DDI
Drug Discovery Institute

Drug

Discovery Institute (DDI)

Symposium

April 29, 2026

8:30AM - 6PM

STUDENT CENTER SOUTH - MULTIPURPOSE ROOM #237

The DDI Annual Symposium is a full-day event highlighting advancements in drug discovery and immunotherapy, hosted by the UH Drug Discovery Institute. The event brings together leading researchers, industry experts, and faculty to showcase innovative research and foster collaboration in biomedical science.

The day features a keynote by Dr. **Patrick Hwu** (President & CEO, Moffitt Cancer Center), faculty research presentations from UH and Texas Medical Center institutions, and a trainee rapid-fire session. Topics span immunotherapy and targeted therapies for cancer, autoimmune disorders, cardiovascular, and neurodegenerative diseases. Interactive poster sessions will offer networking opportunities, and **Poster Awards** will be presented to selected trainees.

Breakfast, lunch, and beverages provided for registered participants.

Agenda

8:00 am Vendor table setup

8:30 am Breakfast and registration

8:50 am **Welcome**
Claudia Neuhauser, VC/VP research
Weiyi Peng, DDI director

Keynote Presentation (9:00-10:00)
Moderator: **Weiyi Peng,** DDI director

9:00-10:00 *Next Generation of T-Cell Therapy for Cancer*
Patrick Hwu, MD, President and CEO and at Moffitt Cancer Center,

DDI-funded scholar highlights (10:10-11:00)

Moderator: **Weyi Peng (DDI)**

10:10-10:20 *A Novel Microfluidic Platform for High-Purity Lymphocyte Isolation from Whole Blood*
Sergey Shevkoplyas, Engineering

10:20-10:30 *Mechanistically Novel Inhibitors of Androgen Receptor to Treat Prostate Cancer*
Alexander V. Statsyuk, Pharmacy

10:30-10:40 *Studies on the Mycobactericidal Properties of Lysates from an Actinobacterial Isolate Tersicoccus Phoenicis*
Madhan Tirumalai, NSM

10:40-10:50 *Improving CAR T Therapy Efficacy and Persistence through Modulation of a Transcriptional Coactivator*
Qin Feng, NSM

10:50-11:00 *Novel Targeted Therapy for Vasculopathy in Cryopyrin-associated Periodic Syndrome*
Yunting Wang, Pharmacy

UH new faculty highlights (11:10-12:00)

Moderator: **Richard Willson,** Engineering

11:10-11:20 *Tunable peptide-based materials for designer drugs and scaffolds*
Vivek Kumar, Engineering

11:20-11:30 *From Clinical Multi-omics toward Mechanistic Insight: Cell-State Regulation in Gastric Adenocarcinoma*
Yibo Fan, Pharmacy

11:30-11:40 *Antibody Conjugates for Targeted Therapy*
Bin Liu, NSM

11:40-11:50 *Developing Potent RNA Vaccines and Immunotherapies*
Akash Gupta, Engineering

11:50-12:00 *From Local Activation to Systemic Immunity: Engineering Innate Responses for Cancer Therapy*.
Fanfei Meng, Pharmacy

Rapid fire talk (12:00-12:15) - 3 min each; 5 talks – 15 mins total.

Moderator: **Vivek Kumar,** Engineering

Audience choice (QR Code)

Lunch and Poster session 1 (12:15-1:50)

12:15-1:50	Lunch
12:50-1:20	Industry sponsor talks / demos
1:20-1:50	Posters (Even Numbers)

Drug Discovery in Cancer (1:50-3:10)

Moderator: **Ping Yi,** NSM

1:50-2:10 *Exploring Next-Gen Therapeutics for Human Health*
Jin Wang, BCM

2:10-2:30 *Phage-encoded peptide bicycles as a unique platform for the development of immunotherapeutic candidates*
Wenshe Ray Liu, Texas A&M

2:30-2:50 *Targeting Cancer Metabolism and Interconnected Cancer Hallmarks with Small Molecule Liver X Receptor Modulators*
Chin-yo Lin, NSM

2:50-3:10 *Collagen degrading T cells for treating solid tumors*
Navin Varadaraja, Engineering

Break and Poster Session 2 (3:10-4:00)

3:10-3:30	*Coffee Break*
3:30-4:00	Posters (Odd Numbers)

Drug Discovery in non-cancer chronic diseases (4:00-5:10)

Moderator: **Bin Liu,** NSM

4:00-4:20 *Targeting adipose tissue endocrine responses for energy balance regulation*
Sean M. Hartig, BCM

4:20-4:40 *Novel Drug Discovery Tools From The Proteomic Toolbox*
Chandra Mohan, Engineering

4:40-5:10 *Therapeutic Targeting of Unfolded Protein Response Pathways in Muscular Disorders*
Ashok Kumar, Pharmacy

5:10-5:30 *Molecular Mechanisms and Potential Treatments for Left Ventricular Noncompaction Cardiomyopathy.*
Mingfu Wu, Pharmacy

Closing Remarks and Reception (5:30-6:30)

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Sponsors listed alphabetically.

Abstract # 1

Tumor-Intrinsic METTL5 Restricts T cell-Induced Ferroptosis by Impairing ATF4 Translation in Ovarian Cancer

Jiakai Hou, Cheng-wei Ju, Nicholas A. Egan, Yanjun Wei, Yunfei Wang, Minghao Dang, Tianyi Zhou, Leilei Shi, Ningbo Zheng, Si Chen, Ashley Guerrero, Xiaofang Liang, Wanfu Wu, Areej Akhtar, Chitra Dhiman, Debanwita Roy Burman, Andro Gerges, Mason D. Flores, Han Li, Li-Sheng Zhang, Marleen Kok, Xiaobo Mao, Linghua Wang, Qin Feng, Yiwen Chen, Sanghoon Lee, Daniel McGrail, Nidhi Sahni, Chuan He, Amir A. Jazaeri, Weiyi Peng
University of Houston, Center for Nuclear Receptors and Cell Signaling

To systematically define tumor-intrinsic mechanisms driving immune resistance in ovarian cancer (OC), we integrated an in vitro genome-wide CRISPR immune screen, in vivo targeted immune screens, and analysis of 16 published ICB patient cohorts. From this pipeline, 693 candidate genes were shortlisted, and METTL5 emerged as a key regulator of tumor-intrinsic immune evasion. Pan-cancer TCGA analysis revealed significant METTL5 upregulation across multiple cancer types, with OC showing the second-highest expression among 34 malignancies. Although METTL5 expression did not correlate with OC stage or overall survival, higher expression was strongly associated with reduced cytolytic activity scores, suggesting suppressed antitumor immunity. In the MDACC HGSOC cohort (NCT03026062), patients with elevated METTL5 expression in baseline tumor samples exhibited significantly poorer responses and shorter overall survival after ICB therapy, supporting its clinical relevance. Mechanistically, METTL5 loss in OC models specifically reduced m6A methylation at A1832 of 18S rRNA, disrupting helix 44 structure and impairing ribosomal scanning and translation. RiboLace-based active ribosome profiling demonstrated that METTL5 knockout reprograms translation, notably downregulating genes enriched in the “Response of EIF2AK1 to Heme Deficiency” pathway, consistent with defective integrated stress response (ISR). Translation of ATF4 was markedly reduced, accompanied by decreased expression of downstream targets SLC7A11 and SLC3A2, key components of the cystine/glutamate antiporter that suppress lipid peroxidation and ferroptosis. As a result, METTL5-deficient OC cells displayed increased lipid peroxidation and heightened sensitivity to T cell-mediated ferroptosis in vitro and in vivo. Reintroduction of ATF4 restored SLC7A11/SLC3A2 expression and reversed ferroptosis sensitivity, while pharmacologic inhibition of ferroptosis produced similar effects. These findings identify METTL5 as a central regulator of ATF4 translation, oxidative stress control, and immune resistance in OC. Elevated METTL5 expression may serve as a biomarker for poor ICB response. Therapeutically, METTL5 inhibition, ATF4 translation suppression or ferroptosis induction represent potential strategies to enhance immunotherapy efficacy. This study establishes the METTL5-ATF4-ferroptosis axis as a critical tumor-intrinsic mechanism of immune evasion and provides a generalizable framework for decoding cancer-immune interactions.

Abstract # 2

Nebivolol Triggers Apoptosis, Ferroptosis and Necroptosis in Triple-Negative Breast Cancer

Wangjia Cao1, Anh Vuong1, Somik Chattertjee1, Tagari Samanta2, Radbod Darabi1, Ashok Kumar1, Benny Abraham Kaipparettu2, Meghana V. Trivedi1

1Department of Pharmacological and Pharmaceutical Science, College of Pharmacy, University of Houston; 2Department of Molecular & Human Genetics, Baylor College of Medicine.

Triple-negative breast cancer (TNBC) lacks effective targeted therapies and remains associated with poor outcomes. We are investigating nebivolol, an FDA-approved third-generation β-blocker, as a candidate for drug repurposing in TNBC. We have previously reported that nebivolol inhibits TNBC cell growth, proliferation, clonogenic potential and disrupts autophagic flux, leading to accumulation of autophagosomes and lysosomes. RNA-seq analysis further revealed enrichment of ferroptosis (FDR = 0.076), apoptosis (FDR = 0.111), and necroptosis (FDR = 0.133) pathways following nebivolol treatment. Here, we aimed to conduct deeper mechanistic investigation of nebivolol-induced cell death pathways. Two TNBC cell lines (MDA-MB-231 and SUM159) were used for all the experiments. The effects of nebivolol (10 μM, 24h) on ferroptosis were assessed using the BODIPY C11 lipid peroxidation assay kit. Apoptosis and necroptosis were evaluated after treatment with 10 μM nebivolol for 24, 48, and 72h using FITC Annexin V Apoptosis Detection kit. Annexin V-positive cells were classified as apoptotic, whereas Annexin V-positive/PI-positive cells represented necroptotic and late-stage apoptotic populations. Nebivolol-induced apoptosis was confirmed using western blot analysis of cleaved/total PARP and caspase-3 and -7 at 24, 48, and 72h. Necroptosis-mediated membrane damage was measured by LDH release following 3-100 μM nebivolol treatment for 24h. All experiments included a minimum of three biological replicates, each with at least three technical replicates. Data were analyzed using GraphPad Prism 10.1, and statistical significance was determined by one-way ANOVA with multiple comparisons ($p < 0.05$). Consistent with RNA-seq results, nebivolol 10 μM significantly increased lipid peroxidation by 1.5- to 2-fold, confirming ferroptosis induction. Nebivolol 10 μM significantly increased Annexin V-positive/PI-positive but not Annexin V-positive/PI-negative populations in a time-dependent manner, suggesting its role in late-stage apoptosis and necroptosis. Nebivolol 10 μM treatment elevated cleaved PARP and caspase-7, but not caspase-3 levels, in a time-dependent manner, confirming apoptosis induction. Nebivolol 30 and 100 μM significantly increased LDH release indicating pronounced necroptosis-mediated membrane rupture. Overall, nebivolol elicits multimodal programmed cell death in TNBC by activating both apoptotic and non-apoptotic pathways. These findings support nebivolol as a promising repurposed drug candidate for TNBC and identify ferroptosis and necroptosis as previously unrecognized components of its antitumor mechanism.

Abstract # 3

AXL Deficiency in Melanoma Promotes Resistance to Adoptive T Cell Therapy

Ningbo Zheng1, Xiaofang Liang1, Yuan Chen2, Si Chen1, Caitlin Creasy2, Chantale Bernatchez2, Michael T Tetzlaff3, Yunfei Wang4, Prashant Menon5, Yibo Dai6, Emily M Hinchcliff7,8, Jian Wang9, Linghua Wang6, Amir A Jazaeri8, Patrick Hwu2,4, Navin Varadarajan5, Michael A Davies2, Jiakai Hou1, Weiyi Peng1*

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Adoptive T cell therapy (ACT) has become a leading immunotherapeutic approach for treating advanced cancers, yet durable clinical responses remain limited for most patients due to immunosuppressive strategies employed by tumor cells. Although AXL, a member of the Tyro3-AXL-Mer (TAM) receptor tyrosine kinase family, has been reported as a key tumor-intrinsic factor driving tumor immune evasion, our findings reveal that elevated AXL expression in melanoma correlates positively with increased tumor sensitivity to T cell-mediated cytotoxicity, greater infiltration of tumor-infiltrating lymphocytes (TILs), and better clinical outcome in ACT-treated patients. In line with these clinical observations, AXL-deficient tumors exhibit diminished responsiveness to paired tumor-reactive T cells both in vitro and in vivo. Mechanistically, loss of AXL in tumor cells results in reduced activation of the STING pathway and increased production of TGFβ, which collectively drive upregulation of Fas on T cells and promote their apoptosis, leading to resistance of AXL-deficient tumors to T cell-mediated killing. Importantly, administration of a STING agonist significantly enhances the antitumor efficacy of ACT in mice harboring AXL-deficient tumors, indicating a synergistic therapeutic effect. Taken together, these findings reveal a unique context-dependent role of AXL in shaping antitumor immunity and support the potential utility of AXL as a prognostic biomarker of ACT and therapeutic target for refining personalized immuno-oncology combination strategies.

Abstract # 4

Cryo-EM Reveals Estrogen Receptor Alpha Induces Nucleosome Remodeling

Xinzhe Yu*, Sakib Hossen*, Ying Wang*, Lance Edward V Lumahan, Mazia Arif, Anil K. Panigrahi, Valerie Dalton, Ethan Boniuk, Mosab M. I. Gasemelseed, Matthew Baker, John P Lydon, David M Lonard#, Zhao Wang#, Ping Yi#
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Cells regulate gene expression in response to extracellular signals through transcription factors (TFs) that modulate chromatin accessibility. The estrogen receptor alpha (ERα), a ligand-activated nuclear receptor, is traditionally viewed as a secondary TF that binds nucleosome-depleted regions, relying on pioneer factors to access chromatin. However, emerging evidence suggests that ERα can also engage nucleosome-occupied DNA and contribute to chromatin remodeling. Here, we present a cryo-electron microscopy (cryo-EM) structure of ERα bound to an estrogen response element (ERE) adjacent to a nucleosome. The structure reveals that ERα directly contacts core histones and induces conformational changes in the nucleosome, including the repositioning of a histone H2A α-helix toward the surface. This movement disrupts histone-DNA interactions and increases nucleosome sensitivity to DNase I digestion. The N-terminal domain of ERα plays an important role in mediating its interaction with nucleosome. These findings reveal a previously unrecognized mechanism by which ERα directly engages nucleosomes to modulate chromatin structure.

Abstract # 5

Volumetric Bioprinting of Kidney Organoid Constructs for Advanced In Vitro Disease Models

Sampa Halder1, Shuvethapriya Sampathkumar2, Tasmia Binte Hai1, Md Rezaul Karim,1 Chandra Mohan1, George Z1. Tan

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Tomographic volumetric bioprinting (TVP) has emerged as a transformative, high-speed biofabrication technique. Unlike traditional methods, it produces complex three-dimensional structures within seconds. The process involves projecting a series of 2D light patterns into a rotating volume of photosensitive resin. Photoinitiators within the resin capture this light energy to initiate localized polymerization. By overlapping these projections, the entire volume is cured simultaneously. This approach eliminates the requirement for sacrificial support structures and the time-consuming layer-by-layer deposition found in conventional systems.

The demand for such technology is driven by significant regulatory shifts, including the FDA Modernization Act 2.0. In April 2025, the FDA announced a plan to phase out animal testing requirements for monoclonal antibodies and other therapeutics. Consequently, there is an urgent need for human-based in vitro models, such as organoids, which replicate the physiological structures and functions of real organs.

While extrusion-based bioprinting is common, it is often hindered by slow processing speeds and high shear stress. Furthermore, Stereolithography (SLA) remains limited by its reliance on repetitive, layer-wise polymerization. TVP offers a superior alternative by reducing cumulative light exposure and preventing structural discontinuities. In this study, we utilized TVP to fabricate advanced 3D scaffolds using a specialized, biocompatible bioink. Following the fabrication process, proximal tubule cells were cultured onto these scaffolds. These cells are essential for renal function, as they are responsible for reabsorbing nutrients and secreting toxins. Because they are primary targets for drug-induced toxicity, modeling these cells in a 3D environment is critical. This research provides a more predictive, human-relevant platform for drug screening and the study of Chronic Kidney Disease (CKD), offering a robust alternative to traditional animal models.

Abstract # 6

Cortisol Modulates Early Amyloid-Beta–Induced Cytotoxicity in a Neuronal Cell Model

Jennifer Nwanna1, Olga Botwinick1, Thao Dang1, Maryam Vasefi2

1. Tilman J. Fertitta Family College of Medicine, University of Houston, Houston, TX 2. Clinical Associate Professor, Tilman J. Fertitta Family College of Medicine, University of Houston, Houston, TX

Background

Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) accumulation and progressive neuronal degeneration. Stress and glucocorticoids, particularly cortisol, influence neuronal survival and brain metabolism. While chronic stress is associated with increased AD risk, emerging evidence suggests that acute glucocorticoid exposure may transiently activate protective cellular pathways. Understanding how cortisol modulates Aβ-induced toxicity may help identify stress-related mechanisms involved in early neurodegeneration.

Hypothesis

We hypothesize that acute exposure to low-dose cortisol reduces $A\beta_{1-42}$–induced cytotoxicity in SH-SY5Y cells by activating stress-related neuroprotective pathways.

Methods

Human SH-SY5Y neuroblastoma cells were cultured in DMEM/F12 with 10% FBS and plated in 96-well plates. After 24-hour attachment, cells were switched to serum-free medium and exposed for 24 hours to pre-aggregated $A\beta_{1-42}$ (1–10 μM), cortisol (1 μM), or their combination. $A\beta_{1-42}$ oligomers were prepared by incubation at 4 °C and validated using dot blot and related biophysical assays. Cell viability was quantified using the MTT assay, and all conditions were normalized to untreated controls. Statistical analyses were performed using one-way ANOVA with Tukey's post-test.

Results

Cells pretreated with cortisol were protected against $A\beta_{1-42}$-induced toxicity in SH-SY5Y cells compared with untreated cells, whereas $A\beta_{1-42}$ alone produced a marked, dose-dependent decrease in cell survival. Across multiple Aβ conditions, 1–10 μM cortisol provided statistically significant protection ($p < 0.01$), partially restoring cell survival toward baseline levels.

Conclusion

Acute exposure to low-dose cortisol, a physiological mediator of the stress response, attenuated early $A\beta_{1-42}$–induced cytotoxicity in SH-SY5Y cells, suggesting a transient neuroprotective role, potentially via glucocorticoid-mediated antioxidant or mitochondrial-stabilizing pathways. These findings support the concept that acute stress–related cortisol signaling may exert short-term protective effects under certain cellular conditions, in contrast to the detrimental effects often associated with chronic stress and prolonged glucocorticoid exposure. Although cortisol itself is not intended as a therapeutic agent, its consistent protective effect warrants detailed investigation of the underlying molecular pathways, which may reveal novel targets for neuroprotection in Alzheimer's disease. Overall, these results highlight the time-, dose-, and stress-context–dependent effects of cortisol on Aβ toxicity and support further studies of glucocorticoid signaling and stress biology as modulators of early AD-related neuronal injury, with potential relevance for therapeutic discovery and stress-targeted interventions.

Abstract # 7

Computational Dissection of Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase 2b C-Terminal Extension Autoinhibition and Its Therapeutic Potential in Darier's Disease

Rulong Ma, James M. Briggs

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The sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) maintains cellular calcium homeostasis by pumping Ca^{2+} from the cytoplasm into the endoplasmic reticulum. Among SERCA isoforms, SERCA2b is unique in possessing a C-terminal extension (CTE) composed of loop L10/11, transmembrane helix M11, and a luminal extension (LE). The CTE inhibits activity, but the mechanism remains unclear because the L10/11 structure is unresolved. Based on SERCA2b cryo-EM structures, we used integrative structural modeling and molecular dynamics simulations to show that L10/11 contains a short helix (Helix1003) that docks into a native cleft formed by loops L6/7 and L8/9 at the pump neck and remains engaged across transport intermediates. This interaction stabilizes specific conformations and slows transitions required for Ca^{2+} transport through a dual "pull-and-block" mechanism. When Helix1003 docking is disrupted by mutation, the helix unwinds, and the L10/11 segment instead engages the phosphorylation (P) domain. These interactions impede the P-domain tilting motion required for effective Ca^{2+} transport. This mechanistic shift explains several previously unresolved experimental observations for SERCA2b. We further show that the LE anchors M11, stabilizing L10/11 so that Helix1003 wedges between L6/7 and L8/9, restricts central-core tilting, and hinders conformational transitions throughout the transport cycle, defining elements of a CTE-mediated autoinhibitory mechanism. Finally, our findings suggest that relieving CTE-mediated autoinhibition may offer a therapeutic strategy for ATP2A2-linked Darier's disease. Together, this work defines the structural basis of SERCA2b CTE autoinhibition and identifies the L10/11 and L6/7-L8/9 cleft as promising therapeutic targets.

Abstract # 8

Beyond Endosomal Escape: Post-Endosomal Release Limits Functional mRNA Delivery from Lipid Nanoparticles

Hoang Quan Truong, Urmila Kafle, Cao Thuy Giang Nguyen, Fanfei Meng
University of Houston

Introduction: Messenger RNA (mRNA) therapeutics represent a transformative platform for the prevention and treatment of infectious diseases, cancer, and immune disorders. However, efficient intracellular delivery remains a major challenge due to mRNA instability and limited cytosolic accessibility. Lipid nanoparticles (LNPs) enable protection, cellular uptake, and endosomal escape of mRNA and are essential to clinically approved mRNA medicines. While endosomal escape is widely regarded as the principal barrier to delivery, the subsequent intracellular dissociation of mRNA from LNPs, which is required for translation, remains poorly understood.

Method: To investigate the mechanistic role of ionizable lipid content in mRNA release, we systematically modulated the molar fraction of clinically validated ionizable lipids (SM-102 and ALC-0315) within benchmark LNP formulations. We evaluated physicochemical properties, cellular uptake, endosomal escape, intracellular mRNA release, protein expression, and immunogenicity.

Results: Reducing ionizable lipid content below that used in clinically approved formulations (46.3–50 mol%) unexpectedly enhanced mRNA transfection efficiency and in vivo immunogenicity. Notably, endosomal escape remained comparable across formulations, whereas intracellular mRNA release was significantly increased in lower ionizable lipid LNPs, indicating that post-escape dissociation rather than escape itself can limit translation efficiency.

Conclusion: These findings identify intracellular mRNA–LNP dissociation as a previously underappreciated determinant of functional mRNA delivery and suggest that balancing electrostatic interactions, rather than maximizing ionizable lipid content, may improve LNP performance. This work provides mechanistic guidance for next-generation mRNA-LNP design beyond conventional optimization of uptake and endosomal escape.

Abstract # 9

Macrophage phagocytosis of cohesive clusters: Insights from engineered microbial assembly

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Cohesive structures such as biofilms and solid tumors can present a challenge to macrophage phagocytosis as macrophages must either overcome the cohesion to engulf individual cells or engulf an entire cluster at once, which becomes impossible beyond a certain size. Yet how macrophages interact with such cohesive structures is poorly understood. To address this knowledge gap, we engineered E. coli to assemble into multicellular aggregates using surface-displayed recombinant protein pairs – noncovalently associating coiled-coil peptides and covalently associating SpyTag/SpyCatcher peptides. When preassembled clusters were added to the macrophages, we observed that macrophages could break apart and eat portions of large cohesive clusters. Surprisingly, cluster disruption and target uptake occurred even when targets were assembled through covalent protein-protein interactions. To dissect the mechanisms involved, we inhibited key pathways. Inhibiting actin polymerization resulted in a near-complete loss of target internalization, supporting actin-dependent phagocytosis as the primary uptake mechanism. Arp2/3 inhibition resulted in a twofold decrease in phagocytosis over the first four hours, although phagocytosis eventually proceeded, while myosin II inhibition had minimal effect. Together, these results suggest a prominent role for protrusive forces driven by polymerization of branched actin networks while arguing against a role for actomyosin contractility. Blocking matrix metalloprotease (MMP) activity likewise had no significant effect, arguing against a role for extracellular proteolysis, at least by secreted and membrane-bound MMPs. Our current findings indicate that macrophages are highly adaptable in mechanically disrupting cohesive targets for phagocytosis, which might lead to the development of new strategies for modulating phagocytosis in therapeutically important settings like tumors and biofilms.

Abstract # 10

Detection and 3D structure prediction of viral xrRNAs with support from evolutionary information

Nivedita Dutta, Quentin Vicens
Postdoctoral Researcher

Exoribonuclease-resistant RNAs (xrRNAs) are complex structural elements found across major viral subfamilies, including mosquito-borne flaviviruses and plant viruses. These structures act as mechanical blocks that protect the viral genome's 3′ UTR from degradation by host exonucleases. Their critical role in viral survival and replication makes them highly attractive targets for novel small-molecule antiviral drugs. Furthermore, understanding their robust folding principles provides a rational basis for engineering highly stable RNA-based therapeutics. However, leveraging xrRNAs as either druggable targets or engineered scaffolds requires precise knowledge of their 3D structures. This relies heavily on evolutionary information from multiple sequence alignments (MSAs), which are difficult to generate due to low sequence conservation, a limited four-nucleotide alphabet, and complex 2D architectures involving pseudoknots. To overcome these complexities, we investigated whether generating reliable RNA MSAs could be automated for the improved detection and downstream structure predictions. We developed and implemented the RNAhub workflow for the automated detection of structural RNAs within the noncoding regions of viral genomes. Query sequences from viral noncoding RNA regions were subjected to iterative homology searches and covariation analysis. Subsequently, we conducted a comparative analysis of three state-of-the-art AI tools to predict the tertiary folds of the detected xrRNAs. Our results demonstrate the successful identification of xrRNAs utilizing RNAhub, including improved detection of covariation signals and critical pseudoknot interactions. Comparing the de novo 3D structure predictions revealed that robust evolutionary evidence also translates to superior accuracy in 3D structure modelling. Overall, our study highlights the necessity of accurate RNA MSAs. By providing high-fidelity structural insights through automated pipelines like RNAhub, our results facilitate the identification of druggable viral RNAs for high-throughput screening. Simultaneously, this enables the design of degradation-resistant, mechanically functional xrRNAs, accelerating both antiviral drug discovery and the development of next-generation RNA medicines.

Abstract # 11

Intramolecular strategy for the synthesis of phenylplumericin derivatives with improved efficiency and diversification for Ewing sarcoma therapy

(1) Anuththara Yoshini Madduma Hallinage, (2) Nenggang Zhang, (3) Rohitesh Kumar, (4,5) Tanja Grkovic , (4,5) Barry R O'Keefe, (2) Debananda Pati, and (1) Scott R. Gilbertson

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Ewing sarcoma (EWS) is an aggressive primary bone malignancy that predominantly affects adolescents and young adults and is associated with poor clinical outcomes in relapsed or refractory disease. Current therapeutic strategies are limited by intrinsic and acquired chemoresistance, a high propensity for metastasis, and the absence of effective targeted treatments, largely due to an incomplete understanding of the disease's molecular drivers. These limitations underscore the need for new therapeutic agents with novel mechanisms of action.

Phenylplumericin, an iridoid natural product identified through screening of the National Cancer Institute Program for Natural Products Discovery (NCI NPNPD) library, has demonstrated selective antitumor activity against EWS in both in vitro and in vivo models. Isolated from Eupatorium fistulosum (Joe Pye weed), phenylplumericin possesses a stereochemically complex, polycyclic framework that presents a significant synthetic challenge. Despite its promising biological activity, the lack of a reported total synthesis has limited further exploration of its therapeutic potential.

Herein, we report the development of a synthetic strategy toward phenylplumericin designed to enable efficient access to this complex scaffold and its derivatives. The approach is guided by a modular design that facilitates structural diversification, allowing systematic interrogation of key functional features through analogue synthesis. This synthetic platform is expected to support detailed structure–activity relationship studies and enable the generation of sufficient material for biological evaluation.

Collectively, this work establishes a foundation for the synthesis and functional exploration of phenylplumericin and related compounds, with the broader objective of advancing new therapeutic strategies for the treatment of Ewing sarcoma.

Abstract # 12

Enhancing CAR T-Cell Therapy for Prostate Cancer via Microfluidic T-Cell Isolation

Kevin Song, Hui Huang, Mubasher Iqbal, Sean Gifford, Sergey Shevkoplyas, Qin Feng
Department of Biology and Biochemistry, University of Houston

Chimeric antigen receptor (CAR) T-cell therapy has demonstrated significant success in hematologic malignancies but remains less effective in solid tumors such as prostate cancer. One contributing factor is the quality of starting T cells, as conventional isolation methods like density gradient centrifugation (DGC) can be time-consuming and may negatively impact T-cell fitness. Controlled Incremental Filtration (CIF) is a microfluidic, label-free technology that isolates high-purity lymphocytes with potential advantages for CAR T-cell manufacturing.This study compares PSMA-specific CAR T cells generated from CIF-isolated T cells to those derived using DGC. T cells were activated, transduced with a PSMA-targeting CAR construct, and expanded in vitro. Transduction efficiency was assessed by GFP flow cytometry, proliferation was measured through cell expansion over time, and cytotoxicity was evaluated using luciferase-based killing assays against PSMA-expressing LNCaP prostate cancer cells. CIF- and DGC-derived T cells exhibited comparable transduction efficiencies, with 60.5% and 56.5% GFP-positive cells, respectively. However, CIF-derived CAR T cells demonstrated enhanced proliferation, with higher cell numbers observed throughout the expansion period. Despite this difference, both CIF- and DGC-derived CAR T cells showed similar, dose-dependent tumor cell killing across increasing effector-to-target ratios.These findings suggest that CIF improves CAR T-cell expansion without compromising antitumor function. CIF therefore represents a promising alternative to traditional T-cell isolation methods and may enhance the scalability and quality of CAR T-cell therapies for prostate cancer and other solid tumors.

Abstract # 13

Screening of KRAS G12D inhibitor resistance in pancreatic cancer

Samuel Borromeo, Mosab Gasemelseed, Ping Yi

Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, University of Houston

Mutations in the KRAS oncogene drive pancreatic ductal adenocarcinoma (PDAC), with KRASG12D accounting for 45% of KRAS-mutant cases. Small-molecule KRAS inhibitors such as MRTX1133 frequently elicit acquired resistance through reactivation or bypass of RAS–MAPK signaling, highlighting the need for combination treatment in KRASG12D-targeted therapies. To identify genes that modulate response to KRAS inhibition, we performed an MRTX1133-anchored CRISPR-Cas9 activation screen (CRISPRa) in KRASG12D-mutant AsPC1 cells. Candidate hits were rigorously prioritized using an integrative pipeline that combined MAGeCK RRA and MLE-based ranking with cross-validation across multiple analytical approaches, followed by downstream validation via targeted knockdown and overexpression. One of the top hits was ASAP2 (ArfGAP with SH3 domain, Ankyrin repeat, and PH domain 2), an Arf GTPase-activating protein involved in cytoskeletal remodeling, cellular trafficking, and cellular migration. ASAP2 has been previously identified as a driver of PDAC and its overexpression is correlated with poor survival. However, its role in KRASG12D inhibition resistance remains poorly understood. Overexpression of ASAP2 was found to promote cell-cycle progression in MRTX1133-treated cells through ERK-independent activation of Cyclin D1 and CDK4 and inactivation of Rb1. This data suggests that ASAP2 may act as an alternative survival modulator, promoting cell-cycle progression by activating an upstream receptor-driven signaling axis that bypasses RAS-MAPK signaling and sustains survival under KRASG12D inhibition.

Abstract # 14

Lipid Nanoparticle–Mediated Targeting of Liver Sinusoidal Endothelial Cells for Therapeutic Intervention in Liver Fibrosis

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Liver sinusoidal endothelial cells (LSECs) are specialized endothelial cells that line hepatic sinusoids and play essential roles in maintaining liver homeostasis. These cells regulate immune surveillance, vascular tone, lipid clearance, and communication with other hepatic cell types. During chronic liver injury, LSECs undergo structural and functional alterations characterized by loss of fenestrations, basement membrane deposition, and inflammatory activation. This process, known as LSEC capillarization, disrupts hepatic microcirculation and promotes liver inflammation and fibrosis. Importantly, LSEC dysfunction occurs early in liver disease and contributes to the activation of hepatic stellate cells, highlighting LSECs as an attractive therapeutic target.

Despite their importance, efficient drug delivery to LSECs remains challenging. Small molecules rapidly diffuse through LSEC fenestrae and distribute to hepatocytes, while nanoparticles are often captured by Kupffer cells, limiting selective delivery to LSECs. To address this challenge, we developed lipid nanoparticle (LNP) formulations designed to enhance LSEC uptake. By optimizing nanoparticle size, lipid composition, and PEGylation, the resulting nanoparticles (~160 nm) exploit the high endocytic capacity of LSECs to promote efficient cellular internalization.

In vivo biodistribution studies using fluorescently labeled nanoparticles demonstrated strong liver accumulation following intravenous administration. Flow cytometric analysis of liver cell populations revealed approximately a 14-fold increase in delivery to LSECs compared with free cargo. Notably, approximately 81% of nanoparticle-associated signal within the liver was localized to LSECs, indicating strong cell-type specificity.

Together, these results demonstrate that lipid nanoparticle engineering enables efficient and selective delivery to LSECs. This strategy provides a promising platform for developing LSEC-targeted therapeutics for liver fibrosis and other chronic liver diseases.

Abstract # 15

Decoding TDRD1 Interactions with Ribosomal Proteins in Prostate Cancer Progression

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Abstract

Tudor domain-containing protein 1 (TDRD1) is aberrantly overexpressed in a substantial fraction of prostate tumors and has been implicated in tumor-associated molecular organization, potentially through liquid-liquid phase separation (LLPS)-dependent assembly. Prior studies have established TDRD1 as a molecular scaffold that recognizes symmetrically dimethylated arginine residues and organizes RNA-protein complexes, particularly in the context of piRNA pathway components and RNA-rich cytoplasmic condensates in germ cells. However, its interaction network in cancer cells remains poorly defined. Ribosomal proteins of the small 40S subunit (RPS proteins) are core components of ribosomes that contribute not only to mRNA translation but also to ribosome biogenesis, rRNA processing, and nucleolar organization. RPS proteins are also known contributors to RNA-protein condensates and higher-order molecular assemblies. In this study, we investigated interactions between TDRD1 and selected RPS proteins identified by mass spectrometry in our laboratory. Co-immunoprecipitation assays were performed in 293T cells following co-expression of TDRD1 with candidate RPS proteins. A focused panel including RPS19, RPS27, RPS4X, RPS25, and RPS29 was examined for association with TDRD1. Among the candidates tested, RPS19 and RPS27 showed the most robust and reproducible associations with TDRD1. These data suggest that TDRD1 may selectively engage small ribosomal subunit components and potentially participate in ribosome-associated RNA-protein assembly or condensate organization in prostate cancer cells.

Abstract # 16

Next-Generation Albumin Nanoformulations: Optimizing Pharmacokinetics, Targeted Delivery, and Immune Modulation

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Albumin nanoformulations have been applied in cancer therapy as safe systems to enhance drug solubility, yielding two FDA-approved drugs (Abraxane® and Fyarro®). However, these formulations are largely limited to improving solubility, as albumin nanoparticles are believed to rapidly dissociate in the bloodstream. Our lab has investigated albumin nanoformulations for over a decade and uncovered properties highlighting their potential beyond solubility enhancement.

We first discovered that strong drug–albumin binding affinity enables highly stable nanoparticles that fundamentally alter pharmacokinetics and reduce on-target toxicity. We developed Nano-1252, an albumin nanocomplex of BCL-2/xL inhibitor prodrug APG-1252, which remained stable after 50,000-fold dilution—unlike Abraxane. Nano-1252 reduced blood drug exposure, suppressed premature prodrug activation, and expanded the platelet toxicity threshold fourfold, while preferentially accumulating in bone marrow, spleen, and lymph nodes. Building on this, we developed Nano-PI, co-encapsulating a PI3Kγ inhibitor (IPI-549) and paclitaxel, which accumulated preferentially in macrophages across tumors and tumor-draining lymph nodes, achieving 2- to 2.5-fold higher drug exposure versus free drug combinations.

We further developed Nano-273 to overcome intrinsic immunotherapy resistance. STING agonists activate myeloid cells but paradoxically expand immunosuppressive regulatory B cells (Breg). We discovered that PI3Kγ inhibition selectively abolishes STING-induced Breg expansion while preserving myeloid STING activation. Nano-273, an albumin nanoformulation of the dual STING agonist/PI3Kγ inhibitor SH-273, systemically remodeled the tumor immune microenvironment and, combined with anti-PD-1, extended median survival to 200 days versus 122 days in transgenic KPC pancreatic cancer mice. Nano-273 is now advancing toward clinical translation through manufacturing scale-up, combination studies, and non-GLP canine PK/toxicity studies for IND submission.

Our long-term vision is to establish albumin nanoformulations as a universal drug delivery platform to optimize pharmacokinetics, reduce toxicity, and enhance therapeutic efficacy across diverse disease indications.

Abstract # 17

Vascular-Targeted Liposomal Delivery for Modulating Neurovascular Inflammation in Vascular Dementia

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Vascular dementia (VaD) accounts for approximately 15-20% of all dementia cases and affects an estimated 1.5-2 million individuals in the United States. Despite its high prevalence, effective clinical treatments remain lacking, largely because the molecular mechanisms linking cerebrovascular injury to neurovascular inflammation and white-matter degeneration are not fully understood. Increasing evidence suggests that vascular inflammation plays a central role in VaD progression.

In experimental models of VaD, we observed pronounced inflammatory activation within the cerebral vasculature, characterized by markedly elevated expression of the endothelial adhesion molecule VCAM-1 along brain blood vessels. This vascular inflammatory phenotype suggests that activated brain endothelial cells may represent an important driver of neurovascular inflammation during VaD progression.

Motivated by this observation, we sought to develop a vascular-targeted therapeutic strategy aimed at selectively modulating endothelial inflammation. Building upon our laboratory's liposome engineering platform, we designed a high–drug-loading liposomal system incorporating the ionizable lipid SM-102 to enhance nanoparticle stability and encapsulation efficiency. The engineered nanoparticles demonstrated robust formulation performance, achieving approximately 80% drug loading (DL) and encapsulation efficiency (EE) with a uniform particle size of ~150 nm. To enable selective targeting of inflamed vasculature, the liposomes were functionalized with VCAM-1–binding ligands, allowing preferential interaction with activated endothelial cells. In vitro targeting assays using OGD-treated bEnd.3 endothelial cells, a model of ischemic vascular stress, demonstrated that VCAM-targeted liposomes exhibited 46.7% higher cellular uptake compared with non-targeted liposomes after only 1 hour of incubation.

To further enhance targeting precision, we expanded our ligand engineering strategy beyond conventional antibodies by developing VCAM-binding peptides and single-domain nanobodies (VHH). These modular ligands provide compact and tunable targeting architectures that may improve vascular penetration and binding specificity while reducing steric hindrance.

Collectively, our findings highlight VCAM-associated vascular inflammation as a key pathological feature of VaD and establish a VCAM-targeted liposomal nanoplatform for selectively engaging inflamed brain endothelium. This strategy provides a promising framework for vascular-targeted anti-inflammatory therapy in vascular dementia and potentially other blood–brain barrier–associated neurological diseases.

Abstract # 18

Putative Computational Design of Novel Inhibitors To Modulate De Novo Targets for Cannabinoid receptor 1

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Cannabinoid receptor 1 (CB1), a class A GPCR, regulates key neurological processes including pain, appetite, and mood, yet conventional therapeutics are limited by adverse neuropsychiatric effects arising from non-selective pathway activation. Recent structural studies of the CB1–β-arrestin complex and broader GPCR signaling frameworks highlight the importance of signaling bias and receptor internalization mediated by β-arrestin. Although GPCRs account for ~35% of marketed drug targets, therapeutic strategies remain predominantly focused on orthosteric ligand-binding sites, with over half of FDA-approved drugs acting through this mechanism. This leaves a critical gap in targeting dynamic transducer-specific interfaces such as the CB1–β-arrestin binding pocket, which are structurally flexible and underexplored.

This study presents a proof-of-concept computational strategy to target the CB1–β-arrestin interface using both small-molecule and cyclic peptide design approaches. Structural analysis of the CB1–β-arrestin complex was used to identify key interaction residues within the intracellular binding pocket, which served as templates for inhibitor design. RFdiffusion was applied to generate backbone conformations for cyclic peptides targeting the interface, followed by LigandMPNN sequence optimization and Rosetta-based scoring for stability and binding affinity. In parallel, Boltzmann-based small-molecule screening was used to identify candidate compounds predicted to bind the same interface, with top candidates ranked by predicted interaction energies. Together, these approaches demonstrate the feasibility of targeting transducer-specific GPCR interfaces computationally. This framework establishes a foundation for future experimental validation and the development of biased modulators that selectively regulate CB1 internalization and downstream signaling.

Abstract # 20

3 Dimensional (3D) peptoid-based pan-KRAS inhibitors for lung cancer treatment

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KRAS is one of the most commonly mutated oncogenes across various cancer types, making it an attractive target for developing pan-KRAS inhibitors to overcome drug resistance caused by tumor heterogeneity. However, conventional drugs have had limited success targeting KRAS, long considered “undruggable” due to its large binding surface without having deep binding pockets and displaying strong GDP/GTP affinity. To overcome these challenges, we hypothesized that branched 3D peptoids could bind KRAS through multi-site interactions and serve as an effective scaffold for pan-KRAS inhibition independent of mutations. We screened a 144,500 3D peptoid library to identify a hit compound targeting KRAS G12V. We identified a hit peptoid, PKR1, which binds both inactive (GDP -) and active (GTP-bound) KRAS G12V with Kd values of 607 nM and 438 nM, respectively. Its unbranched (PKR1.M) and scrambled (PKR1.S) derivatives showed no binding, supporting a multi-site interaction. We also proposed that lipid conjugation of peptoids would enhance their membrane localization, thus increasing efficacy and selectivity. PKR1-C16 coupled with palmitic acid (C16) demonstrated the best pan-inhibitory activity across multiple KRAS mutants (G12V, G12C, and Q61H) and WT cancer cell lines, with IC50 values ranging from 3.0 to 9.4 μM, but not on normal HBEC3-KT cells. TIRF microscopy using AF647-labeled PKR1-C16 revealed strong membrane colocalization, whereas the parent PKR1 showed no detectable membrane association. PKR1-C16 significantly suppressed in vivo tumor growth in H441 xenograft models without observable toxicity. Here, we developed a novel 3D-branched peptoid, PKR1, targeting multiple KRAS mutants. Fatty acid conjugation further enhanced membrane targeting and pan-mutant inhibitory efficacy. These results highlight the potential of peptoid-based therapeutics to effectively and broadly target KRAS-driven cancers and address the limitations of conventional drug development approaches.

Abstract # 21

AI-based Drug Design to Target Allosteric Domains of the Androgen Receptor

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The androgen receptor (AR) is a nuclear receptor that plays critical roles in hormone regulation and human development. AR activity accelerates hormone-driven malignancies, such as spinal and bulbar muscular atrophy (SBMA) and multiple cancers. AR function is highly regulated by protein post-translational modifications (PTMs). Our lab has published that in metastatic breast cancer, AR is modified by the protein PTM SUMOylation at lysine 386 (K386), and that SUMO-modified AR is 1) highly stable, 2) drives oncogenic transcriptional reprogramming, and 3) is resistant to FDA-approved AR-targeted therapies. More AR-targeted approaches for treatment are needed. The AR N-terminal domain (NTD) is responsible for PTM regulation of AR and facilitates both canonical and oncogenic AR activity, making it an attractive drug target. However, the NTD is an intrinsically disordered region (IDR), making conventional drug design using crystal structures and computational small molecule drug screening ineffective.

To address this gap, we utilized all-atom molecular dynamics simulations with ensembles of AR Tau5 (residues 360-485) using Boltz2, modeling six experimental states, including mono- and poly-SUMOylation identifying SUMO site K386 alone and in combination with covalent NTD-targeted binders. Our work 1) investigates how SUMO modification of AR impacts the structural dynamics of the Tau5 regulatory IDR and 2) develops new targeted approaches to treat malignancies driven by PTMs of the Tau5 IDR.

Our results validated that SUMOylation at K386 stabilizes the IDR Tau5 domain, increasing its fold confidence (pTM > 0.80). The addition of covalent small molecules to the poly-SUMOylated Tau5 resulted in helical collapse of the Tau5 domain, revealing its impact on geometry destabilization of NTD-targeted inhibition. This demonstrates that SUMOylation not only stabilizes the disordered AR-NTD through conformational compaction but also dictates the geometric success of targeted inhibition. Our studies provide a structural basis for designing more effective allosteric AR inhibitors as well as targeted protein degraders (PROTACs) and next-generation covalent inhibitors. Concurrently, additional fundamental biochemical assays have been established to test the drug-protein relationship; specifically, AR-NTD binding and AR-transcriptional activity. Our work using dry- and wet-lab approaches lay the foundation to warrant testing new allosteric AR drugs for metastatic disease.

Abstract # 22

Precision Delivery of Antibodies to the Brain Using Targeted Lipid Nanoparticles for Alzheimer's Disease

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Alzheimer's disease (AD) is the leading cause of dementia, yet no curative therapies exist. Monoclonal antibodies targeting amyloid-β (Aβ) have shown clinical promise, as reflected by recent FDA approvals, but their overall benefit remains limited by poor penetration across the blood–brain barrier (BBB). Typically, less than 0.1% of systemically administered antibodies reach the brain, necessitating high doses that increase the risk of adverse effects such as amyloid-related imaging abnormalities.

This project aims to develop a targeted nanomedicine platform to enhance antibody delivery to the brain and improve therapeutic outcomes in AD. We propose a lipid nanoparticle (LNP)-based strategy that enables efficient BBB transport while preserving antibody functionality. Inspired by the high encapsulation efficiency of nucleic acids in LNPs, we re-engineer proteins using a reversible covalent supercharging approach that transiently imparts dense anionic character, rendering proteins compatible with LNP formulation. We demonstrate the feasibility of this strategy using a model protein system.

Ongoing studies focus on extending this approach to therapeutic antibody payloads and further evaluating performance in animal models. This platform has the potential to improve the efficacy and safety of antibody therapies for AD and provides a generalizable strategy for delivering biologics to the central nervous system.

Abstract # 23

N-Terminal Modifications of a Plectin-Targeting Peptoid Improve Cytotoxicity Against NSCLC Cancer Stem Cells

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Cancer stem cells (CSCs) are inherently resistant to conventional therapies, contributing to tumor recurrence and poor clinical outcomes. Effective eradication of these residual cell populations is therefore critical for improving patient survival. We previously identified a peptoid, PCS2, that selectively targets a subpopulation of non-small cell lung cancer (NSCLC) cells through interaction with plectin protein. Although plectin is typically a cytoskeletal protein, it is aberrantly expressed on the cell surface in CSCs—referred to as surface-translocated plectin (STP)—where it contributes to proliferation, invasion, and metastasis. Subsequent optimization of PCS2 led to the development of a dimeric analog, PCS2D1.2, which exhibited significantly enhanced cytotoxic activity. Notably, incorporation of an N-terminal benzophenone moiety—initially introduced for pull-down and target identification—resulted in an approximately 18-fold improvement in efficacy. In this study, we sought to determine whether alternative N-terminal modifications could similarly enhance biological activity. To this end, we synthesized a library of twelve N-terminally modified PCS2D1.2 derivatives, incorporating eleven distinct organic acids and one amine (4-aminobenzophenone). MTS cytotoxicity assays identified three lead compounds—PCS2D1.2-BP, PCS2D1.2-SP, and PCS2D1.2-CM—with IC50 values of 1.32, 1.60, and 1.24 μM, respectively, compared to ~18 μM of the parent PCS2D1.2 compound. These derivatives also demonstrated improved efficacy in blocking CSC survival and migration, evaluated from colony formation and wound healing assays, respectively. Collectively, these findings suggest that N-terminal functionalization enhances peptoid-PCS2 activity, potentially through engagement with an additional binding pocket on plectin. This study provides a promising strategy for improving CSC-targeted therapeutics in NSCLC.

Abstract # 24

Chronic Effects of Insulin-Like Growth Factor 1 supplementation on Microgliosis After Experimental Traumatic Brain Injury

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Traumatic Brain Injury (TBI) is a leading cause of death and disability worldwide and is associated with aberrant signaling within the hypothalamic-pituitary axis, contributing to decreased levels of insulin-like growth factor 1 (IGF-1). IGF-1 supplementation following TBI has demonstrated beneficial effects in preclinical and clinical trials. However, the extent of systemic IGF-1 on neuroinflammation has yet to be ascertained. Microglia are the immune cells of the brain and are involved in regulation of neuroinflammation. Morphological alterations to microglia following TBI contribute to chronic neuroinflammation and increased risk of neurodegenerative diseases. However, the effects of IGF-1 on the microglial response following TBI have not been fully investigated. We hypothesized that IGF-1 supplementation following TBI would alleviate alterations in microglia. Ten-week-old male Sprague Dawley rats received a mild-to-moderate lateral fluid percussion injury (FPI) or sham surgery followed by IGF-1 or vehicle via intraperitoneal injection at 4- and 24-hours post-injury. Brains were collected 35 days post-injury, processed, then stained with anti-Iba1 to visualize microglia. Utilizing unbiased stereology, Iba1+ cells were quantified in the subregions of the dentate gyrus. Quantitative analysis revealed non-significant increases in Iba+ cells in the FPI group that were not reduced by IGF-1 treatment. These findings suggest that at no significant differences were observed for the number of microglial cells in the dentate gyrus. However, morphological or genetic analysis may reveal that despite a lack of quantitative difference, the activation state of microglial cells may be altered by IGF-1 treatment after TBI. Future studies are needed to assess these possibilities.

Abstract # 25

Design and Development of Mitophagic Agonist as a Therapeutic Strategy against Acute Myeloid Leukemia

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Background: Acute myeloid leukemia (AML) is a high-risk malignancy characterized by rapid progression and a high relapse rate in adults. It is also the most common acute leukemia in adults. Hematological malignancies were shown to upregulate and depend on oxidative phosphorylation (OxPhos) for energy production. This metabolic dependency makes OxPhos and mitochondria a promising therapeutic target. Work from our collaborator's (Dr. Kirienko) lab has established the hypothesis that inducing autophagic degradation of mitochondria (mitophagy) could trigger apoptosis (programmed cell death). On this basis, a high-throughput, small molecule screen for mitophagic activators yielded several compounds that are selectively cytotoxic to AML. Structure-activity relationship (SAR) analysis identified a promising hit family containing a nitrostyrene scaffold.

Methods: Cheminformatics was used to expand on the initial hits, which were predicted to have two functions: apoptotic agonism and thioredoxin/glutathione reductase inhibition (T/GRi). We synthesized molecules based on those structural hits and performed SAR analysis. Lead designs were based on systematic bio-isosteric modulation of nitroalkene scaffold, electronic tuning of the aryl moiety, and steric hindrance. Finally, we came up with a functionalized nitrostyrene core, leading to the synthesis of a novel lead series designated as RUNK.

Results: Biological assays identified 6 compounds active against AML MOLM-13 cells. The synthesized series yielded several leads with sub-micromolar potency (CC50 = 0.39 – 0.92 μm) against this cell line. Differential scanning fluorometry indicated direct binding of the prioritized leads to the target enzyme.

Conclusion: This collaborative research identifies a nitrostyrene scaffold core in mitophagic agonists and positions them as novel therapeutics that leverage mitochondrial dysregulation in leukemia for their effect. By triggering apoptotic induction via antioxidant depletion, these leads may offer a high-potential translational strategy for treatment development.

Abstract # 26

Nebivolol Exhibits Cell Growth Inhibition in Drug-resistant HR+/HER2- Breast Cancer and Anti-tumoral Synergism with Abemaciclib in vitro

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We are investigating nebivolol, a third-generation beta-blocker, as a drug-repurposing candidate for breast cancer (BC). While prior studies have focused on triple-negative BC, we evaluated its efficacy and potency in hormone receptor-positive, HER2-negative (HR+/HER2-) BC, which is the most prevalent subtype. Since HR+/HER2- BC is typically treated with endocrine therapy (ET) alone or in combination with CDK4/6 inhibitors (CDK4/6i), we also assessed the effects of nebivolol in ET- and CDK4/6i-resistant models, as well as in combination with ET and CDK4/6i. The efficacy and potency (IC50) of nebivolol were evaluated using MCF7 and T47D parental cells as well as their ET- and/or CDK4/6i-resistant derivatives [estrogen deprivation resistant (EDR), palbociclib-resistant (PalboR), and EDR/PalboR]. Nebivolol inhibited growth in parental and ET- and CDK4/6i-resistant MCF7 and T47D cells in a concentration-dependent manner. Efficacy (%) and potency (μM) of nebivolol were as follows: MCF7-P [84.1 and 7.9]; EDR [79.1 and 12.3]; PalboR [73.5 and 13]; EDR/PalboR [68.4 and 20.4]; T47D-P [96.1 and 5.8]; EDR [94.6 and 5.4]; PalboR [86.7 and 5.7]; EDR/PalboR [91.6 and 5.2]. Additionally, nebivolol demonstrated synergism with abemaciclib in Chou-Talalay and Loewe analysis. Effective combinations included 0.3-10 μM, and 1 or 10 μM of nebivolol with 30-300 nM of abemaciclib (CI < 1 in Chou-Talalay method) in T47DP and MCF7P, respectively. Significant % inhibition in combination compared to single agent alone was observed at 0.3-3 μM of nebivolol with 30 nM of abemaciclib in T47DP and 3 μM of nebivolol with 100 or 300 μM abemaciclib in MCF7P. Loewe analysis also revealed nebivolol-abemaciclib synergism, with the most synergistic area score of >10 (12.51 in MCF7P and 41.14 in T47DP). Nebivolol inhibited the growth of HR+/HER2- BC cell lines sensitive or resistant to ET and/or CDK4/6i and synergized with abemaciclib. Ongoing studies are evaluating nebivolol and ET combinations for enhanced therapeutic potential.

Abstract # 27

Targeting CDK5 with the novel inhibitor TK22 suppresses endothelial-to-mesenchymal transition in idiopathic pulmonary arterial hypertension

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Idiopathic pulmonary arterial hypertension (IPAH) is a progressive vascular disease driven by endothelial dysfunction, smooth muscle cell proliferation, and endothelial-to-mesenchymal transition (EndMT). Cyclin-dependent kinase 5 (CDK5) has recently emerged as a potential regulator of vascular remodeling, although its role in EndMT is not yet fully proofed.

In this study, we designed, synthesized, and evaluated TK22, a novel ATP-competitive inhibitor of CDK5. Docking studies (PDB: 7VDP) predicted stable binding within the ATP-binding pocket, supported by key hydrogen bonding and hydrophobic interactions. TK22 was synthesized in three steps with high purity (97%) and demonstrated strong CDK5 inhibition (IC_{50} = 181.3 nM).

In GFP-labeled mouse endothelial cells, TK22 effectively suppressed TGF-β1–induced EndMT, reducing mesenchymal markers (α-SMA, SM22α, and calponin), decreasing cell proliferation, restoring angiogenic capacity, and limiting contractile behavior.

Single cell sequencing revealed that TGF-β1 drives EndMT from a proliferative $Mki67^{+}$ endothelial population and induces a hypoxia-adaptive state. Notably, TK22 selectively eliminated the EndMT-prone subpopulation, disrupted this transition, and restored endothelial identity without broadly affecting other cell states.

Overall, these findings identify CDK5 as an important regulator of endothelial plasticity and highlight TK22 as a promising therapeutic candidate for IPAH and other diseases driven by EndMT.

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Abstract # 28

Antibody-Targeted Nanoparticles via Polymerization-Induced Self-Assembly for Targeted Therapies

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Antibody-targeted nanomedicine enables precise delivery of therapeutics to disease sites or the immune system, improving efficacy while minimizing off-target toxicity and enhancing the therapeutic window. Such nanoparticles can serve as drug carriers or as antibody-based platforms to modulate the cell surface proteome, including applications such as membrane protein degradation for precision therapy.

Despite their promise, clinical translation is often hindered by complex multistep synthesis and potential immunogenicity associated with conventional nanoparticle systems. To address these challenges, we report a scalable nanomedicine platform based on polymerization-induced self-assembly (PISA). This one-pot strategy enables simultaneous nanoparticle formation and covalent incorporation of therapeutic payloads within a disulfide-crosslinked polymer matrix, while introducing surface-accessible click groups for subsequent functionalization.

Zwitterionic monomers are incorporated to generate polymers with low immunogenicity, excellent biocompatibility, and prolonged circulation, offering a promising alternative to PEG-based systems. The resulting nanoparticles form stable aqueous dispersions with diameters of 100–200 nm and can be prepared at high solid content (10–50 wt%), supporting scalability. The disulfide crosslinks are reductively cleavable, allowing controlled nanoparticle degradation and payload release under biologically relevant conditions. In addition, this platform demonstrates broad compatibility with diverse monomers.

As a proof of concept, antibodies are conjugated to the nanoparticle surface via click chemistry, enabling selective uptake in established cell lines and primary T cells. These functionalized nanoparticles can facilitate the degradation of oncogenic membrane proteins (e.g., EGFR, HER2) or immune checkpoint ligands (e.g., PD-L1), providing a versatile approach for both cancer targeting and immune modulation.

Ongoing studies focus on incorporating clinically relevant prodrugs, evaluating intracellular release, and assessing therapeutic efficacy in vivo. Overall, this work establishes a robust and scalable strategy for the development of targeted nanomedicines for precision therapy.

Abstract # 29

Evaluating RPE-hIL12 efficacy using humanized murine tumor models

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Cancer immunotherapy has become a promising treatment for patients. Cytokines are proteins that help the immune system operate against foreign bodies, used alone or in combination with other immunotherapies. Previous research explored cytokine delivery in syngeneic murine models and demonstrated a decrease in ovarian and colorectal tumor progression. However, this model is not ideal to explore the treatment effects of devices using human cytokine delivery. To overcome the cross-species limitation, a preclinical model that investigates cytokine-producing ARPE-19 cells (RPE-hIL12) is needed to facilitate clinical trial progression. Using human cell lines in humanized mouse models, we hypothesize RPE-hIL12 will elicit superior antitumor effect with limited toxicity when combined with immune checkpoint inhibitors (ICI) in a humanized mouse model. We generated six human ovarian (OC) and pancreatic (PDAC) cancer cell lines expressing luciferase to challenge mice and monitor tumor growth in vivo through bioluminescence IVIS imaging (BLI). Subsequently, we humanized immunodeficient mice using human peripheral blood mononuclear cells (Hu-PBMC). We selected the top two cell lines from each cancer type to evaluate the efficacy of RPE-hIL12 treatment. Our studies found that RPE-hIL12 at a high dose significantly reduced tumor burden in SKOV3 and BxPC3 tumor-bearing mice. To yield better anti-tumor response, we tested hIL12 production at 60k, 30k and 10k pg/day and optimized dosage. Additionally, based on clinical trial results, we combined RPE-hIL12 with anti-CTLA4 (aCTLA4) in the SKOV3 peritoneal tumor model. Overall, we observed smaller tumor size and an increase in interferon gamma (IFNγ) levels in peritoneal fluid, indicating localized treatment effect. As well, capsule-released aCTLA4 elicited superior antitumor response to injected aCTLA4, with increased T cell presence in the tumors in comparison to RPE-hIL12 alone. Based on our results, we will continue to refine localized treatment settings and identify linked mechanisms and potential biomarkers.

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Abstract # 30

Developing a CRISPR Activation Screen to Identify Novel Mechanisms for Regulating Phagocytosis

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Phagocytosis is an essential cellular function that is especially important in the innate immune response to cancer. Understanding the mechanisms involved in regulating phagocytosis is crucial to identifying novel therapeutic targets for improving innate immunotherapies. Here, a CRISPR Activation (CRISPRa) screen is developed to functionally interrogate the impacts of gene overexpression in phagocytosis to identify possible membrane proteins and signaling pathways regulating phagocytosis. CRISPRa utilizes a modified CRISPR-Cas9 system to upregulate gene expression, and by complexing the system with guide RNAs (gRNAs) designed to target the promoter regions of specific genes, precise activation of these genes is possible. Stable cell lines (V2M) were generated with essential CRISPRa components through lentiviral transduction, including in human monocytic THP-1 cells. Receptor overexpression was determined by fluorescent antibody staining and flow cytometric analysis of THP1-V2M cells transduced with gRNAs targeting the CD206 receptor. Having demonstrated the efficacy of the CRISPRa system in THP1-V2M cells, screening conditions were then optimized for future transduction with a gRNA library targeting human membrane receptor proteins and an assay to detect phagocytic activity. Viral MOI was determined by transducing THP1-V2M cells with increasing volumes of the gRNA library virus. Phagocytic activity in THP1-V2M cells was evaluated at different time points after incubation with a phagocytosis assay reagent containing fluorescent bacteria. Using the identified optimized conditions, the screen may then be performed in the future utilizing THP1-V2M cells transduced with the gRNA library and fluorescence automated cell sorting to detect and isolate cells with increased and decreased phagocytic activity. Genomic DNA will be extracted from these cells to be utilized in next generation sequencing to identify possible membrane proteins regulating phagocytosis. By integrating these and previous results from phagocytosis screens, these results can comprehensively elucidate signaling pathways involved in phagocytosis and may identify drug targets to improve innate immunotherapies of cancer.

Abstract # 31

α4β7, IL12p40, or IL23p19 Targeted Nanoparticles as a Theranostic for Inflammatory Bowel Disease

Angela Vu, Dr. John W. Craft Jr, Ron Biediger, Robert Market, Frederick Meece, Amy Caivano, Anna Kazansky, Shahrzad Abbasi, Peter Vanderslice, Darren G. Woodside
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Inflammatory bowel disease (IBD), including Crohn's disease, is characterized by chronic intestinal inflammation driven by dysregulated immune responses and atypical leukocyte trafficking. The disease progression is driven by two key principal immunological pathways: gut-directing leukocyte trafficking mediated by α4β7 integrins and IL-12/IL-23 mediated Th1 and Th17 cytokine activation. Our team will link our α4β7 compounds and IBD biologicals with lipid nanoparticles for dual diagnostic and therapeutic activity, expanding treatment for IBD. IBD treatment often involves the evolution of treatment agents based on each person's personal journey of engagement and success. This might include the use of different biologics like Adalimumab, Briakinumab, Ustekinumab, Risankizumab, and Vedolizumab, based on that persons presentation of IBD and responsiveness to treatment. We will evaluate molecular models based on crystal structures to target linkages for our technology to ride as cargo as antibody-nanoparticle-drug conjugates.

The full battery for each biologic-nanoparticle-drug conjugate has the promise of stage focused and personal care. This has the great advantage that treatment application would be encapsulated within current clinical protocols. AIM 1) Model engineered targeted nanoparticles that directly conjugate to approved IBD biologicals focusing on Vedolizumab, Ustekinumab, and Risankizumab. AIM 2) Model our integrin α4β1/α4β7 dual specificity small molecule compounds

for incorporation into lipid-based nanoparticles (LNPs). AIM 3) Develop a program plan to implement prototype testing of the linked lipid nanoparticles that will coordinate the stakeholders at the University of Houston,

Texas Heart Institute @ Baylor College of Medicine, and the vested pharmaceutical companies.

Models for the IL-12p40: Briakinumab/Fab complex structure will be from PDB: 5NJD.

The IL-12p40:Ustekinumab/Fab complex is PDB: 3HMX. The model for α4β7 integrin will be from our in-house validated model. I will use PyMOL, GROMACS, and AMBER to prepare proposed models for simulation.

Abstract # 32

Drug Discovery: Optimizing SYK Kinase Protein Production to Target Inflammation in Atherosclerotic Cardiovascular Disease

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Atherosclerosis is fundamentally an inflammatory disease, and integrin signaling through SYK (Spleen Tyrosine Kinase) — a non-receptor tyrosine kinase essential for IL-1β production in monocytes and macrophages — represents a compelling therapeutic target for residual cardiovascular risk. This study aimed to optimize recombinant production and purification of His-tagged SYK kinase (residues 6–269) to establish a high-yield protein platform supporting Fragment-Based Drug Discovery (FBDD) and Structure-Activity Relationship (SAR) studies in atherosclerotic cardiovascular disease. SYK was expressed in a bacterial system, lysed by sonication on ice, and clarified by high-speed centrifugation. Purification employed Nickel-NTA IMAC with a 2X bead volume to maximize binding kinetics, followed by 7,000 MWCO desalting for buffer exchange. Yield was validated by Bio-Rad Bradford Assay and SDS-PAGE with ImageJ densitometry. Protein was formulated in 50 mM HEPES pH 7.5, 500 mM NaCl, 5% glycerol, and 1 mM TCEP at -80°C. Compound potency was assessed through cell-based integrin signaling assays across a 400-member library. The optimized protocol produced 12.4 mg of SYK kinase — a 5-fold improvement over previous methods. Post-desalting yield was 7.478 mg, with Pool 1 confirmed as the highest-concentration fraction at 7.41 mg/mL by SDS-PAGE and ImageJ densitometry. Final working concentration was established at 3.75 mg/mL (125 μM). Of 400 synthesized compounds screened, 44 met the NIH activity threshold of ≤10 μM. Lead compounds Ligands C and D, developed through SAR-guided scaffold merging, achieved sub-nanomolar IC50 values (best: 6.75 ± 3.5 nM) while maintaining maximal signal suppression. This work establishes a robust protein production and functional assay platform for SYK-targeted drug discovery in atherosclerotic cardiovascular disease. Future directions include isotopic labeling (^{15}N, ^{13}C) for SAR by NMR and FBDD to resolve binding interfaces at atomic resolution and guide the rational design of next-generation cardiovascular therapeutics.

Abstract # 33

Progesterone suppresses cervical cancer cell proliferation through cooperative progesterone receptor isoform signaling and receptor independent mechanisms.

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Cervical cancer (CC) is the fourth most common cancer among women worldwide and primary cause is persistent infection with high-risk human papillomavirus (HPV), including HPV16 and HPV18. However, it is not sufficient. Hormonal cofactors such as progesterone and estrogen are essential in the development of cervical carcinogenesis. Studies using HPV transgenic mouse models have shown that estrogen (E2) promotes the development of cervical cancer whereas progesterone receptor (PR) signaling activation inhibits tumor progression. PR deletion promotes cervical cancer development even without E2 treatment, identifying PR as a tumor suppressor in cervix. In the cervix, PR is expressed in PRA and PRB isoforms. Prior work from our lab demonstrates that expression of PRA or PRB alone is insufficient to mediate progesterone induced anti-cervical cancer activity, highlighting a critical gap in understanding PR isoform cooperation. In parallel, emerging evidence suggests that non classical progesterone signaling pathways may contribute to PR independent anti-tumor effects. Membrane progesterone receptors have been implicated in mediating non genomic signaling and are associated with improved clinical outcomes, supporting a multi layered mechanism of progesterone action.

To address this, we investigated the effects of progesterone (P4) on cell proliferation and colony formation in cervical cancer cell line SiHa. Using co-expressed PRA/PRB cells along with corresponding empty vector (EV), we evaluated high dose progesterone response. P4 treatment significantly reduced cell proliferation in high dose. In EV cells (no PR expression), P4 significantly suppress colony formation and reduce cell proliferation with 30 uM and 20 uM respectively, demonstrating receptor independent anti-tumor activity. Co-expressed PRA and PRB enhanced P4 mediated growth suppression, with statistically significant reduction at 10 μM and 20 μM. Finally, these findings demonstrate the PR independent and dependent mechanisms of progesterone therapeutic response.

Abstract # 34

Provisional Treatment of Endometriosis using Targeted Nanotherapy via Talin-1, Alpha4Beta1 , and EP2/4.

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Endometriosis is an inflammatory disease that affects 10% of women globally. The inflammatory disease is often discovered within patients in the later stages as a consequence of latency. Due to latency, most patients diagnosed with endometriosis live with deep tissue lesions, cysts, and build up of scar tissue. In order to mitigate this, nanoparticles can be used to target early onset endometriosis by targeting areas of inflammation before the development of larger lesions can occur. This early detection can be achieved through attaching the nanoparticles to upregulated cell surface proteins (i.e. PTGR4(EP4), PTGER2(EP2), α4β1), which then can bind to the receptors (i.e. GPCR) at the site of inflammation. The bonded nanoparticles will then be detectable using MRI imaging for precise diagnosis of early-stage endometriosis. This treatment will aid in streamlining the limited therapeutic pipeline and possible delivery cargo to modulate protein pathways that are important in endometriosis remodeling.

The aim for my project is to evaluate possible molecular markers and/or protein signaling pathways that can be targeted for early diagnosis or treatment. A table of these candidate markers and regulators was developed for evaluation.

My plan is to evaluate each candidate to determine possible strategies for interdiction in endometriosis. Then I will build structural models of each candidate target to be used in docking, molecular simulation and selection of compounds for synthesis that meet a -9 deltaG pseudo energy and have stable molecular interactions upon MD simulation.

A scaffold personalized care centered around endometriosis is possible through the strategic placement of nanoparticles. At the site of inflammation the nanoparticles will display a signal using MRI, and used to treat the area, and lay the grounds for personalized care, noninvasive treatments, and define a new global standard for endometriosis treatment.

Abstract # 35

Effect of Model Scale on Structural Information Encoding in RNA Language Models

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RNA molecules play key roles in genetic information transfer and gene expression regulation, functions that are directly implicated in the development of many diseases. Their structured forms represent promising targets for small-molecule drug design. Accurate prediction of secondary structure is therefore essential, as structural organization determines drug binding sites. Secondary structure prediction is enabled by contact maps, which computationally represent pairwise structural interactions within folded RNA molecules. Existing RNA structure prediction strategies primarily employ thermodynamic folding models or computational approaches that infer structural patterns. Nonetheless, accurate secondary structure prediction remains a significant challenge for novel and disease-associated RNA molecules in contexts where data availability is limited. Recent developments in artificial intelligence demonstrate that large models trained on biological sequences can infer structural patterns from sequence information, without the need for evolutionary comparisons. However, it remains unclear whether larger models encode this information more effectively. To evaluate this, a contact-map prediction pipeline was developed using attention outputs from two RNA language models of different sizes: a compact model (RNABERT, 6 layers) and a larger model (NucleicBERT, 32 layers). Results indicated that NucleicBERT produced more accurate predictions than RNABERT. However, both models showed reduced accuracy under realistic biological contact distributions compared with balanced training conditions, highlighting a limitation for therapeutic applications. These results suggest that larger RNA language models capture more structural information but remain limited for deployment in RNA drug discovery under realistic biological conditions.

Abstract # 36

TRAF4-TMEM9-β-catenin axis promotes lineage plasticity and resistance to AR pathway inhibition in Prostate cancer

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Lineage plasticity represents a key mechanism of resistance to androgen receptor pathway inhibition in prostate cancer (PCa) and contributes to the development of aggressive neuroendocrine prostate cancer (NEPC). The molecular mechanisms underlying plasticity-driven resistance in PCa remains poorly understood and no effective therapies currently exist to target it. Our findings identified E3 ubiquitin ligase TRAF4 as a regulator of Wnt/β-catenin signaling and androgen-independent growth in PCa. TRAF4 overexpression promotes survival under androgen-deprived conditions and confers resistance to the androgen receptor inhibitor enzalutamide. Mechanistically, TRAF4 interacts with the lysosomal membrane protein TMEM9, a regulator of vacuolar ATPase activity and lysosome-mediated degradation. TRAF4 overexpression enhances TMEM9-dependent degradation of the β-catenin destruction complex component APC and resulting stabilization of β-catenin. Consistently, TRAF4 overexpression increases β-catenin transcriptional activity and upregulates stemness/plasticity markers upon enzalutamide treatment. Together, these findings uncover a previously unidentified TRAF4-TMEM9-β-catenin signaling axis that promotes lineage plasticity and resistance to AR targeted therapy in PCa. Targeting this pathway may represent a potential therapeutic strategy to overcome lineage plasticity and resistance to androgen receptor pathway inhibitors in PCa.

Abstract # 37

Cardioprotective roles of Mas and MrgD axis activation by Angiotensin-(1–7) and Alamandine in cardiac remodeling.

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Pathological cardiac hypertrophy is a major driver of heart failure and arrhythmia. Angiotensin II (Ang-II), a key effector of the classical renin–angiotensin system (RAS), promotes hypertrophic remodeling and fibrosis by activating maladaptive transcriptional and metabolic programs in cardiomyocytes. In contrast, the non-canonical RAS peptides Angiotensin-(1–7) and Alamandine exert cardioprotective effects through activation of the Mas and MrgD receptors, respectively; however, the molecular mechanisms underlying their protective actions remain incompletely understood. In this study, we investigated the roles of Alamandine and Angiotensin-(1–7) in modulating cardiac hypertrophy, fibrosis, and cardiac dysfunction using complementary in vitro and in vivo models. In vitro experiments were performed using AC16 human cardiomyocytes and human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs). Pathological hypertrophy was induced by Ang-II stimulation, after which cells were treated with Alamandine, Angiotensin-(1–7), or their combinations with Ang-II. These cellular models enabled evaluation of molecular pathways associated with hypertrophic and fibrotic remodeling, including changes in gene expression and downstream signaling mechanisms regulated by Mas and MrgD receptor activation. To validate these findings in vivo, cardiac hypertrophy was induced in mice through continuous Ang-II infusion for 14 days using ALZET 1002 osmotic pumps. Mice were subsequently treated with Alamandine or Angiotensin-(1–7) to assess their therapeutic and preventive potential. Cardiac structure and function were assessed using echocardiography, while histological and molecular analyses were performed to quantify hypertrophy and fibrosis. Our results show that treatment with Alamandine or Angiotensin-(1–7) effectively prevented Ang-II–induced hypertrophy and fibrosis, demonstrating the protective role of Mas and MrgD axis activation in limiting pathological cardiac remodeling. This study aims to define the distinct and overlapping roles of Mas and MrgD receptor signaling in regulating cardiac remodeling and downstream effector pathways. Elucidating these mechanisms may identify novel therapeutic targets within the protective arm of the RAS for the prevention and treatment of heart failure.

Abstract # 38

Development and Characterization of a Functional in vitro Neuromuscular Junction Model using Human iPSC-Derived Motor Neurons and Skeletal Myotubes

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The neuromuscular junction (NMJ) is a highly specialized synapse critical for voluntary motor function, and its dysfunction is a hallmark of severe neuromuscular diseases such as Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA). Developing robust, human-relevant in vitro models is essential for elucidating disease mechanisms and advancing drug discovery. In this study, we aimed to establish and characterize a functional human NMJ model using induced pluripotent stem cells (iPSCs), which has been a promising source for disease modeling and regenerative medicine due to their source abundance and pluripotency.

Briefly, human iPSCs were directed to differentiate into two distinct cell populations: skeletal myotubes and motor neurons. These populations were subsequently integrated into a co-culture system that automatically innervates to serve as an in vitro model of the NMJ. To evaluate the developmental trajectory, maturation, and synaptic functionality of the model, we performed quantitative PCR (qPCR) targeting key regulatory genes for both cell populations and the synaptic region. Cellular identity and morphological organization were validated via immunofluorescence (IF) staining against lineage-specific markers. Finally, functional neuromuscular connectivity was assessed by monitoring in vitro muscle contraction and conducting calcium imaging assays. In conclusion, we developed an iPSC-derived co-culture model of the NMJ that exhibits appropriate transcriptional, morphological, and functional hallmarks of neuromuscular connectivity. The presence of functional synaptic transmission, validated by muscle contraction and calcium activity, demonstrates that this system is a viable and highly physiologically relevant platform. We expect significant potential of this NMJ models in studying NMJ development, modeling neuromuscular disorders, as well as fabrication of iPSC-derived multicellular tissue for regenerative medicine.

Abstract # 39

Identification of Novel Upstream Activators of PAX7 in Human Skeletal Muscle Cells

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Skeletal muscle regeneration is governed by tightly regulated transcriptional networks, in which PAX7 plays a central role in the specification and maintenance of muscle stem cells (MuSCs). Dysregulation of these processes is associated with impaired muscle repair and a range of degenerative muscle diseases, highlighting the need to better understand the upstream mechanisms controlling PAX7 expression.

In this study, we aimed to identify and functionally characterize novel regulators of PAX7 using human skeletal muscle (HSkM) cells. Using a genome-wide activator gRNA library screen on a human ESC PAX7 reporter cell line, fourteen candidate genes were identified and systematically evaluated using a bidirectional (overexpression and knock down) perturbation approach. Gene knockdown was performed using siRNA-mediated silencing, while gene overexpression was achieved through lentiviral-based expression systems. Following these perturbations, changes in PAX7 and main myogenic genes' expression were assessed using qRT-PCR and/or protein-based assays to determine the regulatory role of each candidate gene. This strategy allowed us to distinguish between positive and negative regulators by comparing the effects observed under loss-of-function and gain-of-function conditions.

Preliminary results so far indicate that multiple candidate genes influence PAX7 expression, with several demonstrating consistent and reciprocal effects across both experimental approaches. These findings suggest that these genes may function as upstream regulators of PAX7 and contribute to the broader regulatory network governing myogenic processes. Ongoing work is focused on validating these candidate genes, improving reproducibility, and further characterizing their role in skeletal muscle biology using muscle-specific conditional knockout murine models. Ultimately, this study provides a foundation for identifying novel upstream PAX7 regulators, which can be leveraged to enhance muscle regeneration as therapeutic targets.

Abstract # 40

Developing a multicellular human iPSC therapy for skeletal muscle regeneration

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Human induced pluripotent stem cells (hiPSCs) offer a promising platform for regenerative medicine due to their pluripotency and capacity for patient-specific therapies. However, the clinical application of hiPSC-derived myogenic progenitor cells (MPCs) remains limited by poor survival and insufficient microenvironmental support following transplantation. Endothelial cells (ECs), as key components of the muscle niche, play a critical role in vascularization and secrete trophic factors that regulate myogenic cell function.

In this study, we aim to develop a multicellular iPSC approach for skeletal muscle regenerative applications using muscle progenitor cells (MPCs) and endothelial cells (ECs). Additionally, we plan to investigate their crosstalk mechanisms in vitro and also to test their in vivo regeneration potential. So far, we have established efficient differentiation protocols for human iPSCs to generate both MPCs and ECs. MPC identity was confirmed by successful differentiation into multinucleated myotubes, while ECs were validated by expression of endothelial markers and characteristic morphology. To investigate cellular crosstalk, we developed an in vitro co-culture system to evaluate the interaction between hiPSC-derived ECs and MPCs using cellular, proteomic, and transcriptomic assays which are in progress.

Our results demonstrate that co-culture with ECs enhances MPC survival under stress conditions, as evidenced by reduced apoptotic markers compared to MPC monoculture. Proteomic analysis of the EC secretome further suggests enrichment of factors associated with anti-apoptotic signaling, angiogenesis, and muscle development, providing potential mechanistic insight into the observed protective effects. These findings support a role for EC-derived paracrine signaling in promoting MPC viability and function. Additionally, co-culture conditions indicate improved functional outcomes in MPCs, highlighting the importance of recreating a physiologically relevant microenvironment. Ongoing studies are evaluating the therapeutic efficacy of combined EC and MPC transplantation in vivo to determine their impact on muscle regeneration and vascularization.

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