Session PO.TB07.03 - Contextual Determinants of Cancer Stemness and Tumor Aggressiveness

4818 / 10 - Establishing novel, representative prostate cancer cell lines from fresh prostatectomy tissues via an optimized protocol

Presenter/Authors

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Disclosures

T. V. Nguyen, None..S. C. Smith, None..L. J. Hampton, None..V. J. Findlay, None..D. P. Turner, None.

Abstract

Background: The existing panel of prostate cancer (PCa) cell lines, often established from metastatic sites or after extensive passaging, frequently fails to fully recapitulate the genetic heterogeneity and tumor microenvironment dependence of primary prostate tumors. Additionally, there is a crucial need for diverse, population-specific cell lines to investigate the biological factors underlying disparities in patient outcomes and therapeutic response. To address this critical resource gap, we optimized and validated a highly efficient protocol for the de novo establishment of patient-derived, primary PCa cell lines from fresh surgical specimens.

Methods: Patients were consented in accordance with VCU IRB protocol #20210623, and their self-reported race was recorded as either White (W) or African American (AA). Fresh tissues were obtained as punched biopsies from 36 radical prostatectomy specimens. Each specimen yielded 1-3 biopsy samples. H&E slides were graded by a licensed pathologist. Optimized from Maitland et al. 2016 protocol, tissue samples digested enzymatically were separated into distinct populations through differential centrifugation, and propagated in optimal media for epithelial and fibroblastic cell lines. The cellular origin of patient-matched lines were confirmed using cytochemistry and further characterized through proliferation assays, Western blot, and short tandem repeat (STR) profiling.

Results: The optimized protocol, carried out in the latter quarter of the trial, demonstrated high efficacy with an 86% success rate (13 out of 15 samples), bringing the total to 30 novel, matched PCa epithelial and fibroblast cell lines successfully established from 18 patients. Among the 30 samples, 18 were benign (11 W and 7 AA) and 10 were cancerous (6 W and 4 AA). Additionally, 3 patient prostatic specimens yielded matched cell lines from both the tumor and the contralateral non-malignant tissue. Critically, these cell lines retained the expression of androgen receptor (AR) and prostate-specific antigen (PSA). Furthermore, the lines exhibited heterogeneous growth patterns reflecting the diversity of the source tumors.

Conclusion: We have established a robust, highly effective protocol for generating patient-derived, primary PCa cell lines directly from prostatectomy tissues. These novel, characterized models significantly enrich the translational research toolkit, providing invaluable resources for several critical applications, including biomarker identification, understanding tumor initiation and progression, resistance mechanism studies, drug discovery and validation, and, most importantly, for studying population-specific differences to guide the development of truly equitable and personalized treatment strategies.

Session PO.CL02.01 - Biostatistics in Clinical Trials / Surgical Oncology

6448 / 15 - The obesity paradox in pancreatic cancer

Presenter/Authors

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Disclosures

J. Lambdin, None..**C. Burch,** None..**W. Royster,** None..**L. Fernandez,** None..**R. Louie,** None..**R. Bello,** None..**J. G. Trevino,** None.

Abstract

Introduction: The “obesity paradox,” in which higher body mass index (BMI) appears to confer a survival advantage despite its role in carcinogenesis, has been reported in several solid tumors, but its relevance across racial groups in patients with pancreatic cancer is unclear. We performed a retrospective database study using TriNetx, a multinational deidentified dataset, to identify patients with pancreatic cancer and to examine associations between BMI, race/ethnicity, survival, and post operative complications.

Methods: Using the TriNetx database, we identified patients with pancreatic cancer and stratified the cohort by BMI at time of diagnosis: underweight (UW) (BMI < 18.5 kg/m²), healthy weight (HW) (18.5-24.9 kg/m²), and overweight (OW) (≥25.0 kg/m²). Subgroups were created of Black, Hispanic, and White patients within each BMI cohort to evaluate for racial/ethnic differences in BMI associated outcomes. The primary outcome was overall survival with secondary outcomes of post-operative complications. Propensity score matching was performed for age, sex, stage, comorbidities, and type of surgical resection performed. Kaplan-Meier curves and multivariable Cox models were used to evaluate survival across BMI categories overall and within racial strata. Multivariable logistic regression was used to evaluate associations between BMI category and postoperative complications.

Results: We identified 247,150 patients with pancreatic cancer, including 51,057 (87%) OW, 3241 (6%) HW, and 3815 (7%) UW patients. In propensity matched models, BMI category was found to be associated with overall survival. Compared with HW, OW was associated with a longer 5-year median survival (895 vs 493) and reduced hazard of death (HR = 0.76, 95% CI (0.70-0.82)), while UW was associated with worse survival than HW (HR = 1.24, 95% CI 0.74-0.87)). The magnitude and direction of these associations differed by race/ethnicity with OW Black (HR = 0.69, 95% CI (0.59-0.85)) and OW Hispanic patients (HR = 0.88, 95% CI (0.62-1.25)) deriving more substantial survival benefit over HW when compared to their OW White counterparts (HR = 0.80, 95% CI (0.73-0.86)). Among propensity matched surgical patients, OW was associated with increased risk intraabdominal abscess (10.2% vs 5.1%, RR = 2, p = 0.02), and increased odds of AKI (19.7% vs 12.9%, RR = 1.53, p = 0.026) compared with HW individuals. No significant difference in postoperative pancreatic leak was identified between the OW and HW cohorts. (11.5% vs 11.8%, RR = 0.97, p = 0.89).

Conclusions: In this large, real-world cohort of patients with pancreatic cancer, BMI and race were significant determinants of survival and postoperative morbidity, with patterns consistent with an obesity paradox. These data may refine risk stratification and motivate studies of adiposity and pancreatic cancer biology across diverse populations.

Session PO.CL09.02 - Real World Data to Provide Real World Evidence

6639 / 8 - Impact of preexisting heart disease on survival and postoperative outcomes in pancreatic cancer: A TriNetX analysis

Presenter/Authors

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Disclosures

C. Burch, None.. J. Lambdin, None.. W. Royster, None.. L. Fernandez, None.. R. Louie, None.. R. Bello, None.. J. G. Trevino, None.

Abstract

Background: Cardiovascular comorbidity is common among patients with pancreatic ductal adenocarcinoma (PDAC) and may influence both long-term survival and perioperative risk, yet its impact in contemporary practice is not well defined. We performed a retrospective database study using TriNetx, a multinational deidentified dataset, to identify patients with PDAC and to examine associations between heart disease, survival, and complications of pancreaticoduodenectomy (PD).

Methods: Using the TriNetx database, we identified patients with PDAC and stratified the cohort by presence or absence of heart disease (ischemic, structural, heart failure). Subgroup analysis was performed of patients who underwent PD. The primary outcome is overall survival, and secondary outcome is rate of post-PD complications. Propensity score matching was performed for age, sex, stage, and comorbidities. Kaplan-Meier curves and log-rank testing were used to determine survival between the groups and multivariable logistic regression was used to evaluate associations between heart disease and postoperative complications. Among patients undergoing PD, secondary outcomes include postoperative pancreatic leak, myocardial infarction (MI), acute kidney injury (AKI), surgical site infection (SSI), and venous thromboembolism (VTE), rates were evaluated using multivariable logistic regression.

Results: We identified 226,966 patients with PDAC, of whom 45,936 (20%) had preexisting heart disease and 181,030 (80%) did not; 12,840 underwent PD. Propensity matched median overall 5-year survival was 703 days for patients without heart disease versus 611 days for those without (HR = 0.90, $p < 0.0001$). In the matched surgical cohort, preexisting heart disease was associated with increased risk of post-operative myocardial infarction (RR = 3.34, $p < 0.0001$) and acute kidney injury (RR = 1.34, $p < 0.0001$) but not associated with post-operative pancreatic leak (RR = 1.11, $p = 0.18$), abscess (RR = 1.15, $p = 0.16$), or surgical site infection (RR = 1.13, $p = 0.16$). Among propensity matched cohorts of patients with PDAC and heart disease who did and did not undergo PD, those who underwent PD had significant improvement in 1-year overall survival (82% vs 63%, $p < 0.0001$).

Conclusions: In this large, real-world cohort of patients with PDAC, preexisting heart disease was an important determinant of overall survival and perioperative morbidity, with clinically meaningful differences in median survival and postoperative complication profiles. The benefit of PD does not seem to be lost to patients with cardiac risk factors, with significant improvement in overall survival seen in the group who underwent PD. These findings may inform risk stratification, treatment selection, and perioperative optimization strategies for this high-risk population.

Session PO.ET03.08 - Targeting Drug Resistance 2: RAS Signaling

1869 / 2 - Combining FGTI-2734 and MRTX1133 to suppress ERK-driven resistance in KRAS G12D pancreatic cancer

Presenter/Authors

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Disclosures

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Abstract

The KRAS G12D-selective inhibitor MRTX1133 marks a significant step forward in targeting mutant KRAS; however, its therapeutic impact is dampened by adaptive resistance driven by ERK pathway reactivation, a process requiring membrane localization of wild-type (WT) RAS. In this study, we introduce a rational approach to circumvent this resistance by using FGTI-2734, a dual inhibitor of farnesyltransferase (FT) and geranylgeranyltransferase-1 (GGT-1) that impairs WT RAS and mutant RAS membrane Localization. FGTI-2734 suppresses the ERK rebound elicited by MRTX1133 and acts synergistically with MRTX1133 to inhibit cell growth and trigger apoptosis in KRAS G12D pancreatic cancer cell lines. In patient-derived organoids from 12 individuals with KRAS G12D pancreatic cancer, including organoids originating from both primary and metastatic sites and spanning diverse co-mutation patterns (KRAS, TP53, CDKN2A, SMAD4, RTKs, PI3K/AKT, JAK/STAT, DNA repair/cell-cycle genes, and chromatin modifiers), the FGTI-2734/MRTX1133 combination produced consistent strong synergy. This effect was observed regardless of prior treatment, disease stage, or intrinsic sensitivity or resistance to MRTX1133. In vivo, FGTI-2734 potentiated MRTX1133's anti-tumor effects, leading to tumor regression in orthotopic patient-derived xenografts established from a KRAS G12D pancreatic cancer patient who progressed after radiation and chemotherapy, as well as in xenografts derived from KRAS G12D human pancreatic cancer cell lines. Importantly, FGTI-2734 treatment prevented MRTX1133-driven ERK reactivation in these KRAS G12D xenograft models. Collectively, these results define a mechanistically grounded combination strategy that neutralizes a key resistance pathway limiting MRTX1133 efficacy, and they highlight a promising therapeutic option for KRAS G12D pancreatic cancers.

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Session PO.ET03.08 - Targeting Drug Resistance 2: RAS Signaling

1882 / 15 - Generation of daraxonrasib-resistant patient-derived xenograft models of pancreatic cancer

Presenter/Authors

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Disclosures

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Abstract

Background: Patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) face limited treatment options and a dismal survival rate. KRAS is mutated in over 90% of PDAC and is a critical driver of tumor initiation and progression. Daraxonrasib (RMC-6236), a newly developed pan-RAS inhibitor, has shown promise in extending the survival of patients with PDAC in ongoing clinical trials. However, acquired resistance to daraxonrasib is anticipated and may limit the efficacy of this new therapeutic. To address this challenge, we developed a biobank of over 60 patient-derived xenograft (PDX) models, including 24 new models of PDAC, and aimed to generate daraxonrasib-resistant lines to investigate mechanisms of resistance and explore strategies to prolong daraxonrasib efficacy.

Methods: PDX cells from six patients with PDAC were injected subcutaneously in NSG mice, and tumor volume was measured weekly by caliper. Daraxonrasib (25 mg/kg) was administered daily by oral gavage when tumor volume reached 10-30 mm3. Following 4-6 weeks of treatment, tumors that were initially responsive were digested and injected into additional mice which were again treated with daraxonrasib. Tumors that grew through treatment were collected for histological analysis and single cell RNA-sequencing.

Results: PDAC was found to be the most KRAS-dependent cancer type in our PDX biobank. Initial daraxonrasib treatment resulted in 63-97% reduction in tumor volume area-under-the-curve (AUC) compared to untreated controls across six models of PDAC. Response was significantly correlated with KRAS dependency score, while no association was found with patient demographics, KRAS mutation, or PDAC subtype. The PDXs with the greatest response were selected to generate resistant lines. Within two passages, the reduction in AUC was no longer significant based on Welch's t-test, indicating that resistance had developed. Transcriptomic analysis of treated tumors revealed upregulation of mucin production and YAP1 signaling, which likely represent early resistance mechanisms.

Future directions: Daraxonrasib was effective in reducing tumor volume in PDX models of PDAC, but prolonged treatment resulted in acquired resistance. Comparing the transcriptomic profiles of newly generated resistant lines and their sensitive counterparts will elucidate the mechanisms by which PDAC develops resistance to daraxonrasib. Furthermore, these models will provide a platform to test strategies to overcome resistance and maximize the efficacy of this promising new therapeutic.

Session LBPO.ET02 - Late-Breaking Research: Experimental and Molecular Therapeutics 2

LB199 / 21 - High-plex spatial transcriptomics reveals triplatin-induced DNA damage signaling and tumor-fibroblast niche reprogramming in pancreatic cancer PDX models

Presenter/Authors

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J. Liu, None..

J. Harrell, None..

N. P. Farrell, None..

J. G. Trevino, None.

Abstract

Abstract is embargoed at this time.

Session PO.ET02.14 - Tumor Microenvironment, Multispecifics, and Immunomodulation

5849 / 18 - Leveraging expression of tumor microenvironment GAGs to enhance platinum-based therapy in pancreatic adenocarcinoma

Presenter/Authors

Vashti L. Bandy[1], Erica Peterson[2], Nicholas P. Farrell[3], Jose G. Trevino[4], Praveen Bhoopathi[2], Vignesh Vudatha[2], Arunima Punjala[5], Dongyu Zhang[2], Jennifer Koblinski[2], Ada Beaudin[1], Thomas M. Clausen[2], Chunqing Guo[1], Larisa Litovchick[1], Nicholas Woods[6]

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Disclosures

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is often diagnosed at an advanced stage, with most patients experiencing disease progression within 6-12 months following frontline FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, leucovorin), underscoring the need for more effective treatment strategies. Recent evidence suggests that overexpression of glycosaminoglycans (GAGs)—particularly chondroitin-4-sulfate (C4S)—contribute to the dense, fibrotic stroma characteristic of PDAC and tumor resistance to chemotherapy. C4S, a tumor-associated GAG linked to proteoglycans such as CD44, glypicans, and syndecans, is prominently expressed on the cell surface within the tumor stroma. Our studies demonstrate that C4S expression predicts PDAC tumor sensitivity to the Phase II polynuclear platinum agent, Triplatin (BBR3464). The highly cationic structure of Triplatin enhances its binding affinity for negatively charged GAGs, promoting drug accumulation and increased formation of platinum-DNA adducts. These findings provide a strong mechanistic rationale for re-evaluating Triplatin in tumors with high GAG expression, particularly C4S.

Our preliminary data shows that modulating GAG levels in PDAC cell lines alters both the cytotoxicity and cellular uptake of Triplatin. First, Triplatin exhibits greater cytotoxicity than oxaliplatin in the CHX1990 mouse cell line, an established model of PDAC derived from the Kras(G12D)/Trp53 null/Pdx1-cre (KPC) model. Second, a GAG-deficient CHX1990 cell line, B4GalT7 (CRISPR KO of β-1,4-galactosyltransferase 7), verified by reduced binding of the CS-binding peptide rVAR2-V5, shows a correlative loss in cytotoxicity. Finally, Triplatin significantly suppresses CHX1990 tumor growth in vivo with minimal changes in body weight relative to untreated controls. Collectively, these findings suggest that GAGs serve as a viable biomarker for Triplatin response in PDAC and may confer significant therapeutic advantage over oxaliplatin in this context.

To further support our studies, we are investigating Triplatin's mechanism of action through proteomic analyses that assess intracellular drug accumulation impacts on DNA repair proteins and apoptosis pathways. To complement this work, spatial transcriptomics will be used to map gene expression within the tumor microenvironment, providing insight into how Triplatin distribution corresponds with tumor cell responses. Additionally, synergy studies examining Triplatin in combination with standard-of-care therapies will help determine its therapeutic effectiveness. Together, these integrated approaches aim to advance Triplatin as a promising therapy for treatment of PDAC.

Session PO.ET03.06 - Drug Resistance 1: Antibodies and ADCs

2956 / 2 - Determinants of sacituzumab govitecan therapeutic response in breast cancer models

Presenter/Authors

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Disclosures

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Abstract

This study identifies markers of Sacituzumab Govitecan (SG) response in triple-negative breast cancer (TNBC) models and introduces new SG acquired resistance patient derived xenografts (PDXs) that can serve as examples of patient-acquired mutations or gene regulation changes that confer resistance to this targeted therapy. SG is an antibody drug conjugate (ADC) that has been approved for treating TNBC and estrogen receptor positive breast cancers that have progressed on initial treatments. SG binds to TROP2 and delivers SN-38 as its payload; resistance to SG could be due to inefficient antibody internalization or lack of payload efficacy. We hypothesize that individual intrinsic and acquired SG resistance mechanisms will uncover features that can be targeted to extend the duration of response to SG. Using a linear mixed effects model, we mapped PDX responses to SG in vivo to their RNA expression in order to identify differences in gene expression that stratify SG response; developing an initial SG response predictor in this process. By administering suboptimal and continuous SG treatments to formerly SG-sensitive PDXs, we created acquired SG resistant (SGR) models. We then compared the RNA expression between these syngeneic pairs of PDXs to identify acquired resistance mechanisms and common pathways of resistance in patients. Performing antibody internalization assays on the paired sets allowed us to investigate if antibody or encapsulation mediated resistance was responsible for the continued tumor growth. Short-term SN38 testing was used to define the extent of payload resistance in paired models. Through these efforts, we identified 9 SG-sensitive and 3 intrinsically resistant TNBC PDXs whose differential expression led us to focus on 13 genes that predict SG response. Three of the most sensitive models were used to create acquired resistance models and analysis is underway to compare these to the intrinsic resistance models utilizing bulk and single-cell RNA-sequencing, proteomics, and cytotoxic compound screens. RNA sequencing of PDXs with innate SG resistance defined differences in gene expression related to extracellular matrix, angiogenesis, and metal ion trafficking. Conversely, acquired resistance models show diversity in resistance mechanisms including notably heightened extracellular matrix protein synthesis. Ongoing studies aim to define these mechanisms so that candidate therapeutics can be prioritized to overcome SG resistance. In conclusion, a preliminary SG resistance signature has been developed, which we will refine for clinical selection of patients to be treated with SG. Additionally, several biological processes are activated during acquired SG resistance and may be targetable.

Session PO.BCS01.01 - Application of Bioinformatics to Cancer Biology 1

61 / 23 - Defining spatial biomarkers of survival across solid tumors using a pan-cancer proteomics atlas

Presenter/Authors

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Disclosures

K. Huynh, None..

J. Reyna, None..

B. Matuck, None.

Abstract

The spatial architecture of the tumor microenvironment (TME) governs cancer progression and therapeutic response, yet pan-cancer analyses linking multicellular organization to patient survival remain unclear. As part of the PROSPECTS (Pancancer Reconstruction Of Spatial Profiles and Therapeutic TargETs) Initiative, we assembled a large-scale spatial proteomic atlas comprising 415 patients across six major malignancies: Head and Neck Squamous Cell Carcinoma (HPV-positive and HPV-negative), Lung Cancer (NSCLC and LUAD), Triple-Negative Breast Cancer, High-Grade Serous Ovarian Cancer, Colorectal Adenocarcinoma, and Hepatocellular Carcinoma (HCC). Our dataset includes over 1,000 tissue cores and over 4.4 million single cells with balanced representation across indications: HNSCC (1,218,385 cells, 145 patients), Lung (906,537 cells; 63 patients), Breast (765,232 cells; 60 patients), Ovarian (590,945 cells; 53 patients), Colorectal (511,610 cells; 37 patients), and Liver (474,237 cells; 57 patients). Using a 30-plex antibody Phenocycler, we spatially mapped 15 major cell types at single-cell resolution. We developed a next-generation multi-scale computational pipeline within AstroSuite (Stratica Biosciences), integrating TACIT and Constellation algorithms to quantify TME architecture at the levels of cell state, intercellular distance, and higher-order motifs including pairwise, triplet, and quartet cellular neighborhoods. These deep spatial metrics were linked to overall survival with adjustment for clinical covariates. We identified marked heterogeneity in TME structure, with each cancer type exhibiting distinct prognostic architectures. In TNBC, Tumor Cell-Neutrophil interactions emerged as one of the strongest adverse prognostic features (P=0.00001). In Lung cancers, vascular-immune and stromal-tumor interfaces were key, particularly vascular endothelial cell-Macrophage adjacency (P=0.0003) and Fibroblast-Tumor Cell interactions (P=0.002). Despite these cancer-specific patterns, PROSPECTS uncovered conserved spatial signatures. A recurrent fibroblast-tumor cell interface motif appeared across malignancies, though stromal drivers varied: Myofibroblast-Treg interactions were prognostic in Colorectal cancer (P=0.002), while Fibroblast-Treg interactions predicted outcome in Ovarian cancer (P=0.002). In HCC, immune-to-immune interactions such as Treg-B Cell crosstalk (P=0.002) were significantly associated with survival. Complex spatial syntax proved superior to simple pairwise interactions for prognosis, highlighting the value of higher-order TME modeling. This work establishes the first pan-cancer spatial proteomic comparison linking TME organization to clinical outcome, revealing that spatially resolved cellular interaction networks constitute a new class of clinically actionable biomarkers.

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Session PO.CL01.16 - Prognostic Biomarkers 2

3944 / 19 - The impact of diversity on transcriptional heterogeneity of skeletal muscle from pancreatic ductal adenocarcinoma patients

Presenter/Authors
Praveen Bhoopathi[1], Vignesh Vudatha[2], Arunima Punjala[2], Vashti Bandy[2], Anna Gibson[2], Dongyu Zhang[2], Katarzyna M. Tyc[3], Mikhail Dozmorov[3], Jeremy Ducharme[4], Martin Schonk[4], Brittney Poole[4], Sarah Judge[4], Leopoldo Fernandez[1], Andrew R. Judge[4], Jose G. Trevino[1]

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Abstract
Objective: Cachexia plays a major role in the morbidity and mortality of pancreatic ductal adenocarcinoma (PDAC) patients. The objective of this study is to delineate the molecular pathways of muscle that contribute to cancer cachexia from surgically resected PDAC patients.
Methods: At surgical resection for PDAC, rectus abdominus muscle was sharply divided and shock frozen immediately for RNA-seq. Total RNA was extracted from the frozen tissue using standard protocols, and RNA integrity was confirmed prior to library preparation. The resulting high-quality RNA was then used for RNA sequencing (RNA-seq) analysis to find distinct variants in addition to a core transcriptional signature of roughly 13,007 frequently expressed transcripts, differential transcript expression was evaluated. KEGG pathways and MSigDB collections (Hallmark, Curated, GO signatures) were used in Gene Set Enrichment Analysis (GSEA), which uses both fold change and ranking of differentially expressed genes (DEGs) to find enriched biological pathways.
Results: Significant transcriptome variations in muscle tissue were found to be associated with patient race and survival. MSigDB gene sets comparing Black and White) patients revealed that the AA cohort had higher activation of pathways linked to inflammation, cardiomyopathy, and muscle atrophy/proteostasis. Three overlapping genes were found by cross-referencing these pathways with significant DEGs: CYP4B1, DDIT4 (upregulated in AA, significantly related with muscular atrophy/cachexia), and GINS1 (downregulated in AA, associated with proliferation). Additionally, eight genes including the physiologically significant genes ADAM28, SENCR, and MEG8 (related with muscle differentiation and tumor progression) were found to be substantially associated with overall survival.
Conclusion: RNA-seq and GSEA of muscle tissue provide critical insights into the systemic molecular alterations associated with PDAC. The identified pathways and genes, particularly those demonstrating racial and survival-associated heterogeneity (e.g., DDIT4, GINS1), represent potential biomarkers and therapeutic targets for addressing muscle dysfunction and cachexia in PDAC.

Session PO.TB03.01 - Therapies Targeting Metastasis

2243 / 18 - Lasofoxifene is a bone protective treatment option for estrogen receptor positive breast cancers

Presenter/Authors

Emily Kate Zboril[1], David C. Boyd[2], Rachel K. Myrick[2], Nina Dashti-Gibson[3], Faith E. Parker[2], Carson Walker[2], Amy Olex[2], Chuck Harrell[2]

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E. K. Zboril, None..

F. E. Parker, None.

Abstract

Estrogen receptor positive (ER+) breast cancer primarily metastasizes to the bone microenvironment, and patients with ER+ disease are almost twice as likely to develop bone metastasis as those with other subtypes. Treatment with current endocrine therapies frequently results in osteoporosis and subsequent bone turnover which can potentially accelerate metastatic progression. This underscores the need for new treatments which will simultaneously inhibit tumor growth and preserve the bone microenvironment. Standard treatments like aromatase inhibitors and ER-antagonists, like fulvestrant, indiscriminately suppress ER signaling, in both breast and bone. Lasofoxifene, a selective ER modulator, exhibits tissue-selective ER-agonist activity in bone and is currently being evaluated in the ELAINE-III clinical trial [NCT05696626] in combination with abemaciclib for the treatment of ESR1-mutant advanced or metastatic ER+ breast cancer. Here, we investigated the physiological relevance of lasofoxifene's bone-selective ER-agonist activity and its impact on metastatic progression. Animal models of ovariectomy-induced osteoporosis were treated with lasofoxifene or standard endocrine therapies, and femurs were analyzed by histology and micro-CT histomorphometry. In parallel, anti-tumor effects of lasofoxifene were evaluated in vitro and in vivo in clinically relevant endocrine therapy-sensitive and -resistant primary and metastatic Patient-Derived Xenograft models. Additionally, drug synergism studies with lasofoxifene and the NCI NExT Oncology Interrogation Tools Set of 555 drugs were performed which identified pathways that were vulnerable to pharmacological inhibition in lasofoxifene-treated cells. We found that lasofoxifene protected against hormone withdrawal-induced bone loss and maintained a robust anti-tumor response in primary and metastatic models of ER+ breast cancer. Drug synergy screens have defined choices for rational combination with lasofoxifene to further potentiate its anti-tumor activity. Overall, this study supports the use of lasofoxifene-based treatment combinations which will concurrently protect bone architecture while suppressing ER+ metastasis progression in the bone niche.

Session PO.BCS01.02 - Application of Bioinformatics to Cancer Biology 2

1416 / 10 - Stress-responsive glucocorticoid receptor signaling shapes the immune tumor microenvironment in lung cancer

Presenter/Authors

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Disclosures

S. Akter, None..

A. Soliman, None..

Z. Madak-Erdogan, None..

S. J. Kim, None.

Abstract

Background: Racial disparities continue to exist in lung cancer, while Black individuals tend to smoke less than Whites, indicating potentially additional factors contribute to lung cancer risk. Our previous work showed that social stressors, including neighborhood violent crime, can shape tumor biology via stress-responsive mechanisms. In this study, we investigated how neighborhood violent crime influences tumor microenvironment with a focus on how glucocorticoid receptor activity impacts the spatial pattern of M2 macrophages and $CD8^+$ T cells as indicators of hot and cold immune phenotypes.

Methods: We analyzed 15 lung tumor spatial transcriptomic samples to quantify pathway activity and cell type associations using gene set co-regulation analysis (GESECA). Spatial co-localization was assessed using univariate and bivariate local Moran's I ($p < 0.05$). To enhance spatial resolution beyond the Visium spot size, we extracted latent spatial features using non-negative matrix factorization (NMF), estimated empirical variograms to characterize spatial autocorrelation, and applied ordinary kriging to generate high-resolution spatial maps.

Results: Neighborhood violent crime rates were positively correlated with glucocorticoid receptor activity, as evidenced by high expression of genes involved in the glucocorticoid biosynthesis pathway activity ($p < 0.05$). Regions with elevated glucocorticoid receptor activity also showed higher abundance of epithelial cells, especially in tumors from high-crime neighborhoods. High-resolution spatial maps further revealed that tumors from high-violent crime neighborhoods displayed strong co-localization between M2 macrophages and $CD8^+$ T cells, suggesting that $CD8^+$ T cells are surrounded by immunosuppressive myeloid cells, creating a functionally "cold" tumor microenvironment. In contrast, tumors from low-violent crime neighborhoods showed more mutually exclusive spatial patterns of M2 macrophages and $CD8^+$ T cells, reflecting a "hot" tumor microenvironment.

Conclusions: Our findings suggest that exposure to social stressors, such as neighborhood violent crime, may influence tumor biology by altering stress-responsive pathways and reshaping immune spatial architecture. The distinct hot and cold immune microenvironment may indicate differential treatment effectiveness across neighborhood contexts, potentially contributing to lung cancer disparities. Different immunotherapy strategies depending on immune tumor microenvironment to improve treatment effectiveness.

Session PO.PR01.04 - Metabolism and Microbiome in Cancer Initiation and Prevention

3626 / 12 - Early life exposures and cancer in adulthood: World Cancer Research Fund International's lifecourse research in cancer

Presenter/Authors

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Disclosures

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H. Croker, None..
P. Mitrou, None..
C. Clary, None..
J. Krebs, None..
M. Baskin, None..
M. van Zutphen, None.

Abstract

Background There is increasing recognition that exposure to certain risk factors in early life (defined as birth, childhood, adolescence, and young adulthood) impacts disease risk (including cancer) in adulthood. The identification of age-specific "windows of opportunity" also enables the development of refined cancer prevention recommendations tailored to different life stages. Despite this, there is a paucity of evidence related to how body size and weight, diet, nutrition, and physical activity in early life influences adult cancer risk. The strength of the available evidence-base has also not been assessed in a systematic way.

Methods WCRF International's Global Cancer Update Programme (CUP Global) undertook a collaboration with Wageningen University and Research (WUR) to conduct systematic literature reviews and meta-analyses focused on early-life exposures (birth size, body weight, and alcohol consumption) and risk of colorectal and breast cancer in adulthood. A 2nd collaboration with the International Agency for Research on Cancer (IARC) reviewed relevant biological mechanisms. The Global CUP Global Panel of Experts then interpreted and graded the evidence using pre-defined criteria to determine likely causal associations.

Results Key exposures during early life related to birthweight, body size and alcohol, as well as the biological mechanisms that underpin them, that impact future cancer risk were identified. For colorectal cancer, birthweight was associated with a 9% (95% confidence interval: 1.01-1.16) increased risk, increased BMI during childhood, adolescence and young adulthood were also associated with increased risk. For breast cancer, greater birth weight, length and taller height in childhood inferred an increased risk. Higher BMI in childhood, adolescence and young adulthood were associated with lower risk. Our Panel of Experts concluded that the evidence for several of the associations was strong enough to suggest a likely causal association. In the future, WCRF International will use these results and further discussions with experts in the field of lifecourse research, public health, and policy to develop guidance and recommendations for researchers, policy makers and the public.

Conclusion The current reviews of the epidemiological and mechanistic evidence demonstrate how exposures related to diet, nutrition, and bodyweight can impact cancer risk in adulthood. Understanding the associations between our early years and cancer risk in adulthood enables a better understanding of the aetiology of cancer, how risk factors impact cancer risk as we age, whether there are critical timepoints/windows for cancer risk, and how our environment impacts cancer risk. These findings, alongside a growing evidence-base, enable the development of cancer prevention policy and public health recommendations.

Session PO.CL05.02 - Adoptive Cell Therapy 2

5199 / 17 - uPAR-targeting CAR-NK cells enhance cytotoxicity against acute myeloid leukemia

Presenter/Authors

Xingliang Guo[1], Nadima Uprety[2], Rejeena Shrestha[2], Francia Reyes Silva[1], Sunil Acharya[2], Bijender Kumar[3], Bin Liu[2], Dexing Fang[2], Bingqian Hu[2], Sha Wang[2], May Daher[1], Ana K. Nunez Cortes[2], Corry Jones[2], LaTretta Harris[2], Vernikka Woods[2], Jerrell E. Scott[2], April Gilbert[2], Cornelio Santibanez[2], Katayoun Rezvani[2], Rafet Basar[1]

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Disclosures

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Abstract

Background: Relapsed/refractory acute myeloid leukemia (AML) remains difficult to treat, highlighting the need for new therapies. NK cell-based immunotherapy offers potent antitumor activity with low risk of GVHD or severe CRS. The urokinase plasminogen activator receptor (uPAR), encoded by *PLAUR*, is highly expressed on malignant and senescent cells while largely absent from healthy HSCs and most normal vital organs. We found *PLAUR* significantly upregulated in AML and confirmed strong uPAR surface expression on primary blasts. Based on this favorable profile, we developed an off-the-shelf uPAR-targeted CAR-NK platform with a CD28 costimulatory domain and secreted IL-15 to enhance persistence.

Methods: Cord blood-derived NK cells were preactivated with IL-12/15/18 and transduced to express (i) uPAR-CAR, (ii) IL-15, or (iii) uPAR-CAR/IL-15. CAR expression, cytokine production, and phenotype were assessed by flow cytometry, ELISA, and CyTOF, respectively. Antileukemic activity against AML cell lines (MV4-11, THP-1, OCI-AML3) and primary blasts was tested by IncuCyte real-time killing and Annexin V staining. Long-term activity was assessed by sequential tumor rechallenge. In vivo efficacy was evaluated in NSG mice engrafted with luciferase-labeled OCI-AML3 and treated with a single NK infusion.

Results: uPAR was highly expressed on AML blasts but minimal on healthy HSCs/HSPCs, confirming its suitability as a CAR-NK target. uPAR-CAR/IL-15 NK cells were efficiently generated, secreted IL-15, and expanded robustly. In vitro, they showed markedly enhanced and antigen-specific killing of all uPAR+ AML lines and primary blasts compared with CAR-only, IL-15-only, or non-transduced NK cells ($p < 0.0001$), while *PLAUR*-knockout cells resisted killing. uPAR-CAR/IL-15 NK cells produced more IFN-γ and TNF-α and maintained superior function during repeated tumor exposure, with CyTOF revealing an activation/cytotoxicity-enriched metacluster. In vivo, a single uPAR-CAR/IL-15 NK infusion significantly reduced leukemia burden, delayed progression, and improved NK persistence in bone marrow. Compared with non-transduced NKs, tumor burden in peripheral blood ($p < 0.05$), bone marrow ($p = 0.001$), and spleen ($p < 0.01$) was substantially reduced, with no observed toxicity or weight loss. Taken together, uPAR is a safe, selective AML target. uPAR-CAR NK cells, particularly when armored with IL-15, display potent, antigen-specific, and durable antileukemic activity, supporting advancement of this platform for AML therapy.

Session PO.CL11.01 - Biological and Clinical Consequences of Cancer Therapy

5226 / 17 - The role of pancreatic adenocarcinoma cancer-stromal interactions on cardiac structure and function

Authors

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Disclosures

A. E. Gibson, None..
E. Mezzaroma, None.

Abstract

Pancreatic ductal adenocarcinoma (PDAC) has a dismal 5-year survival of <13% despite advances in therapy. Patients with PDAC also experience significantly lower cardiac-specific median survival compared to those with other GI cancers. While cancer cachexia impacts survival through skeletal muscle loss, the contribution of cardiac function to outcomes in PDAC is unknown. We aim to evaluate cardiac tissue structure and function in the most representative human preclinical model. This will provide insight into cardiac remodeling associated with PDAC and its clinical implication for possible interventions to improve overall survival. We implanted a PDAC patient-derived xenograft (PDX) into five NSG mice heterotopically and five NSG mice orthotopically, with five NSG mice receiving sham surgeries as controls. Tumor volumes were monitored weekly and once reaching 1.5cm, echocardiography and Millar catheterization were performed to assess cardiac structure and function between the three groups. Cardiac muscle, gastrocnemius muscle and tumors were collected for histologic and molecular analysis, including staining for structural assessment RNA sequencing to assess for changes associated with tumor burden, which is ongoing. An ANOVA and simple unpaired t-test were used with a significance value set at $p < 0.05$.Global longitudinal strain (GLS) measured by echocardiogram was within the normal values (-18 to -25%) across the groups, with no significant difference between the means of the sham (−20.3%), heterotopic (−21.2%), and orthotopic (−19.9%) groups. However, there is a slight trend showing a decline in GLS in the orthotopic group compared to the control group. The PV Loop data show a decline in left ventricular compliance (EDPVR) means in the heterotopic group (0.86) and orthotopic group (1.06) compared to the control group (0.22). The orthotopic group EDPVR mean is statistically different from the control group mean, with a simple unpaired t-test p-value of 0.02. The slight reduction in GLS observed in the orthotopic group relative to controls may indicate the presence of early systolic impairment in PDAC-bearing mice. Additionally, the results suggest that tumor burden is associated with impaired EDPVR, with the orthotopic group showing more stiffening as evidenced by a significantly elevated EDPVR when compared to the control group. This may indicate early diastolic dysfunction in the context of tumor related cardiac remodeling. We also anticipate that PDAC bearing mice will exhibit cardiac tissue remodeling, characterized by histological changes and transcriptional alterations linking cardiac decline and cancer progression. Recognizing early cardiac changes in patients with PDAC will help identify interventions that may ultimately improve treatment tolerance and clinical outcomes.

Session PO.CL05.04 - Immune Checkpoint Blockade

6560 / 26 - Targeting fitness surveillance restores T-cell immunity and sensitizes solid tumors to immune checkpoint inhibitors

Presenter/Authors

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Disclosures

A. Kumar, None..
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P. Bhoopathi, None..
E. Madan, None..
R. Gogna, None.

Abstract

Immune checkpoint inhibitors (ICIs) fail in most solid tumors despite their transformative success in a minority of patients. Here, using integrated human tumor profiling and humanized patient-derived xenograft (PDX) models, we identify Flower-mediated fitness elimination as a dominant, conserved mechanism of T-cell attrition that limits ICI efficacy across epithelial cancers. Stromal compartments in high-grade serous ovarian cancer, non-small-cell lung cancer, colorectal cancer, hepatocellular carcinoma, and pancreatic ductal adenocarcinoma exhibit high Flower-Lose expressioncoupled to severe $CD8^+$ T-cell exclusion. Tumor-infiltrating T-cells themselves acquire a “loser” state marked by elevated Flower-Lose, rendering them vulnerable to competitive elimination by the stromal niche.

Across five orthotopic humanized PDX tumor types and three independent cohorts, ICIs alone produced minimal T-cell restoration, persistent metastatic dissemination, and negligible survival benefit (e.g., median ≈42 days). In contrast, pharmacologic blockade of Flower signaling increased intratumoral T-cell density by 5-7-fold (MixedLM $P < 10^{-15}$), reduced metastatic burden by 54-75%, suppressed tumor growth by >90%, and produced durable survival benefit across all models, with median survival not reached and strong meta-analytic significance ($Z = 10.56$, $P < 10^{-25}$).

Together, these findings reveal Flower-mediated fitness surveillance as a pan-cancer, tissue-level barrier to immunotherapy and establish Flower blockade as a universally effective strategy to restore T-cell persistence and unlock durable ICI responses across historically immune-cold solid tumors.

Session PO.CT01.04 - Phase II Clinical Trials

CT240 / 5 - IOB-032/PN-E40: A phase 2 study of neoadjuvant/adjuvant IO102-IO103 cancer vaccine plus pembrolizumab in resectable HNSCC

Authors

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Disclosures

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Abstract

Abstract is embargoed at this time.

Session LBPO.ET02 - Late-Breaking Research: Experimental and Molecular Therapeutics 2

LB199 / 21 - High-plex spatial transcriptomics reveals triplatin-induced DNA damage signaling and tumor-fibroblast niche reprogramming in pancreatic cancer PDX models

Presenter/Authors

Praveen Bhoopathi[1], Khoa L. A. Huynh[2], Erica J. Peterson[3], Vashti Bandy[4], Anna Gibson[4], Vignesh Vudatha[4], Arunima Punjala[4], Dongyu Zhang[4], Jinze Liu[2], J Chuck Harrell[5], Nicholas P. Farrell[6], Jose G. Trevino[1]

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P. Bhoopathi, None..
K. L. A. Huynh, None..
E. J. Peterson, None..
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A. Gibson, None..
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D. Zhang, None..
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N. P. Farrell, None..
J. G. Trevino, None.

Abstract

Abstract is embargoed at this time.

Session LBPO.PR01 - Late-Breaking Research: Prevention, Early Detection, and Interception

LB217 / 15 - Case-control study of melatonin metabolite excretion and colorectal adenoma formation

Authors

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Abstract

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Session PO.CL01.16 - Prognostic Biomarkers 2

3944 / 19 - The impact of diversity on transcriptional heterogeneity of skeletal muscle from pancreatic ductal adenocarcinoma patients

Presenter/Authors

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Disclosures

P. Bhoopathi, None.. **V. Vudatha,** None.. **A. Punjala,** None.. **V. Bandy,** None.. **A. Gibson,** None.. **D. Zhang,** None.. **K. M. Tyc,** None.. **M. Dozmorov,** None.. **J. Ducharme,** None.. **M. Schonk,** None.. **B. Poole,** None.. **S. Judge,** None.. **L. Fernandez,** None.. **A. R. Judge,** None.. **J. G. Trevino,** None.

Abstract

Objective: Cachexia plays a major role in the morbidity and mortality of pancreatic ductal adenocarcinoma (PDAC) patients. The objective of this study is to delineate the molecular pathways of muscle that contribute to cancer cachexia from surgically resected PDAC patients. Methods: At surgical resection for PDAC, rectus abdominus muscle was sharply divided and shock frozen immediately for RNA-seq. Total RNA was extracted from the frozen tissue using standard protocols, and RNA integrity was confirmed prior to library preparation. The resulting high-quality RNA was then used for RNA sequencing (RNA-seq) analysis to find distinct variants in addition to a core transcriptional signature of roughly 13,007 frequently expressed transcripts, differential transcript expression was evaluated. KEGG pathways and MSigDB collections (Hallmark, Curated, GO signatures) were used in Gene Set Enrichment Analysis (GSEA), which uses both fold change and ranking of differentially expressed genes (DEGs) to find enriched biological pathways.
Results: Significant transcriptome variations in muscle tissue were found to be associated with patient race and survival. MSigDB gene sets comparing Black and White) patients revealed that the AA cohort had higher activation of pathways linked to inflammation, cardiomyopathy, and muscle atrophy/proteostasis. Three overlapping genes were found by cross-referencing these pathways with significant DEGs: CYP4B1, DDIT4 (upregulated in AA, significantly related with muscular atrophy/cachexia), and GINS1 (downregulated in AA, associated with proliferation). Additionally, eight genes including the physiologically significant genes ADAM28, SENCR, and MEG8 (related with muscle differentiation and tumor progression) were found to be substantially associated with overall survival.
Conclusion: RNA-seq and GSEA of muscle tissue provide critical insights into the systemic molecular alterations associated with PDAC. The identified pathways and genes, particularly those demonstrating racial and survival-associated heterogeneity (e.g., DDIT4, GINS1), represent potential biomarkers and therapeutic targets for addressing muscle dysfunction and cachexia in PDAC.

Session PO.CL01.17 - Prognostic Biomarkers 3

5373 / 11 - Prognostic impacts of skeletal muscle gene expression and cachexia in advanced colorectal cancer

Presenter/Authors

Vashti L. Bandy[1], Arunima Punjala2, Praveen Bhoopathi[1], Vignesh Vudatha[1], KATARZYNA TYC[1], Mikhail G. Dozmorov[1], Leopoldo Fernandez[1], Andrew R. Judge[3], Sarah M. Judge[4], Anna Gibson[5]

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Disclosures

V. L. Bandy, None.

Abstract

Background: Cancer cachexia is a complex metabolic syndrome characterized by severe muscle loss, reduced physical function, and diminished therapeutic response. Despite its clinical impacts, the transcriptional landscape of cachexia in patients with advanced peritoneal carcinomatosis from metastatic colorectal cancer (pmCRC) remains poorly defined. Our study aims to characterize alterations in skeletal muscle with associated cachexia in pmCRC patients.

Methods: Muscle biopsies were obtained from 17 pmCRC patients consented for IRB tissue collection and undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), classified as myopenic (n=7) or non-myopenic (n=11) based on skeletal muscle index (SMI cm2/m2). Biopsies were sent for RNA sequencing and differential expression analysis was performed utilizing statistical algorithms within edgeR software. We compared the two cohorts and selected differentially expressed genes (DEGs) with significantly increased or decreased expression (>2-fold change and p-value <0.05). Enrichment analysis identified gene sets and pathways relevant to cachexia pathophysiology. Last, survival analysis was performed to assess the prognostic value of identified DEGs in predicting patient outcomes.

Results: Our analysis revealed 231 genes DEGs, including 75 upregulated and 156 downregulated genes in the myopenic group. Enrichment analysis exhibited several pathways involved in immune cell signaling. Overall survival analysis revealed associations with survival outcomes for seven DEGs-six of which have associated prognostic value in colorectal cancer or other cancer variants including pancreatic adenocarcinoma, hepatocellular carcinoma, renal cell carcinoma and oral squamous cell carcinoma. High expression of one DEG and low expression of the remaining prognostic genes were linked with poor survival in our patient cohort.

Conclusions: Our study highlights molecular features of cancer-induced cachexia in pmCRC and several potential diagnostic and prognostic biomarkers.

Session PO.ET03.04 - Overcoming Chemotherapy Resistance

3109 / 9 - Extracellular matrix glycan signatures predict chemotherapy response in ovarian cancer

Authors

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Disclosures

E. J. Peterson, Bioplatinum Technologies LLC), Travel, Other Intellectual Property R. J. Weiss, None.. J. D. Hampton, None. A. R. S. Beaudin, Bioplatinum Technologies LLC Employment, Travel. T. M. Clausen, VAR2 Pharmaceuticals Employment, Other Intellectual Property. J. B. M. Turner, None.. A. Basu, None.. B. Hu, None.. J. E. Koblenski, None. N. P. Farrell, Bioplatinum Technologies LLC Employment, Travel, Other Intellectual Property. L. Litovchick, None.

Abstract

Background: Ovarian cancer (OC) is a highly lethal gynecologic malignancy, most often diagnosed at advanced stages and prone to recurrence after platinum-based chemotherapy. Nearly 30% of patients exhibit platinum-resistant or refractory disease, with aggressive tumors recurring within six months. Emerging evidence implicates glycosaminoglycans (GAGs) as regulators of tumor progression and treatment response, yet their structural complexity limits accurate assessment by transcriptomic or proteomic methods alone.

Methods: To define how GAGs influence OC biology and platinum sensitivity, we analyzed single-cell RNA sequencing and spatial transcriptomic datasets from normal ovary, primary ovarian/fallopian tube tumors, and metastatic abdominal and colonic lesions. CRISPR/Cas9 XYLT1/2 knockout was used to deplete GAGs in ovarian cancer cells, which were evaluated for morphology, proliferation, migration/invasion, and in vivo tumor behavior. To directly quantify tumor GAG composition, glycan reductive isotope labeling mass spectrometry was performed on OC patient-derived xenografts (with known carboplatin response profiles. Complementary pharmacology studies evaluated efficacy and drug distribution of carboplatin and Triplatin, a GAG-targeting platinum agent.

Results: Single-cell analysis revealed that fibroblasts are the predominant source of proteoglycan gene expression within the tumor microenvironment. Spatial transcriptomics analysis of precursor and invasive lesions showed these changes occur in the later stages of ovarian cancer development. XYLT1/2 knockout cells showed a shift from mesenchymal to epithelial morphology, decreased migration/invasion potential, reduced tumor dissemination and absence of ascites, and increased sensitivity to carboplatin associated with higher drug penetration into the tumor. GRIL-MS profiling of four OC PDX models identified chondroitin-4-sulfate (C4S) as the dominant tumor-associated GAG motif, with high C4S strongly correlating with carboplatin resistance. Importantly, elevated C4S reduced carboplatin efficacy but enhanced Triplatin uptake and antitumor activity. A C4S expression threshold stratified tumors by predicted response, and analysis of patient tissue microarrays showed that 40-83% of OC tumors exceed this cut-off depending on subtype.

Conclusions: GAGs play a central role in ovarian cancer progression, dissemination, and platinum resistance. C4S is a mechanistically grounded biomarker capable of predicting differential sensitivity to carboplatin and Triplatin, supporting its integration into precision-medicine strategies and the clinical evaluation of Triplatin for patients with C4S-high, platinum-resistant ovarian cancer.

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Session PO.MCB02.01 - Cell Death Regulation and Therapeutic Resistance in Cancer

4676 / 25 - Therapeutic exploitation of AUTAC in hematologic malignancies with cardiac protection

Presenter/Authors

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Disclosures

A. M. Elshazly, None.. **N. Hosseini,** None.. **S. K. Radhakrishnan,** None.

Abstract

Background: Myeloid cell leukemia-1 (Mcl1) is a critical member of the Bcl2 family that plays an essential role in regulating apoptosis and maintaining mitochondrial integrity, particularly within cardiac tissue. While Mcl1 overexpression is a major driver of resistance to multiple anticancer therapies, its pharmacologic inhibition has been hampered by dose-limiting cardiotoxicity, representing a significant and unresolved challenge in cardio-oncology. The development of safer therapeutic strategies that selectively target Mcl1 in cancer cells while sparing cardiac cells remains a high-priority goal. In this study, our group investigated a novel autophagy-targeting chimera (AUTAC) designed to selectively degrade Mcl1 via the autophagy-lysosomal pathway. We aimed to determine whether AUTAC could induce selective cytotoxicity in multiple myeloma cells while preserving cardiac cell viability and mitochondrial function.

Methods: Multiple myeloma cell lines (U266B1, RPMI-8226) and cardiac cell lines (AC16, H9c2) were used as tumor and cardiac models, respectively. Cell viability was assessed using the CellTiter-Glo assay and IncuCyte live-cell imaging. Mitochondrial membrane potential was measured by TMRE fluorescence. Effects of AUTAC on Mcl1 and autophagy dynamics were evaluated by Western blotting, confocal microscopy, and inhibition studies with 3-methyladenine (3-MA) and chloroquine (CQ). To confirm autophagy dependence, ATG5 was knocked down using shRNA.

Results: Treatment with AUTAC selectively induced lysosomal degradation of Mcl1, without detectable effects on other anti-apoptotic Bcl2 family members, including Bcl2 and BclxL. Pharmacological inhibition of autophagy with 3-MA (early-stage inhibitor) or CQ (late-stage inhibitor) effectively blocked AUTAC-mediated Mcl1 degradation, confirming that the process required an intact autophagy-lysosomal pathway. Furthermore, knockdown of ATG5 abolished Mcl1 reduction, reinforcing the autophagy dependence of this degradation mechanism. Functionally, AUTAC treatment led to a greater than 50% reduction in cell viability in U266B1 and RPMI-8226 multiple myeloma cells, accompanied by increased apoptotic signaling. In contrast, AUTAC caused minimal cytotoxicity in AC16 and H9c2 cells, maintaining mitochondrial function and morphology. Compared with conventional Mcl1 inhibitors, AUTAC exhibited substantially reduced cardiotoxicity, underscoring its favorable safety profile.

Conclusions: Targeted lysosomal degradation of Mcl1 via AUTAC represents a promising therapeutic strategy that repurposes autophagy for selective oncogenic protein removal. AUTAC effectively degraded Mcl1 in malignant cells while sparing cardiac cells from apoptosis and mitochondrial injury, highlighting its potential as a next-generation, cardio-safe alternative to conventional Mcl1 inhibitors.

Session PO.PS01.11 - Psychosocial and Behavioral Epidemiology, Health Services Research, Implementation Science, Pharmacoepidemiology, and Other Topics

7577 / 25 - Advancing the science, practice and impact of COE

Presenter/Authors

Kimlin Ashing[1], CHARNITA ZEIGLER-JOHNSON[2], Hayley S. Thompson[3], Kim Rhoads[4], Nadine Barrett[5], Lisa Carter Bawa[6], Timiya S. Nolan[7], Monica Baskin[8], Vanessa B. Sheppard[9], Marvella E. Ford[10], Erica Phillips[11], Lorna H. McNeill[12], Folakemi T. Odedina[13]

[1]City of Hope National Medical Center, Duarte, CA,[2]Fox Chase Cancer Center, Philadelphia, PA,[3]Wayne State University School of Medicine, Huntington Woods, MI,[4]University of San Francisco, San Francisco, CA,[5]Wake Forest University, Winston-Salem, NC,[6]Georgetown University, Washington DC, WA,[7]University of Alabama at Birmingham, Birmingham, AL,[8]UPMC Hillman Cancer Center, Pittsburgh, PA,[9]Virginia Commonwealth University, Richmond, VA,[10]Associate Director of Cancer Disparities, Medical University of SC Hollings Cancer Center, Charleston, SC,[11]Division of General Internal Medicine, Weill Cornell Medicine, New York, NY,[12]UT MD Anderson Cancer Center, Houston, TX,[13]Mayo Clinic Florida, Jacksonville, FL

Disclosures

K. Ashing, None.. C. Zeigler-johnson, None.. K. Rhoads, None.. N. Barrett, None.. L. Carter Bawa, None.. T. S. Nolan, None.. V. B. Sheppard, None.

Abstract

Introduction: COE has become the gold standard in addressing health disparities. COE's value is emphasized by NIH and leading cancer-related organizations e.g., AACR. The Alliance for COE (The Alliance) mission is to advance the art, science, and impact of COE; promote community health and wellness; and reduce cancer burden and disparities. Methods: This abstract builds on the Alliance's Science of Community Outreach and Engagement (SoCOE) Conference a NCI R13 funded series. SoCOE Conference is organized by 10 NCI-designated Cancer Centers to provide a platform for COE academic-clinical-policy-community stakeholders to share best practices for solution-focused community responsive cancer prevention, diagnostics, therapeutics and survivorship research and practice. Results: > 500 researchers, clinicians, policymakers, healthcare administrators, with >12% being survivors and/or advocates, participated in our SoCOE Conferences. The delegates' recommendations are:
Decentralize who/entities that hold all the power in science and clinical research (trials). Communities hold valuable, necessary wisdom and resources to inform and guide science Include multisectoral partners early and always Community capacity building and compensation with gratitude Mentoring of junior COE researchers, clinicians, policymakers, healthcare administrators, survivors and advocates with humility is a must Develop virtual communities to share best practices across cancer centers and within regions Develop working groups to identify and explore commonalities across COE work in rural/urban, diverse/homogenous spaces Publish Science of COE papers on various topics related to COE Frameworks and evidenced-solutions Provide community reports on best practice guide that can be widely available to be shared locally and in-person, and digitally Partner and learn from COE teams working with other cultural/ethnic groups Attend to, measure and remedy societal/social drivers of health disparities that mirror barriers to care, and research engagement and participation.
Discussion: Informed by our community advisory boards and the findings for our SoCOE Conferences, we present the pillars of the Alliance to tackle population cancer burden and disparities: Training future COE leaders/advocates, Advocating for public health policies/guidelines, Increasing access to cancer prevention and care that will also increase access to studies, Engaging and partnering with multisectoral stakeholders and communities, Building community capacity, Advancing COE science through catchment-relevant research, and Leading bi-directional communication and information and resource sharing between catchment area communities and cancer centers. The expectation and impact of COE can only be achieved if COE teams are valued, supported cancer center members with community advisory boards and community as cancer centers' priority population.

Presentation:

Session PDS01 - Grant Writing Workshop: Tips for Success from Experienced Scientists
- Preliminary data and research strategy

Presenter/Authors

Katherine Y. Tossas. VCU Massey Comprehensive Cancer Center, Richmond, VA

Abstract

There is no abstract associated with this presentation.

Presentation:

Session DC10 - Advancing Patient-Centered Clinical Trials: Bringing Trials to Patients and Patients to Trials
- The impact of a community-focused approach

Presenter/Authors
Robert A. Winn. VCU Massey Comprehensive Cancer Center, Richmond, VA

Abstract:
Abstract not available

Presentation:
Session PO.BCS01.01 - Application of Bioinformatics to Cancer Biology 1
61 / 23 - Defining spatial biomarkers of survival across solid tumors using a pan-cancer proteomics atlas

Presenter/Authors
Khoa Huynh[1], Joaquin Reyna[1], Bruno Matuck[2], KEVIN BYRD[3], Jinze Liu[4]

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Disclosures
K. Huynh, None.. J. Reyna, None.. B. Matuck, None.

Abstract
The spatial architecture of the tumor microenvironment (TME) governs cancer progression and therapeutic response, yet pan-cancer analyses linking multicellular organization to patient survival remain unclear. As part of the PROSPECTS (Pancancer Reconstruction Of Spatial Profiles and Therapeutic TargETs) Initiative, we assembled a large-scale spatial proteomic atlas comprising 415 patients across six major malignancies: Head and Neck Squamous Cell Carcinoma (HPV-positive and HPV-negative), Lung Cancer (NSCLC and LUAD), Triple-Negative Breast Cancer, High-Grade Serous Ovarian Cancer, Colorectal Adenocarcinoma, and Hepatocellular Carcinoma (HCC). Our dataset includes over 1,000 tissue cores and over 4.4 million single cells with balanced representation across indications: HNSCC (1,218,385 cells, 145 patients), Lung (906,537 cells; 63 patients), Breast (765,232 cells; 60 patients), Ovarian (590,945 cells; 53 patients), Colorectal (511,610 cells; 37 patients), and Liver (474,237 cells; 57 patients). Using a 30-plex antibody Phenocycler, we spatially mapped 15 major cell types at single-cell resolution. We developed a next-generation multi-scale computational pipeline within AstroSuite (Stratica Biosciences), integrating TACIT and Constellation algorithms to quantify TME architecture at the levels of cell state, intercellular distance, and higher-order motifs including pairwise, triplet, and quartet cellular neighborhoods. These deep spatial metrics were linked to overall survival with adjustment for clinical covariates. We identified marked heterogeneity in TME structure, with each cancer type exhibiting distinct prognostic architectures. In TNBC, Tumor Cell-Neutrophil interactions emerged as one of the strongest adverse prognostic features (P=0.00001). In Lung cancers, vascular-immune and stromal-tumor interfaces were key, particularly vascular endothelial cell-Macrophage adjacency (P=0.0003) and Fibroblast-Tumor Cell interactions (P=0.002). Despite these cancer-specific patterns, PROSPECTS uncovered conserved spatial signatures. A recurrent fibroblast-tumor cell interface motif appeared across malignancies, though stromal drivers varied: Myofibroblast-Treg interactions were prognostic in Colorectal cancer (P=0.002), while Fibroblast-Treg interactions predicted outcome in Ovarian cancer (P=0.002). In HCC, immune-to-immune interactions such as Treg-B Cell crosstalk (P=0.002) were significantly associated with survival. Complex spatial syntax proved superior to simple pairwise interactions for prognosis, highlighting the value of higher-order TME modeling. This work establishes the first pan-cancer spatial proteomic comparison linking TME organization to clinical outcome, revealing that spatially resolved cellular interaction networks constitute a new class of clinically actionable biomarkers.

Presentation:

Session PO.BCS01.02 - Application of Bioinformatics to Cancer Biology 2

1416 / 10 - Stress-responsive glucocorticoid receptor signaling shapes the immune tumor microenvironment in lung cancer

Presenter/Authors

Sabrina Akter[1], Aiman Soliman[2], Robert A. Winn[3], Zeynep Madak-Erdogan[1], Sage J. Kim[4]

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Disclosures

S. Akter, None.. A. Soliman, None.. Z. Madak-Erdogan, None.. S. J. Kim, None.

Abstract

Background: Racial disparities continue to exist in lung cancer, while Black individuals tend to smoke less than Whites, indicating potentially additional factors contribute to lung cancer risk. Our previous work showed that social stressors, including neighborhood violent crime, can shape tumor biology via stress-responsive mechanisms. In this study, we investigated how neighborhood violent crime influences tumor microenvironment with a focus on how glucocorticoid receptor activity impacts the spatial pattern of M2 macrophages and $CD8^+$ T cells as indicators of hot and cold immune phenotypes.

Methods: We analyzed 15 lung tumor spatial transcriptomic samples to quantify pathway activity and cell type associations using gene set co-regulation analysis (GESECA). Spatial co-localization was assessed using univariate and bivariate local Moran's I ($p < 0.05$). To enhance spatial resolution beyond the Visium spot size, we extracted latent spatial features using non-negative matrix factorization (NMF), estimated empirical variograms to characterize spatial autocorrelation, and applied ordinary kriging to generate high-resolution spatial maps.

Results: Neighborhood violent crime rates were positively correlated with glucocorticoid receptor activity, as evidenced by high expression of genes involved in the glucocorticoid biosynthesis pathway activity ($p < 0.05$). Regions with elevated glucocorticoid receptor activity also showed higher abundance of epithelial cells, especially in tumors from high-crime neighborhoods. High-resolution spatial maps further revealed that tumors from high-violent crime neighborhoods displayed strong co-localization between M2 macrophages and $CD8^+$ T cells, suggesting that $CD8^+$ T cells are surrounded by immunosuppressive myeloid cells, creating a functionally "cold" tumor microenvironment. In contrast, tumors from low-violent crime neighborhoods showed more mutually exclusive spatial patterns of M2 macrophages and $CD8^+$ T cells, reflecting a "hot" tumor microenvironment.

Conclusions: Our findings suggest that exposure to social stressors, such as neighborhood violent crime, may influence tumor biology by altering stress-responsive pathways and reshaping immune spatial architecture. The distinct hot and cold immune microenvironment may indicate differential treatment effectiveness across neighborhood contexts, potentially contributing to lung cancer disparities. Different immunotherapy strategies depending on immune tumor microenvironment to improve treatment effectiveness.

Presentation:

Session SS08 - Stand Up To Cancer Scientific Session: Strategies Towards Overcoming Cancer Health Disparities

- Bold approaches to lung cancer screening

Presenter/Authors

Robert A. Winn. VCU Massey Comprehensive Cancer Center, Richmond, VA

Abstract

There is no abstract associated with this presentation.

Presentation:

Session PDS05 - Navigating a Path to a Successful Career in Cancer Research

- Building effective collaborations: Working effectively in a team

Presenter/Authors

Katherine Y. Tossas. VCU Massey Comprehensive Cancer Center, Richmond, VA

Abstract

There is no abstract associated with this presentation.

Presentation:

Session PO.PS01.11 - Psychosocial and Behavioral Epidemiology, Health Services Research, Implementation Science, Pharmacoepidemiology, and Other Topics

7577 / 25 - Advancing the science, practice and impact of COE

Presenter/Authors

Kimlin Ashing[1], CHARNITA ZEIGLER-JOHNSON2, Hayley S. Thompson[3], Kim Rhoads[4], Nadine Barrett[5], Lisa Carter Bawa[6], Timiya S. Nolan[7], Monica Baskin[8], Vanessa B. Sheppard[9], Marvella E. Ford[10], Erica Phillips[11], Lorna H. McNeill[12], Folakemi T. Odedina[13]

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Abstract

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Presentation:
Session PDS10 - Special Program for High School Students: The Conquest of Cancer and the Next Generation of Cancer Researchers
- Understanding cancer

Presenter/Authors

Jose G. Trevino. VCU Massey Cancer Center, Richmond, VA

Abstract

There is no abstract associated with this presentation.