U54 CARE Partnership

2024 RETREAT POSTER SESSION PROGRAM

December 11, 2024

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December 11, 2024
11:30 AM -12:45 PM

POSTER 1

Presenters: Suvithanandhini Loganathan (COH) & Rebecca E. Ruggiero-Ruff (UCR)

Title Immune, Tumor, and Stromal Interactions in Colorectal Cancer: A Spatial Proteomics Perspective

Suvithanandhini Loganathan1,, Rebecca E. Ruggiero-Ruff2,*, Gregory Isales2, Meera G Nair2, Edwin R Manuel1*

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy characterized by extensive desmoplasia and an immunosuppressive tumor microenvironment (TME), with tumor-associated macrophages (TAMs) playing a pivotal role in fibrosis, immune evasion, and tumor progression. The prevalence of M2-polarized TAMs, which promote pro-tumorigenic processes, contributes to poor treatment outcomes and is particularly significant in addressing racial disparities in PDAC outcomes. Our study focuses on developing and validating novel tools and therapies to target PDAC desmoplasia and M2 TAMs using mouse models of PDAC and a bacterial-based shRNA plasmid delivery system. PDAC cell lines were implanted in mice to generate tumors and are being characterized for fibrosis, immune subset composition, and cytokine profiles using histology and IF staining. We are using an innovative bacterial-shRNA delivery system, utilizing Salmonella typhimurium vectors with tumor colonizing properties, to deliver shRNA plasmids targeting key M2 TAM-associated genes (Csf1r, Irf4, Cux1, Mst1r), with the goal of reprogramming TAMs toward an anti-tumor M1 phenotype while minimizing systemic toxicity. This system will be tested in PDAC mice models, with expected outcomes including TAM polarization, tumor progression, and therapeutic response. In addition, immunofluorescence (IF) staining will be performed to determine M2 macrophage gene expression in tumors injected with IL-4 complex (IL-4c) and saline control. IF staining will determine expression and localization of TAMs within the tumor and if expression of M2 genes is changed within the tumor microenvironment. Together, these approaches will address critical gaps in modeling PDAC fibrosis and targeting the immunosuppressive TME.

POSTER 2

Presenters: Giulia Alboreggia (UCR)

Targeted Degradation of Pin1 by Protein Destabilizing Compounds

Giulia Alboreggia, PhD

The concept of targeted protein degradation (TPD) is at the forefront of modern drug discovery, which aims to eliminate disease-causing proteins using specific molecules. In this paper, we explored the idea to design protein degraders based on the section of ligands that cause protein destabilization, hence that facilitate the cellular breakdown of the target. Our studies present covalent agents targeting Pin1, a cis-trans prolyl isomerase that plays a crucial role in tumorigenesis. Our design strategy entailed iterative optimizations of agents for potency and Pin1 destabilization in vitro. Biophysical and cellular studies suggest that the agents act like molecular crowbars, displacing protein stabilizing interactions that open the structure for recognition by the ubiquitin-proteasome degradation machinery. This approach resulted in a series of potent and effective Pin1 degraders with potential applications in target validation and in therapeutic development. We propose that our design strategy can identify molecular degraders without engineering bifunctional agents that artificially create interactions between a disease-causing protein and a ubiquitin ligase.

POSTER 3

Presenters: Nikita Jinna (COH)

Kinesin family member C1 (KIFC1/HSET) underlies aggressive disease course in androgen receptor-low triple negative breast cancers

Nikita Jinna1, Yate-Ching Yuan2, Rama Natarajan3, Tijana Jovanovic-Talisman4, Mark LaBarge1, Padmashree Rida5, Victoria Seewaldt1

Quadruple negative breast cancers (QNBCs), or triple negative breast cancers (TNBCs) lacking in androgen receptor (AR) expression, have now surpassed TNBC as the most aggressive BC subtype
QNBC disproportionately afflicts and impacts women of West African ancestry, which contributes to the overall racially disparate burden in breast cancer
Novel actionable targets in QNBC are urgently needed to address this new clinical challenge
Kinesin Family Member C1 (KIFC1) confers survival of cancer cells via clustering supernumerary centrosomes to avoid aberrant mitotic cell division and chromosomal instability
KIFC1 has emerged as a biomarker of aggressive TNBC and a negative prognostic biomarker in African-American women

POSTER 4

Presenters: Maria Ninova (UCR), Enrique Velazquez-Villareal (COH)

Immune, Tumor, and Stromal Interactions in Colorectal Cancer: A Spatial Proteomics Perspective

Maria Ninova, Ph.D. (UCR), Enrique Velazquez-Villarreal, M.D., Ph.D., M.P.H. (COH)

Introduction: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide, claiming over 900,000 lives annually. In the United States, CRC disproportionately affects Hispanic/Latino populations, who experience higher incidence rates, inequitable access to healthcare, and worse clinical outcomes compared to other groups. The tumor microenvironment (TME) plays a critical role in CRC progression, therapeutic response, and overall patient prognosis. However, the complex spatial interactions within the TME that determine effective versus ineffective tumor control remain poorly understood. Addressing these gaps is crucial for enhancing our understanding of spatial heterogeneity and advancing immunotherapy, particularly in underserved populations such as Hispanics/Latinos. Methodology: To explore these dynamics, we employed a multimodal approach using co-detection by indexing (CODEX) technology on publicly available data from 35 late-stage CRC patients. Our systematic workflow classified cells, analyzed protein expression, and spatially visualized the data. Cells were categorized into three primary classes—stroma, tumor, and immune—based on structural features and biological functions. Protein expression analysis was conducted by integrating individual surface protein expression data, enabling direct comparisons across classes. Through this framework, we profiled 56 protein markers to identify conserved cellular neighborhoods (CNs) that define the spatial and functional organization of the CRC TME. Results: Protein expression analysis revealed distinct patterns across stroma, tumor, and immune classes for the biomarkers assessed. These markers exhibited differential expression profiles, highlighting their unique roles within the TME. For example, immune markers such as CD3, CD8, CD68, and PD-1 demonstrated significant variation between the tumor and immune classes, emphasizing their spatial organization and functional importance. Similarly, functional markers such as MMP9 and Ki-67 showed unique expression dynamics, reflecting their roles in tumor progression and immune responses. Auxiliary markers like cytokeratins underscored structural differences specific to the stromal class. These findings provided a comprehensive understanding of the spatial and functional interplay between immune, tumor, and stromal components in the CRC TME. Conclusion: This study provides a deeper understanding of protein expression within the colorectal cancer tumor microenvironment (CRC TME), enhancing the classification and spatial characterization of tumor ecosystems. By uncovering distinct protein expression profiles, these findings highlight the spatial heterogeneity of the TME, offering valuable insights for future drug discovery and therapeutic development. Furthermore, this research holds significant promise for advancing precision oncology. Notably, future studies in spatial biology that focus on the unique challenges and health disparities faced by Hispanic/Latino populations can pave the way for more equitable and effective cancer care, particularly in underserved communities.

POSTER 5

Presenters: Alexandra Huang (UCR)

Pharmacologically Targetable Dynamics of Human eIF4F Function

Alexandra Huang, Seán E. O'Leary

Human cells rely on eukaryotic initiation factor 4F (eIF4F) to initiate protein synthesis ("translation") on most messenger RNAs. The host translation machinery is dysregulated in cancer to facilitate the biochemical demands of the cancer cell. N6-Methyladenosine (m6A), the most prevalent chemical modification of mRNA, plays a significant role in regulating mRNA translation, with its dysregulation potentially linked to oncogenesis. There thus exists a critical gap in exploring whether m6A-mediated cap-dependent translation involves eIF4F subunits and what the molecular mechanism would be. To test this hypothesis, we sought to dissect and contrast interactions between eIF4A1/eIF4F and a series of human mRNA leaders containing and lacking the m6A modification. We first identified a weak interaction between eIF4A1, a DEAD-box RNA helicase, and the m6A "writer" protein complex, METTL3/14. Our findings also suggest a difference in the interaction and subunit coordination of the eIF4F complex in the unwinding of a mRNA both containing and lacking the m6A modification. Together, these initial findings have implications for future strategies and specific design principles required to pharmacologically target eIF4F in cancers.

POSTER 6

Presenters: Minxiao Yang (COH)

KRAS oncogenic activation in Gramd2+ AT1 cells induces lung adenocarcinoma with distinct immunosuppressive myeloid cell composition

Minxiao Yang1,2, Noah Shulkin1, Edgar Gonzalez3, Jonathan Castillo1, Zea Borok4, Evanthia Roussos Torres3, Crystal N. Marconett1*,***

Lung adenocarcinoma (LUAD) is the most prevalent subtype of lung cancer with a high degree of biological heterogeneity, for instance, varying cells of origin that includes alveolar epithelial cells (AECs) in distal lung. The predominant types of AECs are surfactant-producing alveolar epithelial type II (AT2) cells and large, delicate alveolar epithelial type I (AT1) cells. AT1 cells cover over 95% of the alveolar epithelial surface and are largely responsible for facilitating gas exchange. Although AT1 cells had been thought to be terminally differentiated and consequently unable to proliferate, we, and others, have previously reported that Gramd2+ AT1 cells can give rise to histologically-defined LUAD1,2 on transgenic mouse model.

Immunotherapy has shown a major impact on treatment of solid tumors over the past 10 years, particularly LUAD, where it significantly improves patients' survival rates3. However, based on varying expression of key immunosuppressive markers such as CTLA-4 and PD-L1, there is still considerable variability of patient response to therapy across LUAD patients, because largely unknow immunosuppressive states across LUAD cases make immunotherapeutic challenging. Moreover, it is currently unknown whether cell of origin influences tumor immune microenvironment (TIME) composition and response to immunotherapy. Here, we employed single cell RNA sequencing on KRASG12D-overexpressing Gramd2+ AT1 cell-derived LUADs from mice to fully characterize transcriptomic, molecular and cellular changes within the TIME. We demonstrate that myeloid cells within the AT1-LUAD TIME manifest a disordered cell composition and disrupted transcriptome: increased macrophages and decreased myeloid-derived suppressor cells (MDSCs) infiltrate into the AT1-LUAD TIME compared with Sftpc+ AT2 cell-derived LUAD. In addition, tumor-associated macrophages (TAMs) exhibit altered suppressive gene expression patterns and signaling that involve the IL2, NFκB and TNF pathways. Taken together, AT1-LUAD presents a proinflammatory, immunoreactive TIME, while TIME of AT2-LUAD is relatively immunosuppressive. This study suggests that cell of origin of LUAD is associated with transcriptomic aberrations and immune landscape changes that may inform ongoing translational work to improve patient responses.

POSTER 7

Presenters: Xiaoxu Zhang (COH)

Pharmacological inhibition of eIF4A1 suppresses leukemogenesis via specifically rewiring amino acid biosynthesis

Xiaoxu Zhang1,2, Honghai Zhang1,2, Lili Ren1,2, Lei Dong1, Xueer Wang1,2, Hongjie Bi1,2, Alexandra Huang3,4, Seán O'Leary 3,4 , Rui Su1,2,#

Acute myeloid leukemia (AML) is an aggressive hematological malignancy with a dismal five-year survival rate
below 30%. Dysregulation of mRNA translation has been recognized as a hallmark and a driver of tumorigenesis,
including leukemogenesis. However, the precise contributions of translation factors to AML pathogenesis and their
potential as therapeutic targets remain poorly understood.
In this study, we performed a comprehensive multi-omics analysis of currently known translation-related factors
using in-house RNA-seq and proteomics data from AML cells, and the TCGA AML cohort. Among the over hundred
translation factors, eukaryotic translation initiation factor 4A1 (eIF4A1) was identified as one of the most highly
expressed genes in AML. Knockout (KO) of endogenous eIF4A1 in AML cell lines and patient-derived xenograft
(PDX) cells revealed dramatically inhibited AML cell proliferation, suppressed mitochondrial respiration, and
repressed global translation intensity. Integrative analysis of RNA-seq and proteomics showed that eIF4A1 KO
suppressed the biosynthesis of amino acids, underscoring its crucial role in reprogramming AML cell
metabolism. Importantly, Zotatifin, an FDA-approved eIF4A1 inhibitor, significantly repressed AML cell growth in
vitro, with IC50 values in the low nanomolar range, and substantially prolonged the survival of AML mouse models in
vivo.
In conclusion, our findings establish eIF4A1 as a key regulator of AML pathogenesis and metabolism. Targeting
eIF4A1, particularly with Zotatifin, represents a promising therapeutic strategy for AML by specifically disrupting
amino acid biosynthesis.

POSTER 8

Presenters: Christina Vidal (COH)

Chromatin acetylation at H3K9ac, inflammatory signaling, and evidence for immune cell senescence in Los Angeles women with insulin-resistance

Christina M. Vidal, Alva-Ornelas JA, Chen NZ, Senapati P, Tomsic J, Robles VM, Resto C, Sanchez N, Sanchez A, Hyslop T, Emwas N, Aljaber D, Bachelder N, Martinez E, Ann D, Jones V, Winn RA, Miele L, Ochoa AC, Dietze EC, Natarajan R, Schones D, Seewaldt V

Epigenetic changes link medical, social, and environmental factors with chronic medical diseases such as cardiovascular disease, diabetic kidney disease, and more recently with cancer. The links between these factors, particularly the link between metabolic health and epigenetic changes, are only starting to be investigated. In our in vitro and in vivo studies, we performed broad analysis of the link between hyperinsulinemia and chromatin acetylation; our top "hit" was chromatin opening at H3K9ac. Building on our published pre-clinical studies, here we performed detailed analysis of the link between insulin-resistance, chromatin acetylation, and inflammation in an initial test set of 28 women and validation sets of 245, 22, and 53 women. ChIP-seq identified chromatin acetylation and opening at the genes coding for TNFa and IL6 in insulin-resistant women. Pathway analysis identified inflammatory response genes, NFkB/TNFa-signaling, reactome cytokine signaling, innate immunity, and senescence. Consistent with this finding, flow cytometry identified increased senescent circulating peripheral T-cells. DNA methylation analysis identified evidence of accelerated aging in insulin-resistant vs. metabolically healthy women. Conclusions: This study shows that insulin-resistant women have increased chromatin acetylation/opening at inflammatory genes, inflammation, and, perhaps, accelerated aging. Given the role that inflammation plays in cancer initiation and progression, these studies provide a potential mechanistic link between insulinresistance and cancer.

POSTER 9

Presenters: Kendrick Davis, Margarita Monge & Angela Reyes (UCR)

EMOJI: MEASURES OF EMOTIONS & MOODS

Kendrick Davis1, PhD., Margarita Monge1, BA., Angela Reyes, BS1

Background / Context: The History of Emoji
1999 - The first set of emoji was released - created by their Japanese originator Shigetaka Kurita (). Emoji is a transliteration of the Japanese word (e=picture) 文 (mo=write) 字 (ji=character)[8].
2010 - Emoji were added to Unicode
2011 - Frequent use in communication (Added emoji keyboard to iOS devices and android followed) 1998 - Introduced in research measurement and instrumentation
Problem statement: While emojis are increasingly utilized in research across various industries to measure emotions and moods, existing tools fail to effectively differentiate between these two distinct psychological states. This limitation hinders the accuracy and depth of emotional analysis, which is crucial for developing more precise and contextually relevant insights. Addressing this gap is essential for improving the utility of emojis as valid and reliable indicators of emotions and moods.
Response: The Emoji Psychometrics Lab is addressing the challenge of differentiating between emotions and mood states in emoji-based measurement & instrumentation research. Cancer research is lacking in the measurement of emotions and moods and their role in treatment and adherence behaviors of participants. Our studies aim to identify key distinctions between these psychological states and determine the most appropriate contexts and methodologies for capturing each one. By refining the use of emojis as measurement tools, we seek to enhance the accuracy and consistency of emotional data.

POSTER 10

Presenters: Narissa Nonzee (COH)

Implementation of Medicaid expansion for patients with cancer: Community perspectives on the California Cancer Care Equity Act

Narissa J. Nonzee*, Brenda Gascon, Genesis Sandoval, Sophia Yeung, Lauren Cai, Kimlin Tam Ashing

Background: Underinsured cancer patients are at risk for late-stage diagnosis and poor survival. In January 2023, the California Cancer Care Equity Act (SB987; hereon CCEA-SB987), an evidence-based cancer control Medicaid expansion, was implemented to increase access to specialized cancer centers for Medicaid patients with complex cancers. We present preliminary findings on community health system leader perspectives on CCEA-SB987 awareness and multilevel determinants of implementation. Methods: Between March and July 2024, we conducted semi-structured interviews with organizational leaders at community health centers and hospitals serving large Medicaid-insured populations in LA County. Guided by the Consolidated Framework for Implementation Research (CFIR), interviews explored inner and outer setting determinants of cancer care access and policy awareness, implementation, and dissemination, and themes were summarized within CFIR. Data collection is ongoing with additional interviews being conducted. Findings: Participants (n=12) comprised 5 clinician leaders (e.g., medical directors) and 7 organizational leaders (e.g., QI, case management); average years of experience=6 (sd 5); 9 female; 9 ethnic minority (7 Latino, 2 Asian). Overall, participants expressed low CCEA-SB987 awareness. Key barriers to cancer care access emerged within the outer setting, including financing and provider network partnerships/connections (e.g., insurance authorization delays; complexity navigating managed care plans). Within the inner setting, participants frequently discussed limited access to knowledge about CCEA-SB9897 and importance of relational connections to reduce fragmented communication between primary care and specialty care providers. At the individual level, transportation and language barriers were commonly cited. Regarding processes, the majority described a top-down approach to successful implementation of coverage expansion policies, starting with senior leadership, then clinicians and staff. Almost all perceived that CCEA-SB987 patient eligibility would be best determined by clinicians, in coordination with referrals and benefits enrollment. Suggestions for CCEA-SB987 policy dissemination included communication from health system leadership, provider and IPA meetings, brief bulletins, and in-language and low-literacy patient education. Implications for D&I Research: One year after the law began, CCEA-SB987 awareness remained low and challenges to cancer care for Medicaid managed care beneficiaries persisted. Policy dissemination should involve multi-stakeholder engagement and leverage community health system leadership to strengthen processes around CCEA-SB987 eligibility determination and communication to ensure equitable cancer care access.