients. In summary, we present a flexible model of late stage gastric cancer that allows simple genetic manipulation and is ideally suited to study tumor-host interactions.

Rapid Interrogation of Cancer Variants using Base Editing Screens

Francisco J. Sánchez-Rivera[3*], Bianca J. Díaz[1,2*], Alyna Katti[1,2], Edward R. Kastenhuber[1,3,4], Vincent Tem[3], Stella V. Paffenholz[3,4], Josef Leibold[3], Margaret Kennedy[3,4], Scott W. Lowe[3,5] and Lukas E. Dow[1,2].

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Abstract

The advent of large-scale sequencing initiatives in cancer patients have identified thousands of variants of unknown significance (VUS). One strategy to precisely delineate driver from passenger mutations is through the recreation of specific mutations using cytosine (C>T alterations) or adenine (A>G alterations) base editing. However, testing of individual gRNAs to target thousands of cancer variants is costly and laborious. To overcome these challenges, we developed a CRISPR cytosine base editing 'sensor' platform that tethers an sgRNA to its associated genomic target. We generated and screened human and mouse libraries that systematically interrogate over half of all cancer VUS from the MSK-IMPACT dataset. We demonstrate that our approach is able to accurately identify efficient gRNAs that otherwise would have been missed from computational efforts alone. We have validated findings from the sensor screen in vitro and in vivo in a panel of understudied *TP53* tumor suppressor gene mutations. Further we developed a "Gene On" (GO) reporter system that indicates precise cytosine or adenine base editing in situ with high sensitivity and specificity. We then demonstrate the application of GO in detecting in vivo BE activity using a newly generated mouse model with inducible and reversible base editor expression that will enable generation of novel cancer models *in vivo*. Together, we expect that this work will be instrumental in the development of high fidelity pre-clinical models and understanding the contribution of specific and recurrent cancer-associated mutations.

Partnering with patients to discover dependencies of rare tumors

PI: Jesse S. Boehm, PhD
Broad Institute

Precision cancer medicine is based on the ability to predict the dependencies of a given tumor from its molecular makeup. Despite successes in multiple common cancers, such prediction remains challenging for the majority of rare and understudied tumors given the absence of laboratory model systems in which to discover and/or validate therapeutic hypotheses. Here, we describe our efforts to address this challenge systematically through an online consent platform to directly engage patients in research and the creation of over 450 genomically-confirmed patient-derived cell lines, organoids and neurosphere cultures, with >10% of these representing rare cancers. In parallel, I will describe early efforts funded by our OMF R01 to directly perturb rare cancer patient tissue ex vivo utilizing single-cell based imaging biosensor readouts for drug response, focused initially on solid tumor ascites material. Looking ahead, as the barriers to culturing and directly perturbing rare tumor clinical material are overcome, we expect that preclinical functional genomics data will be useful for difficult-to-treat tumors without existing molecularly guided standard-of-care regimens.

Multimodal Functional Imaging of Heterogeneity in Patient-Derived Models of Head and Neck Cancer

Mukund Seshadri
Department of Oral Oncology
Roswell Park Comprehensive Cancer Center

Head and neck squamous cell carcinomas (HNSCC) represent a diverse group of epithelial neoplasms that exhibit considerable heterogeneity in biological behavior and therapeutic response. It would therefore be important to develop preclinical models that can adequately capture this heterogeneity. In this regard, imaging methods allow for non-invasive mapping of the functional heterogeneity within the tumor microenvironment (TME). Unfortunately, despite their translational applicability, functional imaging methods are not routinely applied in preclinical studies. To address this gap in knowledge, we have been utilizing a multi-modal imaging approach to map the TME in patient-derived xenograft (PDX) models of HNSCC. Using a combination of non-invasive magnetic resonance imaging (MRI), ultrasound (US) and photoacoustic imaging (PAI), we demonstrate the degree of stromal, vascular and hypoxic heterogeneity in HNSCC. While MRI offers excellent soft tissue contrast and enables anatomic and functional imaging, US with co-registered PAI enables imaging of the vascular and hypoxic profiles of tumors in a time-efficient and cost-effective manner. Our results illustrate the translational utility of multimodal imaging in profiling the inter- and intra-tumoral heterogeneity in HNSCC. Our observations also demonstrate the potential role of imaging read-outs as early biomarkers of tumor response to chemotherapy and radiation. Ongoing studies are focused on the application of machine learning methods for the analysis of multimodal imaging datasets in preclinical models of HNSCC.

This work was supported by grants from the National Cancer Institute 1R01CA24345601A1, National Institutes of Health - Office of Director, S10OD010393 and utilized shared resources at Roswell Park supported by the Cancer Center Support Grant from NCI P30CA016056 (Johnson, CS).

Title: Occult polyclonality of preclinical pancreatic cancer models drives in vitro evolution.

Authors: Maria E. Monberg [1,2,3*#], Heather Geiger [4*], Jaewon J. Lee [1,3,5*], Roshan Sharma [4], Alexander Semaan [1,3], Vincent Bernard [1,3], Daniel B. Swartzlander [1,3], Bret M. Stephens [1,3], Ken Chen [6], Matthew Katz [5], Nicolas Robine [4+], Paola A. Guerrero [1,3], Anirban Maitra [1,3+]

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Abstract: Heterogeneity is a hallmark of cancer. The advent of single-cell technologies has helped uncover heterogeneity in a high-throughput manner in different cancers across varied contexts. Here we apply single-cell sequencing technologies to reveal inherent heterogeneity in assumptively monoclonal pancreatic cancer (PDAC) cell lines and patient-derived organoids (PDOs). Our findings reveal a high degree of both genomic and transcriptomic polyclonality in monolayer PDAC cell lines, custodial variation induced by growing apparently identical cell lines in different laboratories, and profound transcriptomic shifts in transitioning from 2D to 3D spheroid growth models. We also map single-cell RNA expression data to unique genomic clones identified by concurrent scCNV datasets obtained from PDAC cell lines. Furthermore, we investigate a PDO model to highlight their transcriptional evolution that may alter drug sensitivity, in addition to mechanistic shifts that occur in organoid seeding that differentiate from the tumor's original state.

Imaging studies in a preclinical model of pancreatic cystic neoplasia

Kenjiro Date[1], Takashi Okumura[1], Prasanta Dutta[2], Sonja M Woermann[1], Lotfi Abou-Elkacem[1], Pratip K Bhattacharya[2], and Anirban Maitra[1]

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Abstract:

Introduction: Early diagnosis of PDAC is recognized as one of the highest priority areas by the NCI, focusing on identifying more sensitive and specific biomarkers and imaging strategies in discernible precursor lesions. Pancreatic cysts are identified in greater than 2% of the general patient population, with nearly 500,000 new cysts diagnosed each year due to the increasing use of abdominal imaging. Many of these cystic lesions are essentially benign and can be followed by serial imaging if the diagnosis is specific. In contrast, intraductal papillary mucinous neoplasms (IPMNs) are bona fide precursor lesions of PDAC. Although IPMNs are readily detectable on abdominal imaging, the challenge remains in our inability to accurately predict which cysts are indolent and are highly likely to progress to invasive cancer. Therefore, there is a critical need for an alternative imaging platform to predict malignant IPMNs accurately. The Warburg-effect is a metabolic feature of cancers that causes them to metabolize pyruvate via a glycolytic pathway preferentially to lactate. Our group generated mice with IPMNs that also express a constitutively active form of GNAS in the pancreas and studied tumor development and early detection of aberrant metabolism in IPMN using Hyperpolarized MRI.

Results: In PDAC cell lines, induction of GnasR201C on a mutant KrasG12D background (LGKC) revealed a significant enrichment of glycolysis and hypoxia pathways using gene set-enrichment-analysis (GSEA) for hallmark pathways. The co-expression of GnasR201C on a mutant KrasG12D background leads to increased glucose uptake and lactate production. Next, we performed a live cell-extracellular flux assay, which confirmed that activation of GnasR201C significantly increased the proton efflux rate.
Furthermore, we performed an ex vivo assessment of NMR spectroscopy-based metabolic activity of LGKC cell lines and observed that GnasR201C induced cells on a mutant KrasG12D background showed significantly higher glycolytic activity compared to controls. To confirm if the autochthonous Kras;Gnas tumors increase glycolysis in vivo upon GnasR201C activation, we performed a metabolic imaging using HP-13C MRS in IPMN mice. The pyruvate-to-lactate conversion in vivo was significantly higher in GnasR201C tumors. Furthermore, HP-MRI showed a complete loss of conversion from pyruvate to lactate after one week of GnasR201C deactivation. In summary, these findings support that activation of GnasR201C leads to increased glycolysis.

Conclusion: Our preliminary data confirm the feasibility of using HP-MRI for measuring HP pyruvate-to-lactate conversion in a mouse model of GNASR201C-induced pancreatic cystic neoplasms, with clear distinctions in metabolic flux observed between low-grade and high-grade IPMNs.

Credentialing Patient-derived Organoid Models of Head and Neck Cancer

Vui King Vincent-Chong

Post-doctoral Fellow
Seshadri Lab
Department of Oral Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA.

Head and neck squamous cell carcinomas (HNSCC) are locally and regionally aggressive neoplasms that result in debilitating changes in speech, appearance, and respiratory function in patients. Clinical response rates have remained relatively unchanged over the years highlighting the critical need to investigate novel treatment strategies for this patient population. In this regard, patient derived organoid (PDO) models provide an important platform for evaluating the therapeutic activity of novel agents. However, the literature on the credentialing and utilization of PDO models to assess response to standard of care agents and novel agents against HNSCC is limited. To address this gap in knowledge, we developed and credentialed the histologic, molecular and therapeutic response profiles of a panel of human papillomavirus (HPV) positive and HPV-negative PDO models of HNSCC. The sensitivity of our organoid panel to standard of care chemotherapy (Cisplatin, Cetuximab), radiation and targeted agents (EGFR-TKIs) was also studied. All PDOs retained the histology, p16/HPV status and mutational landscape of donor patient tissues. PDOs exhibited differential sensitivity to chemotherapy and radiation and exhibited good concordance with patient outcomes. Molecular profiling of PDOs revealed potential signatures of sensitivity and resistance. Ongoing studies are focused on the application of PDOs as a high-throughput screening platform to identify FDA-approved drugs (‘drug repurposing) that exhibit therapeutic efficacy against HNSCC.

A Novel Pre-Clinical Model to Further Understand Role of Immunity in Cervical Cancer

Talia Henkle[1], Brandon Lam[1], Yu Jui Kung[1], John Lin[1], Ssu-Hsueh Tseng[1], Louise Ferrall[1], Deyin Xing[1, 2,3], Chien-Fu Hung[1,2,3], T.-C. Wu[1,2,3,4]

Department of Pathology[1], Department of Oncology[2] , Department of Obstetrics and Gynecology[3] , Department of Molecular Microbiology & Immunology[4] The Johns Hopkins Medical Institutions, Baltimore, MD 21287 USA.

We developed a novel HPV16 E6/E7-expressing carcinoma mouse model for the preclinical study of cervical cancer. Unlike current preclinical models for HPV+ cancers which lack important clinical and pathological features, our novel model features 1) expression of HPV oncogenes E6 and E7 in the female reproductive tract of mice and 2) spontaneous progression through high grade squamous intraepithelial lesion (HSIL) to carcinoma. This improved preclinical model was accomplished by injecting plasmids expressing HPV16 E6/E7-Luciferase, AKT, c-myc, and Sleeping Beauty transposase into the cervicovaginal tract of C57BL/6 mice followed by *in vivo* electroporation. However, due to the immunogenicity of the plasmids and electroporation procedure, HPV+ plasmid electroporation needs to be accompanied by immune suppression to generate tumors in immunocompetent mice. We first described that transient CD3+T cell depletion could achieve tumorigenesis upon plasmid transfection by electroporation. Alternatively, we discovered that tumorigenesis was also possible upon induction of peripheral tolerance via co-administration of CTLA4-IG and anti-CD40L immunomodulators, a technique first described to permit allograft acceptance in transplant immunology. Due to their improved clinical relevance, these HPV+ tumor models may serve as important preclinical models for the development of therapeutic HPV vaccines or novel therapeutic interventions against HPV E6/E7 expressing tumors. The potential usage of these preclinical tumor models will be discussed.

Modeling K-Ras allelic variation in mice

Kevin Haigis

Department of Cancer Biology, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School

More than 140,000 Americans are diagnosed with colorectal cancer (CRC) each year and almost 52,000 individuals die from it. Activating mutations in the K-Ras oncoprotein are common in CRC and are generally associated with particularly poor response to both conventional and targeted therapies. The spectrum of *KRAS* mutations in CRC is distinct from other epithelial cancers and patient outcomes vary according to *KRAS* genotype. The mechanisms underlying the distinct outcomes are not clear. To understand why cancers differ in their K-RAS genotype, we generated an allelic series of Cre dependent K-RAS activating mutations in mice. We found that each mutant allele produced qualitatively and quantitatively distinct phenotypes. We also used multiplexed mass spectrometry to characterize the effect of different K-RAS mutants on the proteome and phospho-proteome, finding that each allele has unique signaling properties that are tissuespecific. These observations indicate that each mutant form of K-RAS has a distinct function, which is consistent with our bioinformatic analysis demonstrating that the genes co-mutating with *KRAS* are different for every allele. This work demonstrates how genetically engineered mice can be used to dissect the function of related oncogenes and, further, that the specific oncogenic allele must be considered when choosing a therapeutic approach.

Highly penetrant and immunogenic mouse models of non-viral HCC that are suitable for evaluation of immune checkpoint inhibitors

Michael Karin, UCSD School of Medicine

The U.S. incidence of hepatocellular carcinoma (HCC) had tripled in the past 40 years. While some of the initial increase has been due to HCV-induced HCC, at the present time the incidence of virally induced HCC is declining, but HCC due to non-alcoholic steatohepatitis (NASH) is on the rise. We have used the MUP-uPA mouse to model both NASH and NASH-related HCC. MUP-uPA mice overexpress the secretory protein urokinase plasminogen activator (uPA) from a liver specific promoter and therefore suffer from ER stress induced liver damage, early in life. When placed on high fat (HFD) or high fructose (HFrD) diets, at the time when their initial liver damage subsides, these mice develop classical NASH signs within 3-4 months and progress to HCC within 8 months. Progression to HCC is particularly robust with 80-90% of mice showing visible HCC nodules on the liver's surface at 10 months of age. In addition to inflammation dependent tumor promotion driven by TNF, HCC development in these mice depends on the disruption of autophagy, accumulation of the autophagy substrate and chaperon p62 and p62-mediated NRF2 activation. Importantly, tumor development in MUP-uPA mice also depends on disruption of immune surveillance. NASH in MUP-uPA mice and humans is associated with the onset of liver fibrosis and a large increase in production of TGFβ and other cytokines (IL-21), which lead to the generation of IgA producing plasma cells through class switch recombination. These IgA_+ plasma cells have strong immunosuppressive activity toward HCC-directed cytotoxic $CD8_+$ T cells (CTLs), due to high-level expression of IL-10 and PD-L1. Accordingly, PD-L1 neutralization or IgA_+ B cell depletion result in attenuation of HCC development. Thus, HCC-bearing MUP-uPA mice provide an excellent model for testing the efficacy of immune checkpoint inhibitors that disrupt the PD-1 checkpoint and lead to re-invigoration of exhausted $CD8_+$ T cells.

Expanding a rectal cancer organoid platform to study individual responses to chemoradiation

Bryan Szeglin[1,3], Chao Wu[2,3], Yajing Gao[2,3], Jin Kim[4], Julio Garcia-Aguilar[3], Paul Romesser[4], and J. Joshua Smith[2,3] on behalf of the Colorectal DMT at Memorial Sloan Kettering Cancer Center.

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Rectal cancer (RC) is rising in incidence, remains a challenging disease to treat, and requires neoadjuvant chemotherapy and radiation followed by surgery to provide a chance for cure. Patients have varying response to this treatment paradigm. Prior to our work, no accurate model of RC existed to study chemo- and radio-sensitivity. We established a biorepository of 65 patient-derived RC organoid cultures (tumoroids) from patients with primary, metastatic, or recurrent disease, and have now expanded this resource to 129 tumoroids. RC tumoroids retain the histologic and genomic features of the tumors from which they were derived. *Ex-vivo* chemosensitivity assays demonstrate heterogenous sensitivity to 5-fluorouracil-based therapy which correlates with progression-free survival observed in the corresponding patients from which each tumoroid was derived. *Ex vivo* radiosensitivity assays also reflect the corresponding clinical response outcomes measured in patients. Analysis of tumoroids derived from individual patients longitudinally throughout treatment shows clinically relevant sensitivities to chemotherapy and the development of resistance with ongoing treatment. This resource is being utilized to investigate the biologic underpinnings of resistance to various treatments, identify radiosensitizers to improve tumor-specific killing, and improve treatment monitoring strategies for patients throughout their disease course.

Modeling acute inflammation in Patient Derived Xenografts (PDX) of Chronic Myelomonocytic Leukemia (CMML)

Hannah Newman, Tim Kodalle, Maria Balasis, Eric Padron

Chronic myelomonocytic leukemia is a clinically heterogeneous myeloid neoplasm hallmarked by peripheral monocytosis, ineffective hematopoiesis, and a propensity for AML transformation. While ultimately lethal in the majority of cases, patients often experience a clinically asymptomatic period before the disease progresses and symptoms occur. We have previously demonstrated that inflammatory cytokines are linked to adverse clinical outcomes and disease progression in CMNs. Further, the current pandemic has highlighted the well described elaboration of inflammatory cytokines seen in severe infections that overlaps exactly with those known to drive disease progression in CMML. We therefore hypothesize that severe infection, and the resulting increased inflammatory state, may be a facilitator of clonal selection and fatal disease progression. We have previously shown that CMML patient-derived xenografts (PDX) recapitulate the genetic and pathologic features of the disease. More recently, we have demonstrated that these models are also able to recapitulate clinical response. Due to the fidelity of our models and there oligoclonal composition, we believe our PDXs represent a unique opportunity to study the role of inflammatory insults in clonal selection and disease progression.

Two to five million bone marrow mononuclear cells (BMNCs) from CMML patients or normal controls were transplanted into 18 NSGS mice as described in (Yoshima, *Blood* 2017). Seven to fourteen days post-transplant, mice were randomized into two treatment groups to receive 10µg LPS via IP or saline vehicle. Mice were then divided equally into 3 groups that were euthanized at 6 and 24 hours post injection and at endpoint. At necropsy, peripheral blood, bone marrow, and splenocytes were collected for further analysis by FACs. Plasma was isolated to measure inflammatory cytokine levels and confirm mice had experienced a “cytokine storm” after LPS treatment. To demonstrate our model is an accurate depiction of inflammation, especially that caused by endotoxemia, we will be comparing the transcriptomic changes after LPS treatment in peripheral blood leukocyte to the response observed in previously generated data sets from human inflammation and immunocompetent mice as described in (Seok, *PNAS* 2013). To study clonal selection and myeloid skewing, we will also be performing single cell DNA sequencing and immunophenotyping on hCD45+ sorted bone marrow cells.

Our preliminary data have demonstrated that human CMML cells within PDX models were able to elaborate a cytokine release syndrome after LPS-treatment. Increased levels of human IL-1β, IL-6, IL-8, TNF-α, IL-10, and IL-12p70 were observed 6 hours post injection in LPS mice compared to vehicle ($p<0.0001$). We hypothesize that this model will more accurately reflect the inflammatory insults sustained throughout the life of a CMML patient and aim to demonstrate that our PDX model recapitulates both genomic and biologic response from inflammatory insults to that observed in humans. We further hypothesize that the inflammatory insults of acute infection lead to myeloid skewing and result in clonal selection, driving disease progression.

Rescue of cognitive function following fractionated brain irradiation in a novel preclinical glioma model

Xi Feng[1,2], Sharon Liu [3,6], Susanna Rosi [1,2,3,4,5#], Nalin Gupta [3,6#]

[1]Brain and Spinal Injury Center, [2]Department of Physical Therapy and Rehabilitation Science, [3]Department of Neurological Surgery, [4]Weill Institute for Neuroscience, [5]Kavli Institute of Fundamental Neuroscience, [6]Brain Tumor Center, University of California San Francisco, San Francisco, CA

More than half of long-term brain tumor survivors develop irreversible cognitive decline that severely affects their quality of life. However, there is no pre-clinical model that allows long-term assessment of cognition, and there is no treatment which ameliorates cognitive deficits in patients. Human-derived xenograft models require immunodeficient host animals which greatly limits the ability to study immunologic responses in the brain. We have developed a novel glioma mouse model based on the GL261 rodent glioma line that offers manageable tumor growth and reliable assessment of cognitive functions in a post-treatment manner. Using this model, we found that fractionated whole-brain irradiation (fWBI), but not tumor growth, results in memory deficits. Transient inhibition of CSF-1R during fWBI prolongs survival of glioma-bearing mice and fully prevents fWBI-induced memory deficits. This result suggests that CSF-1R inhibition during radiotherapy can be explored as an approach to improve both survival and cognitive outcomes in patients who will receive fWBI. Taken together, the current study provides a proof of concept of a powerful tool to study radiation-induced cognitive deficits in glioma-bearing animals. Although GL261 allows detailed analyses of brain and immune cell interactions in immunocompetent animals, some of its features such as a high mutational burden and high MHC-I expression are not consistent with human tumors. We have also begun to develop models using SB28 glioma cells, which have a low mutational burden and low MHC-I expression.

No abstract submitted:

Living tissue imaging-based dependency biosensors for gastroesophageal tumors
PI: Jesse Boehm, PhD
Broad Institute

Interrogating cellular heterogeneity in liver regeneration and cancer
PI: Hao Zhu, MD
Children's Medical Center Research Institute at UT Southwestern

Modeling necrosis and the tumor microenvironment in glioblastoma to improve therapeutic targeting
PI: Dan Brat, MD
Northwestern University

Improving hepatocellular carcinoma mouse modeling by understanding the malignant potential and biology of liver cell subpopulations
PI: Hao Zhu, MD
Children's Medical Center Research Institute at UT Southwestern

Development of combination regimens for myeloid malignancies in humanized mice
Leighton Grimes, PhD, Cincinnati Children's Hospital
Stephanie Helene, MD, Yale University

Modeling necrosis and the tumor microenvironment in glioblastoma to improve therapeutic targeting
PI: Daniel Brat, PhD
Northwestern University

Credentialling a genetically engineered clinically relevant mouse model of multiple myeloma
PI: Marta Chesi, PhD
Mayo Clinic