Presentation Abstracts

Survivin inhibitor 7I14 synergizes with docetaxel in castration-resistant prostate cancer by disrupting survivin dimerization and inducing its proteasome-dependent degradation

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Survivin, the smallest member of Inhibitor of Apoptosis Protein (IAP) family, forms homodimers and coordinates with other IAPs to inhibit apoptosis by suppressing caspase 3/9 activation, contributing to drug resistance. Due to its overexpression in cancer cells and lack of expression in normal adult tissues, survivin is an attractive cancer target. However, developing survivin-selective inhibitors has been challenging due to the absence of suitable active sites for targeting. Strategies have been pursued to inhibit survivin expression by targeting its upstream transcriptional regulators, including YM155, which unexpectedly exhibits poor pharmacokinetics and is a multitarget compound. We recently developed a novel approach to directly disrupt its dimerization, thereby exposing the hydrophobic interface and promoting proteasome-mediated degradation. Compound 7I, a quinoxaline-based survivin degrader, likely interacts with key residues for survivin dimerization via π-π interactions. Thus, we hypothesized that electron-withdrawing groups on 7I enhance its binding to survivin. To test this hypothesis, we synthesized a series of 7I analogs and identified two improved leads, 7I10 and 7I14, with up to 20-fold greater activity, selectively degrading survivin in castration-resistant prostate cancer (CRPC) cell lines C4-2 and PC-3. 7I10 and 7I14 specifically degrade survivin over other IAP members via the proteasome-mediated pathway, and they can dissociate the dimeric survivin and also block the survivin dimerization. Consequently, 7I10 and 7I14 dose-dependently induced spontaneous apoptosis and synergized with docetaxel, a first-line therapy for metastatic CRPC. In a PC-3 xenograft model, 7I14 at 15 mg/kg administered via IP twice per week effectively suppressed tumor growth and enhanced docetaxel's effects by degrading survivin, with no added toxicity, as assessed by body weight, white blood cell counts, and hemoglobin levels. Therefore, targeting survivin's dimerization domain is a promising strategy for its degradation, and 7I10 and 7I14 have potential as single agents or in combination with docetaxel for treating metastatic CRPC.

MTA-Cooperative Targeting of PRMT1: A Novel Therapeutic Strategy

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Cancer-specific metabolic vulnerabilities provide opportunities for selective therapeutic intervention. Homozygous deletion of methylthioadenosine phosphorylase (MTAP), a frequent event across cancers due to its proximity to the CDKN2A tumor-suppressor locus, leads to accumulation of 5′-methylthioadenosine (MTA), an endogenous inhibitor of protein arginine methyltransferase 5 (PRMT5). This liability has been successfully exploited by MTA-cooperative PRMT5 inhibitors (MTA:PRMT5i), which selectively target *MTAP*-deficient tumors.

Here, we tested whether this paradigm can be extended to other S-adenosylmethionine-dependent methyltransferases. Analysis of shRNA dependency datasets identified PRMT1, the major type I arginine methyltransferase responsible for asymmetric dimethylarginine (ADMA), as a top candidate exhibiting synthetic lethality with MTAP loss. Given the functional interplay between PRMT1 and PRMT5, together with the emergence of resistance to PRMT5 inhibitors, PRMT1 represents a compelling complementary therapeutic target.

To identify MTA-cooperative PRMT1 inhibitors (MTA:PRMT1i), we implemented an AI-guided virtual screening pipeline integrating molecular docking and machine learning. Approximately one million ZINC20 compounds were docked into multiple PRMT1 conformations to train a predictive model (PyRMD), which was subsequently applied to screen approximately 48 million compounds from the Enamine REAL library. Top-ranked candidates were prioritized, yielding ~200 compounds for experimental evaluation.

We identified a lead compound that selectively inhibited ADMA levels and induced preferential cytotoxicity in *MTAP*-knockout (*MTAP-KO*) isogenic cancer cell lines compared with wild-type (WT) controls. Target engagement was confirmed by the cellular thermal shift assay (CETSA), demonstrating direct binding of the compound to PRMT1 in cells.

Conclusion: These findings establish the feasibility of MTA-cooperative targeting of PRMT1 and support the development of MTA:PRMT1 inhibitors as a promising therapeutic strategy for MTAP-deficient cancers, particularly in combination with MTA:PRMT5 inhibitors or in the setting of acquired PRMT5 inhibitor resistance.

From Escape to Release: Engineering Lipid Nanoparticles for Efficient Intracellular RNA Delivery

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Introduction: Lipid nanoparticles (LNPs) have transformed nucleic acid therapeutics by enabling the clinical translation of RNA-based medicines. However, inefficient intracellular delivery remains a critical barrier limiting their potency and broader therapeutic applications. While endosomal escape has long been considered the primary bottleneck, effective RNA delivery requires overcoming multiple sequential intracellular barriers, including both cytosolic access and subsequent cargo release.

Methods: Here, we present two complementary biomaterials engineering strategies designed to overcome key intracellular limitations in LNP-mediated nucleic acid delivery. First, we developed salt-loaded lipid nanoparticles (SLNPs), an osmotic pressure–driven platform that enhances endosomal escape by introducing sodium chloride into the nanoparticle core. Following endocytosis, encapsulated salt generates localized osmotic forces that promote endosomal destabilization and facilitate cytosolic delivery through a mechanism distinct from conventional ionizable lipid–mediated membrane disruption. Second, we systematically tuned ionizable lipid composition to investigate how mRNA–LNP interactions regulate intracellular cargo availability after endosomal escape.

Results: SLNPs significantly enhanced functional nucleic acid delivery across multiple cargos and clinically relevant LNP formulations by improving endosomal escape while maintaining favorable biocompatibility. Beyond endosomal escape, we identified intracellular mRNA dissociation from LNP carriers as a previously underrecognized barrier controlling translational efficiency. Optimizing ionizable lipid content promoted efficient mRNA release from LNPs, leading to improved protein expression despite comparable cellular uptake and endosomal escape.

Conclusion: Together, these studies redefine the intracellular delivery cascade of RNA-LNP systems by demonstrating that successful delivery requires both efficient endosomal escape and timely cargo release. These findings establish new design principles that balance nanoparticle stability, membrane disruption, and RNA accessibility, providing a framework for engineering next-generation LNP platforms with enhanced potency and translational potential.

Proteolysis-targeting chimeras (PROTACs) as an effective strategy for targeting epigenetic factors

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Proteolysis targeting chimeras (PROTACs) are heterobifunctional small molecules with an E3 ubiquitin ligase binding moiety linked to a protein of interest (POI) binding moiety. The induced proximity leads to selective polyubiquitination of the POI, followed by its degradation by the ubiquitin-proteasome system (UPS). The main advantage of PROTACs over traditional occupancy-driven small-molecule inhibitors is that PROTACs can completely deplete the POI, thereby eliminate its oncogenic functions and deliver potentially more robust therapeutic effects than inhibitors. Specifically, PROTACs are more effective than inhibitors at targeting epigenetic factors, as many epigenetic factors have enzymatically independent functions, such as EZH2, which has a critical scaffold function. Altogether, PROTACs are promising therapeutic modalities. In my lab, we have successfully developed and patented several novel small-molecule AKT degraders and AURKB degraders together with Dr. Jian Jin. Recently, we discovered and developed a novel PROTAC degrader for targeting NSD2 in Triple-Negative Breast Cancer (TNBC). We discovered that NSD2 degradation with a PROTAC degrader or depletion via CRISPR knockout could activate estrogen signaling pathways. Mechanistically, we found that NSD2 represses Estrogen Receptor (ER) gene expression through a scaffold function that is distinct from its known canonical gene-activation function via H3K36me2 deposition. In addition, NSD2 depletion alters breast cancer lineage plasticity, converting the TNBC basal lineage into an ER+ luminal lineage both in vitro and in vivo, as evidenced by upregulation of luminal lineage markers. Moreover, we found that NSD2 degradation or knockdown could inhibit TNBC cell proliferation and sensitize TNBC cells to endocrine therapy. Thus, NSD2 PROTACs, which eliminate both catalytic and non-catalytic functions of NSD2, could provide a novel and effective therapeutic strategy for treating TNBC.

A robust, accessible resource for mapping the uncharacterized extracellular interactome

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Background: The majority of clinically approved therapeutics target secreted or cell-surface-bound proteins. However, drug discovery is continuously bottlenecked by receptor deorphanization, as many extracellular interactions remain uncharacterized due to their transient, low-affinity nature (K! in the micromolar range) and rapid dissociation kinetics.

Methods: To overcome these biochemical limitations, we engineered an advanced, high-avidity screening platform that couples CRISPR-Cas9 guide-mediated transcriptional gene activation (CRISPRa) with sequential, bead-based magnetic-activated cell sorting (MACS) and flow cytometry monitoring. By designing multimerized ectodomain (ED)-conjugated magnetic bead baits, our platform establishes a dense, "Velcro-like" orientation that mimics native cellular architecture, drastically enhancing binding avidity and rescuing weak, transient interactions that escape conventional screening modalities. This platform incorporates a newly optimized, high stringency gRNA library design that eliminates off-target promoter activation and promiscuous ionic profiling, ensuring superior sensitivity and highly accurate target identification.

Results: Leveraging this sensitive architecture, we successfully deorphanized key immunological and microenvironmental pathways, validating novel, low-affinity *in trans* receptor-ligand pairs. Notably, we discovered and characterized Siglec-4 as a direct functional binding partner for the costimulatory receptor 4-1BB (CD137), demonstrating its capacity to modulate T-cell immunoregulatory function. Furthermore, using this platform to map extracellular interactomes within the tissue matrix, we identified a novel physical interaction between cancer-associated fibroblast and tumor-associated macrophage, providing a key molecular link in macrophage stromal crosstalk.

Conclusion: Collectively, our findings establish a robust, accessible resource for mapping the uncharacterized extracellular interactome. By illuminating previously hidden low-affinity checkpoint and microenvironmental interactions, this work provides immediate biochemical targets for the engineering of next-generation oncology therapeutics and immunotherapies.

Development of peptide-based BioPROTAC degraders against undruggable transcription factors using PPI-guided structure modeling

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Transcription factors (TFs) govern nearly every cell-fate decision in cancer development and progression, and the ability to tune TF abundance would provide powerful research tools and potential therapeutic strategies. However, most of the approximately 1,600 TFs encoded in the human genome remain pharmacologically inaccessible because they often lack well-defined ligandable pockets and instead function through broad, shallow protein-interaction surfaces. Targeted protein degradation offers an alternative to conventional inhibition, but for most TFs, a major bottleneck remains the identification of selective binders that can be converted into degraders.

Our lab addresses this challenge by extracting target-binding motifs (TBMs) from protein-protein interaction interfaces of endogenous TF partners, leveraging binding events already selected by nature. Experimentally validated PPIs from resources such as BioGRID and STRINGDB are combined with structure modeling to nominate candidate binding motifs based on predicted interface contacts. By fusing these TBMs to E3 ubiquitin ligases, we generate genetically encoded proteolysis-targeting chimeras, or BioPROTACs, designed to redirect the cellular degradation machinery toward otherwise inaccessible TF targets.

Using this computational-experimental TBM extraction workflow, we identified candidate TBMs for FOXA2, a pioneer TF implicated in neuroendocrine prostate cancer. Several FOXA2-directed BioPROTACs reduced FLAG-tagged FOXA2 protein levels by approximately 50–90% within 48 hours, with degradation efficiency depending on both the selected TBM and E3 ligase. We are currently evaluating degradation specificity, endogenous FOXA2 regulation, and downstream functional consequences in prostate cancer models. If successful, these BioPROTACs will provide first-in-class tools for FOXA2 degradation and establish a generalizable strategy for converting TF interaction interfaces into functional intracellular degraders. In parallel, we developed a web portal to enable researchers to apply this pipeline to design peptide binders against proteins of interest.

Metabolic Control of Cell Fate and Immune Function in Cancer

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Metabolic reprogramming is a fundamental hallmark of cancer that shapes both tumor cell plasticity and the tumor microenvironment. Among emerging metabolic regulators, acetate has gained attention as both a bioenergetic substrate and a signaling metabolite that integrates nutrient availability with gene regulation. Here, we investigate how acetate metabolism governs cell fate decisions and immune function across cancer contexts. We demonstrate that acetate availability influences epithelial-to-mesenchymal transition, a key process underlying tumor progression, invasion, and metastasis. Mechanistically, acetate-driven metabolic pathways modulate transcriptional and epigenetic programs that promote cancer cell plasticity. In parallel, we show that acetate plays a critical role in regulating T cell survival and effector differentiation within the tumor microenvironment, thereby shaping anti-tumor immunity. By integrating transcriptomic, proteomic, and metabolomic analyses, our work identifies distinct metabolic circuits that coordinate tumor-intrinsic behavior with immune responses. These findings highlight acetate metabolism as a central node linking metabolic adaptation to both cancer progression and immune regulation. Collectively, this study provides a framework for understanding how metabolic cues control cell fate in cancer and suggests new therapeutic opportunities to target tumor metabolism while enhancing anti-tumor immunity.

Lipid droplets heterogeneity shape adaptation in metastasis

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Metastasis remains the leading cause of cancer-related mortality, and intratumoral heterogeneity is a major driver of poor patient outcomes. Although intracellular lipid droplet (LD) accumulation is a hallmark of many solid tumors, whether and how LD heterogeneity contributes to metastasis remains unclear. Here, in clear cell renal cell carcinoma (ccRCC), we identify two clonally maintained metastatic subpopulations distinguished by LD size and regulated by the opposing activities of ACSL3 and MGLL. Small-LD (SM) cells display enhanced lipid turnover and high invasive capacity but experience elevated oxidative stress that constrains proliferation. In contrast, large-LD (LA) cells are lipid-storing and highly proliferative but display limited invasive potential. To overcome this proliferation–invasion trade-off, these subpopulations engage in cooperative interactions mediated by migrasomes and previously unrecognized migrasome-associated tubules (MATs), enabling directional lipid exchange. Specifically, SM cells transfer arachidonic acid to LA cells, whereas LA cells supply oleic acid to SM cells. This division of labor enhances the fitness of both subpopulations and maximizes metastatic potential. Importantly, combined disruption of this cooperative axis through targeting ACSL3 and TSPAN4 markedly suppresses lung colonization, uncovering a previously unrecognized therapeutic vulnerability in metastatic cancers.

Metabolic Control of Tumor Immune Evasion in Lung Cancer

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My laboratory studies how cancer cells adapt to metabolic stress and evade immune-mediated destruction, using lung cancer as a major disease model. We are particularly interested in how metabolic signaling and protein post-translational modifications regulate intracellular organelle organization, membrane protein trafficking, tumor cell plasticity, and tumor-immune interactions. Our long-term goal is to uncover fundamental mechanisms that control tumor immune visibility and therapeutic resistance, and to translate these discoveries into new strategies to improve immunotherapy for solid tumors.

To address these questions, our laboratory uses an integrated set of experimental models and technologies. We employ genetically engineered lung cancer cell lines, patient-derived lung cancer organoids, tumor-immune co-culture systems, and in vivo tumor models to study how tumor-intrinsic signaling programs influence immune recognition and treatment response. Patient-derived organoids provide a clinically relevant platform to model tumor heterogeneity, therapeutic adaptation, and interactions between cancer cells and immune or stromal components. These models are combined with CRISPR-based genome engineering, live-cell imaging, quantitative proteomics, glycoproteomics, single-cell analyses, and functional immune-cell assays, including cytotoxic T cell and CAR-T cell killing assays.

Future research in the laboratory will focus on defining how metabolic and stress-responsive pathways reshape tumor cell states and regulate communication between cancer cells and the immune microenvironment. We are especially interested in understanding how intracellular organelle architecture, membrane trafficking, and surface protein remodeling contribute to immune evasion and therapy resistance in lung cancer. By integrating mechanistic studies with patient-derived organoid systems and immune co-culture platforms, we aim to identify actionable vulnerabilities that can be exploited to sensitize resistant lung tumors to endogenous anti-tumor immunity and engineered immune therapies.

Targeting Metabolic Vulnerabilities to Overcome Therapeutic Resistance in Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) remains one of the most aggressive breast cancer subtypes due to its high rates of metastasis, recurrence, and therapeutic resistance. Increasing evidence indicates that metabolic reprogramming and breast cancer stem cells (BCSCs) play central roles in tumor progression and treatment failure. My research focuses on understanding how metabolic adaptation regulates cancer stemness and identifying actionable metabolic vulnerabilities that can be therapeutically exploited to overcome drug resistance. Using integrated functional genomics, metabolomics, and mechanistic studies, we identified BBOX1 as a previously unrecognized metabolic dependency in TNBC and demonstrated that metabolic heterogeneity shapes tumor progression. More recently, we discovered that the kinesin protein KIF20A promotes BCSC maintenance by regulating chromatin remodeling, revealing a novel mechanism linking metabolic adaptation, stemness, and chemotherapy resistance. Building upon these discoveries, my current research integrates genome-wide CRISPR screening and preclinical mouse models to identify molecular determinants of sensitivity and resistance to DHODH inhibitors in TNBC. Our goal is to uncover metabolic mechanisms that enable tumor cells to evade therapy and to develop rational combination strategies that eliminate treatment-resistant breast cancer cells. Together, these studies establish an integrated research program focused on defining metabolic vulnerabilities in aggressive breast cancer and translating these discoveries into innovative therapeutic strategies to improve patient outcomes.

Systems Biology Reveals P80 as a Therapeutically Targetable Synthetic Lethal Vulnerability in VHL-Deficient Clear Cell Renal Cell Carcinoma

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Clear cell renal cell carcinoma (ccRCC), the most common subtype of kidney cancer, is frequently driven by loss of the VHL tumor suppressor gene, yet effective treatments remain limited, particularly for patients resistant to HIF2α inhibitors. To uncover alternative therapeutic targets, we employed an integrative systems biology approach, combining SJARACNe and NetBID2, to analyze bulk omics data from 97 ccRCC patients. This analysis identified P80, an understudied mitochondrial regulator, as a novel hidden driver selectively activated in VHL-deficient tumors. Functional studies demonstrated that P80 depletion induces synthetic lethality in VHL-deficient ccRCC, markedly suppressing tumor growth in vitro and in xenograft models.

Mechanistic investigations revealed that P80 knockdown disrupts mitochondrial homeostasis, supported by AP-MS interactome analysis showing enrichment of energy metabolism-associated proteins, including TSPO, a key mitochondrial regulator. Notably, P80–TSPO binding was significantly reduced in the presence of VHL, suggesting a VHL-dependent mechanism governing mitochondrial function. To translate these findings therapeutically, we developed first-in-class P80-targeting PROTACs, which selectively degrade P80 and exhibit potent anti-tumor efficacy in preclinical models.

Collectively, our findings establish P80 as a therapeutically actionable synthetic lethal target in VHL-deficient ccRCC, offering a promising avenue for overcoming resistance to current therapies.

HSF1-driven proteostasis as a metabolic vulnerability in pancreatic cancer

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Dr. Su's research focuses on the role of heat shock factor 1 (HSF1), a key regulator of proteotoxic stress response, in modulating metal-induced cellular toxicity, autophagy, mitochondrial lipid metabolic reprogramming, and regulated cell death during pancreatic tumorigenesis using in vitro systems, in vivo models, and preclinical platforms. Pancreatic ductal adenocarcinoma (PDAC) remains the most lethal common solid tumor, with a 5-year survival rate of only 13%, reflecting its remarkable capacity to adapt to chronic metabolic and proteotoxic stress while sustaining mitochondrial function. Copper is an essential mitochondrial cofactor, but excess copper promotes aggregation of dihydrolipoamide S-acetyltransferase and impairs TCA cycle flux, generating mitochondrial proteotoxic stress. Despite elevated intratumoral copper levels, PDAC cells remain metabolically active, suggesting an adaptive proteostasis program that protects mitochondria from copper-induced damage. Our work identifies HSF1 as the central regulator of this adaptation. HSF1 overexpression rescues copper-induced protein aggregation and cell death, whereas HSF1 loss exacerbates amyloid fibril formation and sensitizes PDAC cells to copper stress through both ferroptotic and proteotoxic death mechanisms. HSF1 also preserves mitochondrial quality via AMPK-dependent mitophagy, while pharmacologic HSF1 inhibition triggers compensatory JNK-dependent autophagy. Because PDAC cells become dependent on HSF1 to survive copper and proteotoxic stress, this adaptive mechanism creates a therapeutic vulnerability. Pharmacologic HSF1 inhibition collapses adaptive proteostasis and sensitizes PDAC cells to copper ionophore-induced death. These findings position HSF1 as a master regulator of mitochondrial stress adaptation and a therapeutic vulnerability in pancreatic cancer.

Patient-Derived Uveal Melanoma Organoids Enable Integrated HLA-I Antigen Discovery and Tumor-Reactive T-Cell Identification

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Background:

Metastatic uveal melanoma (mUM) is an aggressive low tumor mutation burden (TMB) malignancy with limited response to immune checkpoint blockade. We developed a patient-derived uveal melanoma organoid platform to integrate HLA-I restricted tumor antigen discovery and tumor reactive T cell receptor identification from matched patient samples.

Methods:

Patient-derived organoids (PDO) were established from percutaneous fine needle aspiration specimens from patients with metastatic uveal melanoma. Whole-exome sequencing and RNA sequencing were used to compare organoids with parental tumors and to support proteogenomic antigen discovery. HLA-I immunopeptidomics was performed using W6/32-mediated immunoprecipitation followed by LC-MS/MS. Peptides were analyzed using canonical protein databases and expanded proteogenomic search strategies incorporating customized database based on RNA-seq and WES results. Tumor specificity of canonical and noncanonical HLA-I restricted peptide candidates was assessed using normal tissue transcriptomic filtering. To evaluate immune recognition, IFN-γ–primed organoids were co-cultured with matched autologous PBMCs, followed by flow cytometry and single-cell RNA/VDJ sequencing to identify tumor-reactive T cell receptors.

Results:

mUM PDOs preserved parental tumor genomic and transcriptomic features. HLA-I immunopeptidomics identified recurrent melanoma lineage–associated peptides across diverse HLA alleles. No mutation-derived HLA-I peptides were detected despite WES-predicted neoantigens. Expanded proteogenomic search nominated tumor-restricted noncanonical peptide candidates arising from non-coding RNAs, novel transcripts and alternative splicing. In autologous co-culture, organoid restimulation induced HLA-I–dependent CD8 T-cell activation. Single-cell RNA/VDJ sequencing identified activated candidate tumor-reactive clonotypes for downstream TCR–pMHC validation.

Discussion:

This work establishes a matched platform linking PDO immunopeptidomics, noncanonical antigen discovery, autologous T-cell activation, TCR recovery, and immunogenicity validation. This platform may support target identification for personalized tumor vaccines and TCR-based therapies for mUM and other low-TMB cancers.

Interleukin-34–Induced Arg1^{+} Macrophages Play a Key Role in Breast Cancer Brain Metastasis

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Brain metastases occur in up to 40% of patients with stage IV breast cancer, and the cerebellum is a common site for metastases in HER2-positive breast cancer. We developed a syngeneic, immunocompetent mouse model of breast cancer brain metastases (BCBM) by stereotactically injecting murine breast cancer organoids into the cerebellum. Spatial transcriptomics on these brain metastases revealed that breast cancer cells produce interleukin-34 (IL34), which induces ARG1^{+} macrophages at the invading edge of metastases. IL34 expression in human brain metastasis samples was measured in two independent datasets, and IL34 was expressed widely in both HER2^{+} and HER2^{-} human BCBM. Remarkably, IL34-deficient breast cancer cells failed to establish tumors in the mouse cerebellum. Furthermore, treatment with a blocking antibody against the IL34 receptor, CSF1R, led to tumor shrinkage, highlighting the translational potential of these findings, as a CSF1R-blocking antibody is FDA-approved for another indication, graft-versus-host disease.

Significance:

Targeting IL34–CSF1R is a potential new approach to treat BCBM and could be combined with existing therapies. IL34 expression is widely found in human BCBM.

Defining Neuron–Tumor Crosstalk in Aggressive Prostate Cancer

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Aggressive prostate cancer, particularly castration-resistant and neuroendocrine disease, remains a major clinical challenge because of poor outcomes and limited treatment options. While most studies have focused on tumor-intrinsic changes, the role of the peripheral nervous system in prostate cancer progression is still poorly understood. We hypothesize that aggressive prostate cancer develops within a remodeled peripheral neural niche and co-opts neuron-derived signaling programs to promote tumor growth and plasticity. To test this, we will (1) define the peripheral neural microenvironment in human prostate cancer tissues, (2) use sensory neuron–prostate cancer co-culture models to identify molecular pathways induced by neural exposure, and (3) apply a neuron-centered CRISPRi-based functional genomics approach to identify neuron-intrinsic genes that regulate tumor-supportive crosstalk. This work will establish a mechanistic framework for understanding cancer–nerve interactions in aggressive prostate cancer and may reveal new biological pathways for therapeutic targeting, with broader relevance to other solid tumors.

Hijacking the hijackers: Nanotherapeutic targeting of immunosuppressive myeloid cells in glioblastoma

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Myeloid cell-driven immunosuppression is a hallmark of glioblastoma (GBM), the most aggressive and lethal brain malignancy in adults, significantly dampening anti-tumor immunity and effectiveness of both immunotherapies and conventional therapies. As a key driver of GBM immunosuppression and therapy resistance, tumor-associated myeloid cells (TAMCs) are the most abundant immune cell subset within the GBM microenvironment and have thus been recognized as a promising therapeutic target. We have engineered an antibody-directed immune targeting (ADIT) nanotechnology platform that enables precision in vivo targeting and modulation of TAMCs in GBM. Harnessing the overexpressed immune checkpoint molecules in these immunosuppressors, our nanotherapeutics demonstrated high efficiency as well as specificity in delivering various types of therapeutics, including small molecules and nucleic acid therapeutics, for robust elimination or reprogramming of TAMCs in vivo. Such strategies dramatically blunted GBM immunosuppression and induced effector T cell infiltration, activation, and anti-tumor immunological memory to potentiate anti-GBM immune response and synergize with standard-of-care GBM treatments. The presentation will overview our TAMC targeting approaches and discuss our recent work on developing RNA therapeutics to target myeloid metabolism as a new immunotherapy strategy for GBM and other myeloid-rich immunologically “cold” tumors.

A neutrophil interferon program predicts immunotherapy resistance and limits durable anti-tumor immunity

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Despite the remarkable success of immune checkpoint blockade (ICB), durable clinical benefit remains limited to a subset of patients, highlighting the need for predictive biomarkers and new therapeutic targets. Here, we investigated the early immune dynamics associated with anti-PD1 responsiveness using longitudinal single-cell transcriptomics, spatial transcriptomics, and neutrophil-specific genetic perturbations in preclinical models of triple-negative breast cancer. We identified a conserved neutrophil interferon-stimulated gene (ISG) program that emerges before overt tumor divergence and predicts resistance to anti-PD1 therapy. Successful treatment was associated with an early reduction of IFN-responsive neutrophils in both blood and tumor tissues, whereas persistent neutrophil IFN signaling correlated with therapeutic resistance. Mechanistically, genetic disruption of either type I or type II interferon signaling in neutrophils enhanced anti-PD1 efficacy and promoted durable anti-tumor immune memory. Spatial analyses further revealed an inverse association between IFN-responsive neutrophils and tertiary lymphoid structure-enriched regions during effective therapy. Together, these findings identify IFN-responsive neutrophils as early determinants of immunotherapy outcome and establish dynamic neutrophil interferon programs as candidate blood-based biomarkers and therapeutic targets for cancer immunotherapy.

Targeting Collagen Prolyl Hydroxylation to Overcome Breast Cancer Therapy Resistance

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Collagen is a key extracellular matrix (ECM) component of the tumor microenvironment. Collagen prolyl 4-hydroxylase (P4H), an α-ketoglutarate (α-KG)-dependent dioxygenase that catalyzes 4-hydroxylation of proline, is crucial for collagen triple helix structure formation and secretion. Enhanced tissue stiffness driven by increased collagen deposition is strongly associated with breast cancer progression and poor patient prognosis. However, the precise mechanisms by which increased collagen production drives breast cancer progression remain poorly understood. We report that P4HA1, the major isoform of the P4H α-subunit (P4HA), is highly expressed in breast cancer tissue, particularly within aggressive triple-negative breast cancer (TNBC), HER2-positve, and luminal B subtypes, compared with luminal A subtype. Elevated P4HA1 expression significantly correlates with shorter relapse-free survival in breast cancer patients. Furthermore, this upregulation is associated with chemotherapy resistance in TNBC and hormone therapy resistance in luminal breast cancer. Mechanistically, we demonstrate that high P4HA1 expression promotes breast cancer progression and therapy resistance by enabling survival adaptations to metabolic and cellular stresses. Finaly, function studies using both in vitro and in vivo models show that genomic perturbation or pharmacological inhibition of P4HA1 successfully abrogates this aggressive, drug-resistance phenotype and sensitizes breast cancer cells to conventional therapies. Together, these findings suggest that P4HA1 serve as both a valuable prognostic marker and an attractive therapeutic target for advanced breast cancer.

Advanced Therapeutic Strategies to Modulate B Cell Immunity Against Cancer

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Current cancer immunotherapies primarily focus on modulating T cells and innate immune cells, leaving the role of B cells in onco-immunity historically neglected. Recently, however, their critical importance has emerged: while tumor-infiltrating B cells promote anti-cancer immunity and correlate with favorable patient outcomes, regulatory B cells (Bregs) drive immune suppression and therapeutic resistance. Because targeted therapeutics capable of modulating B cell immunity are currently lacking, our research focuses on developing strategic interventions that target B cells—specifically by either boosting anti-cancer B cell immunity or inhibiting suppressive Bregs.

First, we developed a therapeutic cancer nanovaccine that promotes B cell antigen presentation for durable efficacy. While conventional vaccines target dendritic cell-mediated antigen presentation to activate T cells—often yielding only short-term efficacy—our work demonstrates that B cell-mediated antigen presentation critically enhances CD4+ and CD8+ T cell responses. Leveraging these insights, we engineered mRNA- and peptide-based nanovaccines that augment B cell antigen presentation and foster B/CD4+ T cell crosstalk for sustained immunity (ACS Nano, 2024; 2025).

Second, we investigated Breg-mediated suppression in pancreatic ductal adenocarcinoma (PDAC), where both Bregs and myeloid cells in tumors and lymph nodes drive severe immune suppression. While current strategies heavily emphasize myeloid cells, they overlook Bregs. We discovered that STING agonists expand suppressive Bregs via a PI3Kγ-dependent but PI3Kδ-independent mechanism, while activating antitumor myeloid cells independent of PI3Kγ. Consequently, PI3Kγ inhibition selectively decreases STING-induced IRF3 phosphorylation and Breg expansion while preserving myeloid activation. To exploit this, we developed Nano-273, an albumin nanoformulation delivering a dual-targeting compound that simultaneously stimulates STING and inhibits PI3Kγ. Nano-273 effectively targets tumors and lymph nodes, remodeling the immune microenvironment to overcome both myeloid and Breg suppression. Combined with anti-PD1, Nano-273 achieved durable therapeutic efficacy in transgenic KPC mice, offering a promising strategy for PDAC treatment (Nature Cancer, 2026).

ZBP1 Signaling as a Regulator of Programmed Cell Death, Antiviral Immunity, and Cancer Biology

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Programmed cell death is a central mechanism by which the host eliminates infected, damaged, or transformed cells. Our laboratory studies how innate immune sensors detect viral and cellular danger signals and convert these signals into inflammatory cell death programs. A major focus of our work is Z-DNA binding protein 1 (ZBP1), an innate immune sensor that recognizes Z-nucleic acid structures and activates RIPK3-dependent signaling pathways, including necroptosis, apoptosis, and inflammatory immune responses. ZBP1 has emerged as an important regulator of host defense during viral infection, but its role in cancer biology remains incompletely understood. Because tumors often evolve mechanisms to suppress immune recognition and evade cell death, reactivating ZBP1-dependent signaling may provide a strategy to enhance tumor immunogenicity. In particular, ZBP1-driven necroptosis has the potential to promote inflammatory tumor cell death, release damage-associated molecular patterns, and reshape the tumor microenvironment to improve antitumor immunity. These properties make ZBP1 signaling especially relevant to cancer immunotherapy and oncolytic virus-based approaches. Our research program integrates molecular virology, innate immune signaling, programmed cell death biology, and tumor models to define how ZBP1 is activated, how its signaling is regulated, and how this pathway can be leveraged therapeutically. By understanding the molecular mechanisms that license ZBP1 activation and determine downstream immune outcomes, our long-term goal is to identify new strategies to convert immune-suppressed or cell-death-resistant tumors into immunologically responsive tumors. Together, our work positions ZBP1 as a promising molecular link between viral sensing, inflammatory cell death, and cancer immune surveillance, with broad implications for the development of next-generation cancer therapies.

Multimodality Imaging of the Tumor Microenvironment and Cancer Therapy Response

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The long-term goal of our laboratory is to use noninvasive molecular imaging to better understand tumor biology and improve the evaluation of cancer therapies. Our research focuses on the tumor microenvironment, particularly tumor vasculature, oxygenation, metabolism, therapeutic delivery, and treatment response. By combining imaging with molecular and histologic analyses, we aim to define how tumors respond and adapt to therapy and to identify strategies that improve treatment efficacy.

Over the past two decades, we have established an integrated imaging platform that combines bioluminescence imaging (BLI), magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescence imaging, chemiluminescence imaging, and multispectral optoacoustic tomography (MSOT). Our studies integrate in vitro experiments using cancer cell lines with in vivo investigations in mouse tumor models, including human tumor xenografts, syngeneic tumors, orthotopic models, genetically engineered models, and patient-derived xenografts of lung, kidney, breast, and bladder cancers. These complementary imaging approaches allow longitudinal, noninvasive assessment of tumor growth, vascular function, oxygenation, molecular activity, therapeutic delivery, and treatment response in vivo. Using these imaging platforms, we have investigated vascular disrupting agents, heme-targeting agents, radiation therapy, immunotherapy, targeted therapies, and nanoparticle-based therapeutics. Our studies have demonstrated that functional imaging of tumor vascular oxygenation provides a quantitative measure of therapeutic response and has helped define imaging biomarkers associated with vascular disruption, vascular normalization, and treatment-induced changes in the tumor microenvironment.

Current studies focus on imaging-guided evaluation of combination therapies that modulate tumor vasculature and antitumor immunity. By integrating functional imaging with molecular and histologic analyses, we aim to understand how treatments reshape the tumor microenvironment, identify mechanisms of resistance and determine how vascular and metabolic changes influence antitumor immune responses in preclinical cancer models.

Future work will expand these imaging approaches to additional cancer models and emerging therapeutic strategies, including immunotherapy, targeted therapy and combination therapies. We are also developing quantitative image analysis methods to improve assessment of treatment response and to support the preclinical evaluation and optimization of cancer therapies.

Mechanisms of leukemia transformation and immune evasion, and targeted therapies

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I received my PhD in Developmental Biology from Wuhan University, China. In 2011, I joined the Medical College of Georgia as a postdoctoral fellow studying transcriptional regulation by long non-coding RNA from Human Endogenous Retroviruses in Hematopoiesis. In 2016, I began to work on blood malignancies driven by different chromosome translocations in the Georgia Cancer Center, where I was promoted to Research Scientist and then Assistant Professor. My laboratory uses unique mouse models of Chronic Myeloid Leukemia (CML) carrying BCR-ABL1 (Philadelphia (Ph) chromosome), Acute Myeloid Leukemia (AML) carrying CBFB-MYH11 and FLT3-ITD, as well as Myeloid/Lymphoid neoplasms with FGFR1 rearrangement (MLN-FGFR1; also known as Stem Cell Leukemia/Lymphoma (SCLL) syndrome), to investigate molecular mechanisms regulating leukemia initiation and progression. My most recent research endeavors focus on investigating the mechanisms underlying immune evasion processes during leukemia progression. My lab performed the very first comprehensive investigation of the mechanisms of immune evasion during CBFB-MYH11 AML progression. Immune profiling confirmed a global immune suppression during leukemia progression by the leukemia cells. Using a combination of bulk and single cell RNA-Seq, CUT&RUN and ChIP-Seq, we further revealed that mechanistically, CBFB-MYH11 directly binds to promoters and activates critical immune suppression genes including TGFβ and PD-L1 in both mouse and human AML cells, which suppress the antitumor immune response to ensure leukemia progression. We also revealed that there was global immunosuppression during CML initiation and progression, which was directly driven by BCR-ABL1 expressing CML cells. On one hand, the BCR-ABL1 oncogene drives the differentiation of leukemia cells toward the neutrophil lineage. On the other hand, the oncogene also transcriptionally activities master immune regulators, including arginase and TGF-β through C/EBPβ. Therefore, combination therapy targeting both leukemia cells and exhausted T cells provides rapid remission and delayed relapse in a preclinical mouse CML model.

Our basic mechanism study revealed that CBFB-MYH11 oncogene directly upregulates both TGFB1 and CD274 (encoding PD-L1) to orchestrates this immune evasion process, providing a very strong rationale to a novel dual-targeting strategy of PD-L1/PD-1 and TGFβ for immunotherapy of CBFB-MYH11 AML. Targeting both PD-L1/PD-1 (to reactivate exhausted T cells) and TGFβ (to reverse its broad immunosuppressive effects, including T cell exclusion and suppression) may offer a synergistic strategy. Blocking TGFβ could potentially "prime" the tumor microenvironment, making it more permissive for T cell infiltration and function, thus enhancing the efficacy of PD-1/PD-L1 blockade. Considering the potential that immunotherapy alone may not be sufficient for initial bulk tumor reduction in aggressive diseases like AML, we are also actively evaluating whether combination of chemotherapy (cytarabine) with novel PD-L1/TGFβ dual targeting regents could provide superior disease control and even disease-free survival. Using the humanized HLA-A*02:01 (A2) transgenic mouse CML model, we have demonstrated that CD8 T cells are responsible for efficient eradication of all BCR-ABL1 expressing leukemia cells in recipient mice after primary CML cell transplantation, using both antibody mediated CD8 T cell depletion and adoptive T cell transfer experiment. Furthermore, rechallenge experiments in CML-inoculated, but leukemia-free mice, revealed that they were completely protected against a new tumor challenge. Importantly, we successfully identified 3 epitopes derived from the BCR-ABL1 oncogene that can be efficiently presented by A2 molecules and confirmed a direct CD8 T cell mediated clearance of Ph+ leukemia cells upon the recognition of the BCR or ABL1 antigens. We are actively cloning and studying the antitumor function of a panel of TCRs with different affinities, hoping to obtain the optimal TCRs to create TCR-Ts of potent antitumor effect with tolerable toxicity that can be used for the treatment of CML and even all Ph+ ALL and AML.

Rhythmic QTLs Link Circadian Regulation to Cancer Risk

Dongyin Guan

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The circadian system regulates 24-hour physiological rhythms that shape metabolism and influence disease risk. Genetic and lifestyle-driven variation in circadian rhythms contributes to cancer development and progression, creating opportunities for circadian medicine to optimize disease diagnosis and treatment timing. By incorporating time-dependent strategies into clinical practice, circadian medicine has the potential to reduce medication burden, enhance therapeutic efficacy, and improve diagnostic accuracy and specificity. However, how individual genetic variation modulates 24-hour rhythmic processes and contributes to cancer risk remains largely unexplored. In this presentation, Dr. Guan will describe approaches for studying circadian rhythms in human peripheral tissues and introduce a newly defined class of molecular quantitative trait loci, termed rhythmic QTLs, which regulate interindividual variation in rhythmic gene expression. Dr. Guan will further discuss the underlying molecular mechanisms, their contributions to human disease risk and complex traits, and the potential applications of rhythmic QTLs in cancer diagnosis, prognosis, and precision medicine.

Beyond Gene-Centric Biology toward an Isoform-Centric Understanding of Glioma

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The remarkable cellular heterogeneity and plasticity of glioma pose major challenges to understanding tumor progression and developing effective therapies. While most transcriptomic studies have focused on gene-level regulation, growing evidence suggests that much of the functional diversity in tumors is encoded through RNA alternative splicing at the isoform level, often without changes in overall gene expression. My research aims to uncover the isoform-mediated mechanisms that drive glioma progression and shape tumor-immune interactions.

In this seminar, I will present our work demonstrating how alternative splicing contributes to glioma malignancy, shapes developmental hierarchies, and regulates interactions between tumor cells and the immune microenvironment. By integrating single-cell transcriptomics, long-read RNA sequencing, and functional genomics, we have uncovered previously unrecognized isoform programs associated with glioma progression and immune regulation. I will also discuss our ongoing efforts to investigate the functional roles of RNA alternative splicing using CRISPR/Cas13-based splicing manipulation and screening, together with human iPSC-derived macrophage and microglia models to study glioma-immune interactions. Together, these studies aim to establish an isoform-centric framework for understanding glioma biology and reveal molecular mechanisms that drive tumor heterogeneity, immune regulation, and disease progression.

Phase separation in telomere maintenance of ALT cancer cells

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All cancer cells must actively maintain telomere length to achieve replicative immortality. While most cancer cells reactivate telomerase, 10-15% utilize an alternative lengthening of telomeres (ALT) pathway based on homology-directed DNA repair. ALT cancer cells exhibit many unique features, including mislocalization of PML bodies to telomeres, telomere clustering, and upregulation of long non-coding telomere repeat-containing RNA (TERRA). These features serve as biomarkers for ALT cancer cells, but their origins and roles in the ALT pathway remain poorly understood. My lab's work provides evidence that abnormal phase separation in ALT cancer cells drives the formation of these features, and principles of phase separation are exploited to facilitate DNA repair-mediated telomere lengthening in ALT cancer cells.

Genetic architecture and epigenetic regulation in aging and cancer

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Aging and cancer are closely intertwined biological processes driven by complex interactions between inherited genetic variation, somatic alterations, and epigenetic regulation. Although genome-wide association studies (GWAS) have identified thousands of disease-associated loci, the vast majority reside in noncoding regions of the genome, making it challenging to understand their molecular functions and contributions to disease susceptibility. Deciphering how genetic variants influence cell-type-specific regulatory programs during aging and tumorigenesis remains one of the central challenges in human genetics.

Our laboratory develops and applies integrative computational and experimental approaches to investigate the genetic architecture and epigenetic mechanisms underlying aging and cancer. By combining single-cell multiomics, functional genomics, large-scale human genetic studies, and machine learning, we systematically map regulatory variants to their target genes, characterize tissue- and cell-type-specific gene regulatory networks, and identify molecular mechanisms that connect genetic variation to complex traits and diseases. We also investigate the roles of transposable elements, chromatin accessibility, DNA methylation, and three-dimensional genome organization in shaping cellular aging and cancer-associated regulatory landscapes.

In this presentation, I will highlight recent advances from our laboratory, including the development of integrative frameworks for variant-to-gene mapping, atlas-scale regulatory annotation across human tissues, and computational tools for interpreting noncoding genetic variation. These studies provide new insights into the regulatory principles governing aging and cancer and establish a foundation for translating human genetic discoveries into biological mechanisms and therapeutic opportunities.

Epigenetic Control of Lung Cancer Cell Identity and Therapeutic Response

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Lung cancer cells can escape therapy by transitioning between transcriptional and histologic states, yet the epigenetic mechanisms that establish, destabilize, and redirect these identities remain incompletely defined. I investigated how chromatin regulators control neuroendocrine identity, subtype plasticity, and histologic transformation in small cell lung cancer (SCLC) from EGFR-mutant lung adenocarcinoma (LUAD).

Using CRISPR/Cas9-based genetically engineered mouse models (GEMMs), we first examined Kdm6a loss in an autochthonous Rb1/Trp53/Rbl2-deficient SCLC model. KDM6A loss shifted tumors away from a canonical ASCL1-positive state and permitted emergence of NEUROD1-positive SCLC. Integrated RNA-seq, ATAC-seq, ChIP-seq, and immunofluorescence showed that KDM6A maintains enhancer states permissive for ASCL1-lineage genes, whereas its loss represses the ASCL1 program and indirectly enables NEUROD1 activation. Mechanistically, KMT2A/MLL1–Menin activity was enriched in KDM6A-mutant tumors, and Menin inhibition reduced NEUROD1 expression, nominating an actionable epigenetic axis that may influence resistance to DLL3-targeted therapy.

I next targeted Eed, an essential PRC2 scaffolding subunit, in the same SCLC GEMM. EED deletion delayed tumorigenesis, increased survival, reduced metastasis, and unexpectedly caused escaped tumors to adopt LUAD-like histology. Multi-omic analyses revealed that EED maintains ASCL1-positive neuroendocrine identity by repressing bivalently marked RAS/MAPK/PI3K-AKT signaling genes. Loss of EED derepressed these LUAD-associated oncogenic programs and promoted a NEUROD1-positive intermediate state, with the tumor immune microenvironment selecting for full LUAD histology. Finally, we developed a doxycycline-inducible EGFR L858R; Rb1/Trp53-deficient SCLC transformation GEMM and found that EED is required for SCLC histology to emerge following EGFR oncogene withdrawal.

Together, these studies identify epigenetic regulators as functional determinants of therapy-resistant lung cancer cell states. Future work will leverage this genetically tractable platform to test clinical EED inhibitors and perform focused in vivo CRISPR screens for epigenetic drivers of lineage transformation, with the goal of blocking therapy-resistant cell-state transitions before they become clinically dominant and ultimately improving durability of targeted and immune therapies.

Uncovering the crosstalk between EZH2 and tRNA methylation in advanced prostate cancer

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Transfer RNAs (tRNAs) are subject to numerous modifications, which controls tRNA folding, stability, and function. Growing evidence suggests that dysregulation of tRNA modifications is linked to developmental disorders and cancers. As a conserved tRNA modification in eukaryotes, 2′ -O methylation of guanosine at position 18 (Gm18) is catalyzed by TARBP1 in humans. Although increased TARBP1 expression is associated with tumor aggressiveness in several cancer types, its functions and regulatory network in prostate cancer (PCa) remain elusive. Here, we report that Polycomb group protein EZH2 exerts an additional role in tRNA modification regulation via targeting TARBP1. Our overall hypothesis is that EZH2 maintains a hyper-tRNA Gm18 state in AR+ PCa cells through promoting AR-dependent TARBP1 transcription, while restrains Gm18 level in AR- cells through weakening TARBP1 mRNA stability. In this project, we aim to uncover the role of EZH2-TARBP1-Gm18 axis in cancer-related translational control, and determine whether combinational targeting of EZH2 and TARBP1 could achieve a synergistic effect in lethal PCa treatment. The completion of this project will allow us to dissect how EZH2 and tRNA methylation are orchestrated to influence PCa tumorigenesis and lay the foundation for the development of novel therapeutic strategies that improve the outcome of advanced PCa patients.

NRF2 activation suppresses GPX4 expression and confers ferroptosis vulnerability under selenium-restricted conditions

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Mutations in the KEAP1–NRF2 pathway are among the most frequently genetic alterations in non-small cell lung cancer (NSCLC) and are associated with resistance to standard therapies. NRF2 is the master regulator of antioxidant responses, yet how NRF2 regulates selenium metabolism and selenoprotein expression remains incompletely understood.

We examined the effects of NRF2 activation on selenoprotein expression across multiple NSCLC cell lines. NRF2 overexpression consistently increased TXNRD1 protein levels while reducing GPX4 expression. Conversely, restoration of KEAP1 or genetic ablation of NRF2 reversed these effects, establishing a NRF2-dependent regulatory mechanism. GPX4 mRNA levels were not consistently altered under these conditions, indicating that NRF2 regulates GPX4 at the level of protein translation rather than transcription.

Because selenoprotein synthesis requires selenium as a limiting substrate, we next investigated whether selenium availability mediates the effect of NRF2 on GPX4 expression. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) revealed that standard culture medium (PRIM+10% FBS) contains approximately 1 ppb selenium, compared to approximately 90 ppb measured in lung tumor interstitial fluid (TIF), indicating that conventional cell culture conditions have selenium deficiency relative to the in vivo tumor microenvironment. Supplementation of culture medium with selenite rescued NRF2-dependent GPX4 suppression, demonstrating that selenium availability is a critical determinant of GPX4 protein expression. We therefore propose that NRF2 activation preferentially drives TXNRD1 synthesis, sequestering available selenium and limiting its incorporation into GPX4. Consistent with this model, genetical ablation of TXNRD1 restored GPX4 protein expression, supporting competitive selenium partitioning between those two selenoproteins.

NRF2 activation promotes ferroptosis defense through multiple mechanism, including promotion of GSH synthesis and recycling, upregulation of FSP1, and NADPH production. However, under selenium-restricted conditions, elimination of FSP1-CoQ10 axis rendered NRF2-active cells sensitive to GPX4 inhibition, revealing a context-dependent ferroptosis vulnerability in NRF2-driven tumors.

In xenograft models maintained under defined dietary conditions, we found that NRF2 loss impaired tumor growth under selenium-restriction but had no effect under selenium replete conditions. GPX4 protein expression was markedly reduced in selenium-deficient tumors and was partially restored upon NRF2 loss, consistent with our in vitro observation.

Collectively, these findings demonstrated that under selenium restricted conditions, NRF2 activation suppresses GPX4 expression through competitive selenoprotein synthesis, sensitizing cells to GPX4 inhibition. This selenium-dependent vulnerability defines a mechanistic basis for targeting ferroptosis in NRF2-driven NSCLC.

5β-Dihydrotestosterone reveals a mutant androgen receptor vulnerability in prostate cancer

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Bipolar androgen therapy (BAT) exploits the paradoxical vulnerability of castration-resistant prostate cancer (CRPC) cells to rapid cycling between castrate and supraphysiologic androgen concentrations, but clinical BAT uses testosterone, which can also activate wild-type androgen receptor (AR) in androgen-responsive tissues, causing systemic side effects. 5β-dihydrotestosterone (5β-DHT) is a naturally occurring testosterone metabolite generally considered androgenically inactive because it binds wild-type AR weakly, yet its activity against clinically relevant AR mutants has not been systematically evaluated. Here, we tested whether 5β-DHT and related 5β-reduced testosterone metabolites activate AR signaling and growth programs in prostate cancer models that carry AR mutations. In C4-2 cells, 5β-DHT and 3β-etiocholanediol (3β-ecdiol) increased canonical AR target genes, including KLK3 and TMPRSS2, with weaker activity than testosterone, whereas other 5β metabolites showed limited activity. In androgen-responsive LNCaP and C4-2 models, 5β-DHT and 3β-ecdiol promoted cell growth under androgen-depleted conditions, and this effect was suppressed by enzalutamide, supporting AR dependence. This is also supported by our RNA sequencing results that 5β-DHT and 3β-ecdiol induced androgen-response gene sets that substantially overlapped with testosterone, while retaining lower transcriptional magnitude. Further, we found that 5β-DHT, but not 3β-ecdiol, suppresses cell proliferation of LNCaP, C4-2, and PC-3 cells stably expressing the clinically relevant AR gain-of-function mutants W742C and H875Y through overactivating AR-induced senescence-like features after high-dose exposure, consistent with the therapeutic logic of BAT. These findings identify 5β-DHT as an overlooked mutant-AR agonist capable of BAT-like tumor suppression and propose it as a testosterone surrogate in BAT with potentially reduced systemic androgenic side effects.

Targeting Surface Protein Heterogeneity in Prostate Cancer

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Tumor specific surface proteins have emerged as promising therapeutic targets of radiation-based and immunotherapeutic strategies for advanced prostate cancer. For instance, the FDA's approval of Pluvicto (177Lu-PSMA-617) marked a major recent breakthrough for patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). DLL3, a single-pass transmembrane ligand that acts as a negative regulator of the Notch signaling, is selectively overexpressed in neuroendocrine prostate cancer (NEPC), the most aggressive and lethal subtype of mCRPC that is PSMA-negative. Overexpression of DLL3 leads to low-level cell surface expression, while in normal tissue it is restricted to intracellular compartments. The exquisitely selective expression of surface DLL3 on NEPC cells presents an excellent therapeutic target. A DLL3-CD3 bispecific T-cell engager tarlatamab (AMG-757) was recently FDA-approved for treating extensive stage small cell lung cancer (SCLC) and showed promising clinical results for treating NEPC. DLL3 antibody-drug conjugates also demonstrated promising pre-clinical potential. However, a key limitation to the clinical success of DLL3-targeted therapies is the substantial heterogeneity in DLL3 expression across and within tumors. Studies from the tarlatamab clinical trials revealed that DLL3 levels strongly correlate with patient response, and acquired resistance often involved loss or downregulation of DLL3. Using a genome-wide CRISPR screen in a SCLC cell line, we identified CDK5 as negative regulator of DLL3, and observed that pharmacological inhibition of CDK5 markedly increased DLL3 levels in both SCLC and NEPC cell lines. In collaborating with a cell therapy expert at Emory, we also designed a DLL3-Chimeric Antigen Receptor (CAR) as a novel targeting approach. Next, we will evaluate CDK5 inhibition as a strategy to enhance existing DLL3-directed immunotherapy agents and develop an anti-DLL3 CAR-T adoptive cell therapy as an alternative strategy to combat acquired resistance to tarlatamab. This represents a generalizable framework to strengthen surface protein-targeted therapies in their depth, durability, and breadth of benefits.

Long non-coding RNAs in prostate cancer lineage plasticity and therapeutic resistance

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Resistance to androgen receptor (AR)-targeted therapies remains a major clinical challenge in metastatic castration-resistant prostate cancer (mCRPC). A major mechanism underlying this resistance is lineage plasticity, whereby prostate cancer cells lose their AR-dependent luminal identity and acquire alternative, therapy-resistant cell states. Defining the transcriptional, epigenetic, and non-coding regulatory mechanisms that govern lineage identity is therefore critical for developing new therapeutic strategies to overcome treatment resistance.

My previous research focused on the role of zinc finger protein 397 (ZNF397) in maintaining AR-driven luminal lineage identity in prostate cancer. I identified ZNF397 as an AR-associated regulatory factor that sustains the transcriptional program of AR-dependent prostate cancer cells. Loss of ZNF397 drives a transition toward a TET2-associated plastic cell state, promoting resistance to AR-targeted therapies. These findings demonstrate that disruption of lineage-maintaining transcriptional programs facilitates epigenetic rewiring and the emergence of therapy-resistant phenotypes.

Building on this work, my current and future research investigates long non-coding RNAs (lncRNAs) as an additional regulatory layer controlling lineage plasticity and therapeutic resistance in prostate cancer. By integrating functional genomic screening, prostate cancer cell models, xenograft-based in vivo models, patient-derived organoids, and multi-omics approaches, I aim to identify and characterize lncRNA-driven regulatory networks that govern cell identity, epigenetic states, and treatment response. Ultimately, this research seeks to uncover novel mechanisms by which lncRNAs drive lineage plasticity and therapy resistance, providing a foundation for innovative therapeutic strategies to improve outcomes for patients with this devastating disease.

DSTYK predicts Chemoresistance in Triple-Negative Breast Cancer Patient-Derived Xenograft Models

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Patient-derived xenograft (PDX) models are widely regarded as robust preclinical platforms because they preserve the histopathological and molecular features of primary tumors. In this study, we established twenty triple-negative breast cancer (TNBC) PDX models using freshly resected patient tumors, including ten with high DSTYK expression and ten with low DSTYK expression. Tumor fragments were orthotopically implanted into the fourth mammary fat pads of NSG mice. DSTYK expression was validated by immunohistochemistry and western blotting. Histological evaluation across three serial passages demonstrated that PDX tumors retained the cellular morphology, stromal architecture, and lineage characteristics of their corresponding primary tumors. Using these models, we assessed in vivo responses to combination chemotherapy with doxorubicin and docetaxel. DSTYK-low PDX tumors exhibited significantly greater chemosensitivity, whereas DSTYK-high tumors showed marked resistance, indicating a critical role for DSTYK in mediating chemotherapy resistance. Consistent with these findings, analyses from The Human Protein Atlas and Kaplan-Meier Plotter databases revealed that high DSTYK expression is associated with poor survival outcomes in TNBC patients. Collectively, our results from clinical specimens, PDX models, and public datasets identify DSTYK as a promising prognostic biomarker and predictor of chemotherapeutic response in TNBC, with potential implications for patient stratification and treatment optimization.

TRAF4-mediated ubiquitination in prostate cancer progression and therapeutic resistance

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Ubiquitination is one of the most versatile post-translational modifications, regulating not only protein degradation but also protein interactions, trafficking, and signaling. The E3 ubiquitin ligase TRAF4 is frequently amplified and overexpressed across multiple cancer types. Our research has identified TRAF4 as a key driver of metastatic castration-resistant prostate cancer (mCRPC), where it promotes tumor progression through multiple distinct mechanisms. We discovered that TRAF4 mediates K27-linked ubiquitination of the androgen receptor (AR), reprogramming the AR transcriptional landscape to sustain castration-resistant cell cycle progression. In addition, TRAF4 enhances prostate cancer metastasis by promoting nerve growth factor-induced ubiquitination and activation of the receptor tyrosine kinase NTRK1. More recently, we demonstrated that TRAF4 regulates iron homeostasis and suppresses ferroptosis, thereby contributing to therapy resistance. Together, these findings establish TRAF4 as a central regulator of prostate cancer progression and therapeutic resistance. Building on this work, our laboratory is currently developing TRAF4-targeted therapeutic strategies to enhance treatment efficacy in advanced prostate cancer.