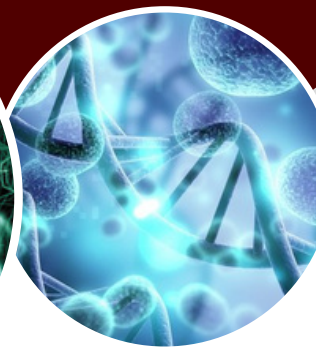
2026

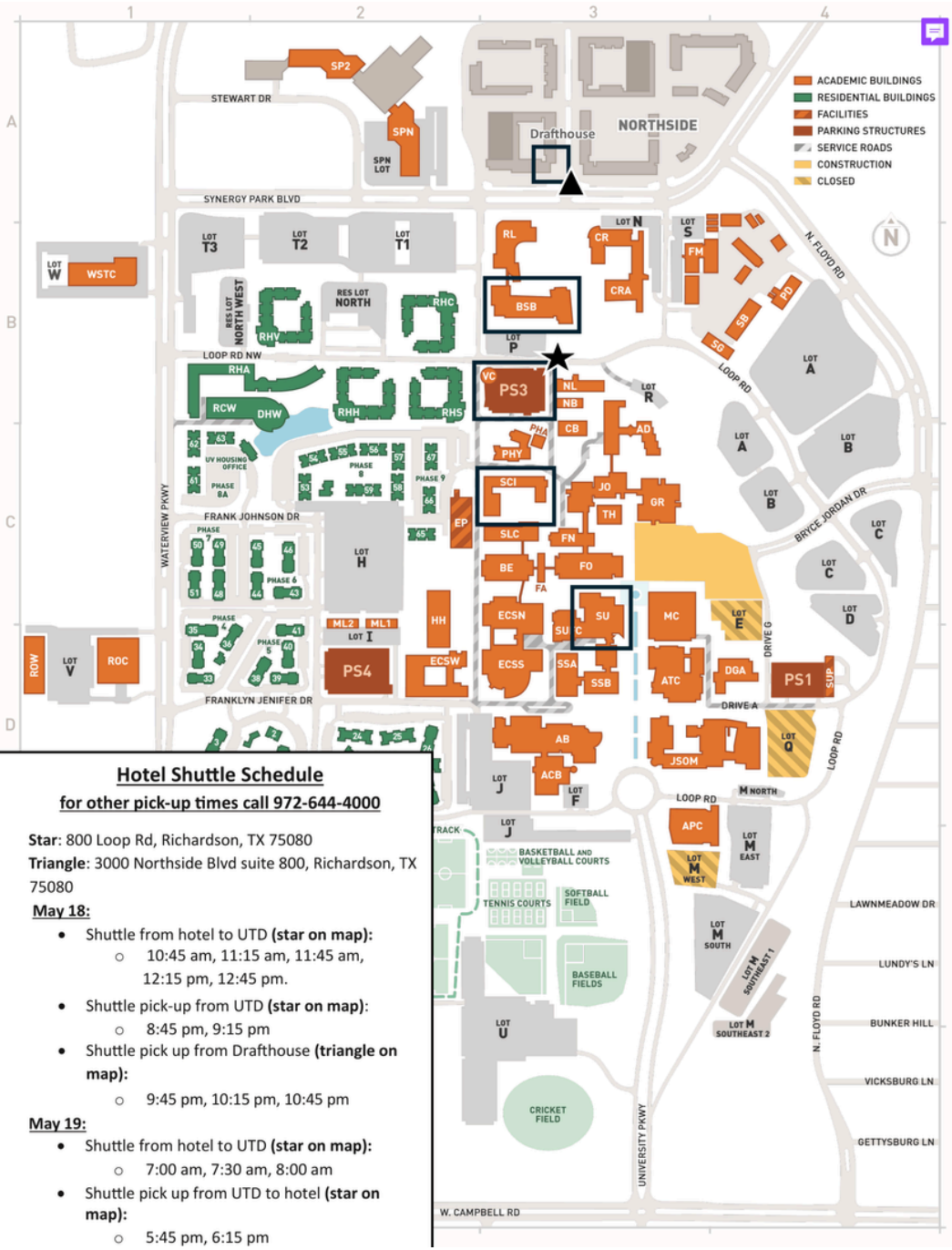
Texas Chemical Biology Conference

WHERE CHEMISTRY MEETS BIOLOGY :
DECODING LIFE'S LANGUAGE



MAY 18-19, 2026

THE SCIENCE BUILDING AND BIOENGINEERING SCIENCES BUILDING
UNIVERSITY OF TEXAS AT DALLAS



Hotel Shuttle Schedule

for other pick-up times call 972-644-4000

Star: 800 Loop Rd, Richardson, TX 75080
Triangle: 3000 Northside Blvd suite 800, Richardson, TX 75080

May 18:

- Shuttle from hotel to UTD **(star on map):**
  - 10:45 am, 11:15 am, 11:45 am, 12:15 pm, 12:45 pm.
- Shuttle pick-up from UTD **(star on map)**:
  - 8:45 pm, 9:15 pm
- Shuttle pick up from Drafthouse **(triangle on map):**
  - 9:45 pm, 10:15 pm, 10:45 pm

May 19:

- Shuttle from hotel to UTD **(star on map):**
  - 7:00 am, 7:30 am, 8:00 am
- Shuttle pick up from UTD to hotel **(star on map):**
  - 5:45 pm, 6:15 pm

Event Schedule

May 18th, 2026

11:00 a.m.	Check-in @ Sciences Building: SCI 1.220
12:00 p.m.	Lunch
1:00 p.m.	Welcome Remarks

Session 1 — **Imaging with Chemistry**
Moderator: Jack Russo (Baylor)

1:10 p.m.	Achieving optical transparency in live animals with absorbing molecules *Zihao Ou (UT Dallas)*
1:35 p.m.	Localized Realtime Biosensors for Metabolism *Lulu Cambrinne (UT Austin)*
2:00 p.m.	Cryptochromes: Magnetoreception and Isoform Selective Drug Design *Brian Zoltowski (SMU)*
2:25 p.m.	Elevated intracellular copper induces CTR1 monomerization and prevents copper uptake *Tai-Yen (U Houston)*
2:50 p.m.	Coffee Break

Session 2 — **Studying Microbes with Chemical Biology**
Moderator: Mary Burns (UTSW)

3:10 p.m.	A unified semantic model of chemical function for scalable discovery of bioactive molecules *Despoina Mavridou (UT Austin)*
3:35 p.m.	Illuminating metal ions in the gut microbiota with flavin- and bilin-binding fluorescent protein sensors *Melissa Zastrow (U Houston)*
4:00 p.m.	Activity-based profiling of carbohydrate metabolism in the gut microbiome in health *Aaron Wright (Baylor)*

Event Schedule

May 18th, 2026

Sponsor Presentation

4:25 p.m.	William Zhang (MedChemExpress)
4:30 p.m.	Chris Lunn (Promega)
4:35 p.m.	Jiaqui Liu (ChemeScence)
4:45 p.m.	Photo (Outside of Student Union (SU)
5:00 p.m.	Dinner (Galaxy Rooms, SU 2.602)
6:00 p.m.	1st Poster Session (1st floor of SU): **Poster 1-52**
	Vendor Shows (SU 2.602)

Session 3 **Interrogating Macromolecular Structure**

Moderator: Yougant Airan (UT Southwestern)

7:00 p.m.	Converging Allosteric Regulation from Distant Sites in Liver Pyruvate Kinase *Sheena D'Arcy (UT Dallas)*
7:25 p.m.	Switchable RNA Surface Chemistry for Productive Delivery and Room-Temperature mRNA Storage *Quanbing Mou (Rice)*
7:50 p.m.	Exploring RNA Structure, Protein Binding, and Translation through In-Cell Chemical Probing *Lauren Hagler (TAMU)*
8:15 p.m.	Dynamic mechanisms of human mitochondrial translation *Jinfan Wang (UTSW)*
9:00 p.m.	Social Hour @ Northside Drafthouse

For more information regarding speaker topics, scan QR code or visit: https://www.txchembio.org

Event Schedule

May 19th, 2026

8:00 a.m.	Breakfast
Session 4	**Biopolymers and Bioconjugates** Moderator: Chandra Kanth Bandi, UT Dallas
8:30 a.m.	Microscale Single-Cell Analyses of Protein Complexes in Pediatric Cancer *Julea Vlassakis (Rice)*
8:55 a.m.	Enabling De Novo Protein Sequencing Through Innovations in Bioconjugations and Large Language Models *Joe Buonomo (UT Arlington)*
9:20 a.m.	Synthetic Strategies for Near-Infrared Fluorophores in Chemical Biology *Syed Muhammad Usama (UTSA)*
9:45 a.m.	Can VSEPR-re-engineered recarbonized nanoarchitectures intervene in anthropogenic exposome-associated neurodegenerative trajectories *Mahesh Narayan (UTEP)*
10:10 a.m.	Coffee Break
Session 5	**Small Molecule Therapeutic Approaches** Moderator: Trae Hampton, TAMU
10:30 a.m.	Hit-to-Lead Discovery via High Throughput Screening at UT Southwestern *Bruce Posner (UTSW)*
10:55 a.m.	Boron Chemistry for Bioconjugation and Drug Discovery *Shiqing Xu (TAMU)*
11:20 a.m.	Targeting Undruggable Protein with Small Molecular Degrader *Yaxia Yuan (UTHSSA)*
11:45 a.m.	Small molecule ligands for RPS23 activate the integrated stress response and display anti-leukemia activity *Joe Ready (UTSW)*

Event Schedule

May 19th, 2026

Sponsor Presentation

12:10 p.m.	Doug Carlton (Shimadzu)
12:15 p.m.	Scott Hutto (Beckman)
12:20 p.m.	Wenshe Liu (TAMU Drug Discovery)
12:25 p.m.	Rudi Fasan (UTD Center for High-Throughput Reaction Discovery and Synthesis)
12:35 p.m	Lunch
01:05 p.m.	2nd Poster Session and Vendor Shows @ Bioengineering Biosciences (BSB) Atrium: **Poster 53-135**

Session 6 — **Next-generation Therapeutic Approaches**

Moderator: Shelby Phelps (UT Dallas)

02:45 p.m.	Macrocyclic Peptides for the Disruption of KRAS Nanoclusters *Steven Millward (MD Anderson)*
03:10 p.m.	Application of AI and High Throughput Proteomics for Molecular Glue Discovery *Jin Wang (BCM)*
03:35 p.m.	Expanding the Druggable Proteome with Molecular Glues *Hojong Yoon (MD Anderson)*
04:05 p.m.	DT2216, a BCL-XL Selective Degrader: from Laboratory to the Clinic *Daohong Zhou (UTHSSA)*
04:25 p.m.	Coffee Break
04:45 p.m.	Presentation of Travel and Poster Awards
05:00 p.m.	The 2026 SynthX Texas Chemical Biology Young Investigator Lecture: Probing Membrane Structures from the Inside-Out for Epithelial Biology Discovery and Therapeutic Delivery *Brian Belardi (UT Austin)*
05:30 p.m.	Closing Remarks

For more information regarding speaker topics, scan QR code or visit: https://www.txchembio.org

Poster Session

Poster #	Presenter Name	Poster Title
1	The University of Texas at Dallas	Center for High-Throughput Reaction Discovery & Synthesis
2	MedChemExpress	Advancing Drug Discovery Through DNA-Encoded Library Technologies: Innovations, Applications, and Future Directions
3	Abdalrahman Khalifa *(Texas A&M University)*	Development of Small-Molecule YEATS4 Inhibitors for Lung Cancer
4	Abeda Sultana Shamma *(The University of Texas at Dallas)*	Molecular Dynamics Simulation Study of Unphosphorylated B-RAF: Wild-Type and Cancer-Associated Mutations
5	Achini Eliiyapura *(Baylor University)*	MCM8/9 Ensures Genomic Continuity during Mitotic Progression
6	Adebowale Alade *(Baylor College of Medicine)*	Tag and Trash: A Mechanism-Guided Discovery Platform Identifies ELAVL1 Degrader
7	Alan Pham *(Texas A&M University)*	Deciphering the Neddylation Pathway through Advanced Proteomic and Drug Discovery Methods
8	Allison Goetz *(Texas A&M University)*	Exploring the Impact of Asymmetrically Modified CpGs and Nucleosome Sequence on TDG Activity in Chromatin
9	Alvaro Silvestre *(The University of Texas Rio Grande Valley)*	FloDisMod: Community Outreach Project for Vector-Borne Diseases Prevention in the Rio Grande Valley
10	Andrea M. Gonzalez *(The University of Texas at El Paso)*	Assembly and Structural Characterization of the Hsp90-Hsp70-HOP-MAPKAPK2/RAF1

Poster Session

Poster #	Presenter Name	Poster Title
11	Arunprasath Duraisamy *(The University of Texas at Arlington)*	Developing Cancer-Relevant Genomic Mutations of U1 snRNA Using CRISPR/Cas9 with Circular Single-Strand Donors from the pScaf Phagemid System
12	Arvin B Karbasi *(Stanford University*	Sol-moiety: Discovery of a Water-Soluble Prodrug Technology for Enhanced Oral Bioavailability of Insoluble Therapeutics
13	Baiyu (Boris) Zhu *(Texas A&M University)*	Thymine DNA Glycosylase Binds to R-loops and Excises 5-Formyl and 5-Carboxyl Cytosine from DNA/RNA Hybrids
14	Brian Chou *(Texas A&M University)*	Breakdown of Biotin: Bacterial Catabolism of Vitamin B7
15	Chandra Bhushan Mishra *(Baylor College of Medicine)*	Development of Quinoxiline-Containing Inhibitors of the Protein-Protein Interactions between Transcription Coactivator AF9/ENL and DOT1L/AF4: Design, Synthesis, Structure-Activity Relationships, and Antitumor Activity
16	Chia-Lung Tsai *(Texas A&M University)*	LipiX-MS: A Novel Crosslinking Mass Spectrometry Strategy for Studying Lipid-Protein Interactions
17	Daniel Pearson *(The University of Texas at Dallas)*	Molecular Dynamics Simulations of BRAF Kinase Mutant Complexes Reveal Variant Effects and Activation Mechanisms
18	Debdatta Das *(The University of Texas at Arlington*	Biomolecular Condensates Formed by Designer Antimicrobial Peptides

Poster Session

Poster #	Presenter Name	Poster Title
19	Demonta D. Coleman *(Texas A&M University)*	Site-Specific Immobilization of ZNRF3 Reveals the Importance of Target Structural Integrity on Macrocyclic Peptide Selections
20	Dorsa Rabie *(Texas A&M University)*	Phage-Assisted Discovery of Anti-Cancer Peptides for Histone Deacetylase (HDAC) Proteins
21	Duc Minh Ngu *(The University of Texas at Arlington)*	The U1 snRNP-Specific Protein U1C Is a Key Regulator of SMN Complex–Mediated snRNP Formation
22	Dylan Wicherts *(The University of Texas at Dallas)*	Development of a Red Fluorescent Biosensor for Nitrate
23	Edwin Biju *(The University of Texas Rio Grande Valley)*	Predicting the Northward Expansion of the Central American Locust (Schistocerca piceifrons) Using Machine Learning and Citizen Science
24	Kalista Vanden Berge *(Texas A&M University)*	Improving Heterochiral Aptamer Interactions through 2'OMe Modified SELEX
25	Elizabeth K. Pack *(The University of Texas at Dallas)*	The C-Terminal Region Tunes Nitrate Binding Affinity in Nitrate Sensors from Staphylococcus
26	Emily Burningham *(Texas A&M University)*	Influences of Native ESI Buffers on Protein Structure Captured by Native Mass Spectrometry
27	Evelyn Luiton *(The University of Texas Rio Grande Valley)*	Citizen Science: Establishing a Community-Based Monitoring Network for the Central American Locust in the Rio Grande Valley

Poster Session

Poster #	Presenter Name	Poster Title
28	Kelly Aguirre *(University of Texas at El Paso)*	Structural Insights into the DapC, DapD, DapE, and DapF: Key Enzymes of the meso-Diaminopimelate (mDAP) Pathway
29	Fernando Montalvillo *(The University of Texas at Dallas)*	Molecular Dynamics Reveal Mechanistic Divergence Between the Two Pores of Fluc
30	Fernando Chavira *(The University of Texas at El Paso)*	Structural Understanding of Protein Interac9ons that Regulate Ca2+ Homeostasis in Arabidopsis Thaliana
31	Fnu Biakengzaua *(The University of Texas at San Antonio)*	A General Strategy for Photostable and Bioconjugatable Pentamethine Cyanine Fluorophores
32	Francis N. Eze *(The University of North Texas)*	Development of Sulfated Flavonoids as Selective Allosteric Inhibitors of Plasmin
33	Gen Chen *(Southern Methodist University)*	Working Towards Energy Transfer Near IR Chemiluminescence Probe
34	Giang T. Tran *(The University of Texas at Arlington)*	Synthesis and Analysis of Host-Activated Prodrugs
35	Gladys Owusu-Addo *(Texas A&M University)*	Influence of Intramolecular Epistasis on Catalytic Promiscuity and Enzyme Specificity among Protein Homologs
36	Gopal K. Dubey *(Texas A&M University)*	Design and Application of Genetically Encoded Phage-Derived Peptide Probes for High-Throughput Screening of Bromodomain Protein 9
37	Hailee McCulloch *(The University of Texas at San Antonio)*	Methodology for Functionalized Enneamethine Cyanines Enables Synthesis of Diverse Fluorophores above 850 nm

Poster Session

Poster #	Presenter Name	Poster Title
38	Haiyang Zheng *(Baylor College of Medicine)*	GlueMiner: Powering Next Generation Molecular Glue Discovery through Data Integration, Templated AI Folding and High-throughput Virtual Screening
39	Haley Sachse *(The University of Texas at Austin)*	Phospholipid Bilayer Fatty Acid Composition Controls Membrane Electrostatics and Fluidity
40	Hannah K. Pyle *(Texas Christian University)*	Breaking the Keap: Unlocking Nrf2 for Neuroprotection in Alzheimer's Disease
41	Haoyue Dong *(Rice University)*	GlycoRNA and Cell Surface RNA Biogenesis Study Through Flow-Cytometry Based CRISPR Screen
42	Henry Neal *(The University of Texas at Dallas)*	Stereochemically Defined Cyclohexylamide Scaffolds as Chiral Peptidomimetics for Mimicking α-Helical Surfaces
43	Hongyuan Yang *(Texas A&M University)*	An Integrated Platform for High-Throughput Native Mass Spectrometry Screening and Thermodynamic Profiling
44	Imogen Hoffman *(Southern Methodist University)*	Visible Light 3D Printing of Microneedles
45	Ilsmail lalami *(The University of Texas at Dallas)*	Selective Inhibition of HAT1 Using AB Oligomers: A Tunable Platform for Targeting Enzymes
46	Jack Russo *(Baylor University)*	Electronically Tuned Quinone Methide Probes Enable Functional Profiling of Carbohydrate Metabolism in the Gut Microbiome

Poster Session

Poster #	Presenter Name	Poster Title
47	Jack W. Sibert *(The University of Texas at Dallas)*	Discovery of a Color and Chloride Tuning Hotspot in a Red Fluorescent Protein
48	Jessica Adoma Osei *(The University of Texas Rio Grande Valley)*	Development of New Antibacterial Candidates against Helicobacter pylori: Rational Design of an Initiation Factor 1 derived Peptide based on IF1 Structure and Function and Identification of New Inhibitory Compounds
49	Jessica Steiner *(Texas A&M University)*	The Chemistry and Enzymology of Riboflavin (Vitamin B2) Catabolism
50	Jiawei Dong *(The University of Texas at Austin)*	A Split Intein Reaction to Modulate Dynamics of Protein Condensates
51	Jie Zhang *(The University of Texas at Austin)*	Rapid Biocatalysis of Stereocomplex Polyketides by in vitro Reconstituted Assembly Lines
52	Jin Yang *(The University of Texas Southwestern Medical Center)*	Biochemical Basis of the Regulation of the SCF(Met30) E3 Ubiquitin Ligase by Sulfur Metabolism and Cadmium
53	The University of Texas at Dallas	Center for High-Throughput Reaction Discovery & Synthesis
54	MedChemExpress	Advancing Drug Discovery Through DNA-Encoded Library Technologies: Innovations, Applications, and Future Directions
55	Jishan Khan *(Texas Tech University)*	Investigating Eph Receptor Endocytosis in Cancer and Model Cells: A TIRF Microscopy Approach

Poster Session

Poster #	Presenter Name	Poster Title
56	Daniella Chacon *(The University of Texas at El Paso)*	Structural Regulation and Dynamic Chaperone Activity of Hsp27 in Cellular Stress Responses
57	Jonathan Martinez-Garcia *(The University of Texas at Dallas)*	Characterization of MctB: a Copper Transporter of the Mycomembrane
58	Juan E Martinez Urbay *(The University of Texas at El Paso)*	Evaluation of αGal-Liposomes on Macrophage Polarization
59	Jyotish Kumar *(The University of Texas at El Paso)*	Carbon Quantum Dots as a Neuroprotective Platform Against Environmental Neurotoxicant-Induced Neurodegeneration
60	Kacie Evans *(Texas A&M University)*	Using Variable-Temperature Native Mass Spectrometry to Probe the Role of Hydration in Thermodynamics for Multi-Ligand Protein Complexes
61	Katana Mireles *(The University of Texas Rio Grande Valley)*	Confusion Matrix Analysis of Machine Learning Models for Crop Pest Prediction
62	Kyren Miller *(The University of Texas at Austin)*	Propagation of Alpha-Synuclein Misfolding Is Tuned by Proteostasis Activity
63	Lai Hoang Son Le *(Texas A&M University)*	In silico Design of Disulfide-Stabilized Macrocyclic Peptides with Ligand-Directed and Site-Selective Targeting Moieties for Protein Engagement

Poster Session

Poster #	Presenter Name	Poster Title
64	Lan Jiang *(The University of Texas at Austin)*	Frustration in Coiled-Coil Pairing Promotes Biomolecular Condensate Assembly
65	Laura Patricia Sanchez Rosario *(The University of Texas at El Paso)*	Structural and Functional Insights into the ΦEL-Encoded Chaperonin gp146
66	Leslie Barrera *(The University of Texas at San Antonio)*	Development of Potent and Selective YAP-1 Inhibitors towards Cancer: Lead Optimization and in vitro Proof-of-Concept Studies
67	Madison Adam *(Texas Christian University)*	Investigating the Effects of Peptide Mimics on the Binding Interaction between BRCA1 and PALB2
68	Mahedi Hasan *(Texas Tech University)*	Interactions between Insulin-Like Growth Factor 1 Receptor and EphA2 and their Relevance to Cancer
69	Mary W. N. Burns *(The University of Texas Southwestern Medical Center)*	Time-Resolved Secretome Tracking of Intracellular, Cell Surface, and Extracellular Glycoconjugates with a Mini-Tetrazine N-Acetylglucosamine
70	Md. Imrul Kaisar *(The University of Texas at El Paso)*	Mitigating PFAS-Induced Protein Damage Using Carbon Quantum Dots: Insights from BLG Interactions
71	Md. Didaruzzaman Sohel *(The University of Texas Rio Grande Valley)*	Histological and Immunohistochemical Responses to Sertraline Exposure in Goldfish: Evidence of Nitrative Stress and Proteasome Regulations
72	Meagan McMann *(Texas Christian University)*	Connecting protein function to phenotype: investigating nucleosome ubiquitylation by BRCA1 in C. elegans

Poster Session

Poster #	Presenter Name	Poster Title
73	Melanie Rodriguez *(The University of Texas Southwestern Medical Center)*	Platform-Based Discovery of New degraders as Therapies: Targeting ecDNA driven Drug Resistance in Aggressive Cancers
74	Michelle Hendricks *(The University of Texas at Dallas)*	In-Cell Assembly of Stapled Peptides for Targeting Protein-Protein Interactions
75	Moujab Choukeife *(Texas A&M University)*	Targeting Structured RNA: Modified L-DNA Aptamers Against pre-miR-155 and Small-Molecule Discovery for Therapeutic Development
76	Mozhdeh Ghafari *(The University of Texas at Dallas)*	Impact of a Cancer-Associated Mutation and Post-Translational Modifications on Poly(ADP-ribose) Polymerase 2 Inhibition
77	Nadeesha T. Liyana Withanage *(The University of Texas at Dallas)*	Cu(I) P-type ATPases function as electrogenic uniporters of Pt(II)-drugs
78	Nagaraju Vodnala *(Southern Methodist University)*	Direct Cellular Screening of Pd-Mediated Arylation of Cyclic Peptide Binders Targeting Ubiquitin Chains: Toward Modulating NEMO Liquid-Liquid Phase Separation
79	Nagarjun R. Mallampudi *(Texas A&M University)*	Bench-stable Boryl Thianthrenium Dication Enables Aziridinyl Boronate Synthesis via Metal-free Late-stage Aziridination with Diverse Nitrogen Nucleophiles
80	Neha Satish *(The University of Texas at Austin)*	Dense DNA Functionalization of Lactoperoxidase Enhances Antimicrobial Potency against Drug-Resistant Wound Pathogens

Poster Session

Poster #	Presenter Name	Poster Title
81	Nora Del Bosque *(Texas Christian University)*	A Manganese CAT/SOD Mimic Attenuates H_2O_2-Driven Oxidative Stress in Immortalized Human Keratinocytes
82	Ogonna W. David *(The University of Houston)*	Overcoming Oxygen Limitations: Method Development for the Anaerobic Expression of ZapNIR1 in E. coli Top10 Cells
83	Om Prakash Narayan *(The University of Texas at Austin)*	Reversible Protein Assembly via Light-Responsive β-Strand Interfaces and Chromophore–Driven Conformational Coupling
84	Pamela Agredo *(The University of Texas at Dallas)*	Bicyclic MOrPHs: Leveraging Genetic Code Expansion for the High-Throughput Discovery of Functional Bicyclic Peptides
85	Pearl Fernandes *(Baylor College of Medicine)*	Engineering Entry-Competent DNA-Encoded Libraries for Gram-Negative Bacteria: Design, Assembly, and Screening
86	Prakriti Budhathoki *(The University of Texas at Dallas)*	Identification and Characterization of a Putative Fe^{2+}-ZIP Transmembrane Transporter in the Human Brain-Eating Amoeba
87	Priya Verma *(Texas State University)*	G-Quadruplex-Dependent and dCas9-Mediated Stalling Leads to Transcriptional Blockage
88	Rae M. Sammons *(The University of Texas at Austin)*	A Focused Set of Biochemical Assays for Characterizing Small Molecule Inhibitors of eEF-2K/CaM Binding

Poster Session

Poster #	Presenter Name	Poster Title
89	Raheleh Ravanfar *(Texas Tech University)*	Nature's Redox Machines: Engineering Proteins for Self-Powered Biosensors and Energy Harvesters
90	Rezwan Ahmed *(Texas Tech University)*	Microfluidic Assessment of Gold Nanoparticle-Induced Platelet
91	Rokia Osman *(Southern Methodist University)*	A 1,2-dDioxetane-Based Chemiluminescent Probe for in vivo Copper Imaging
92	Rosemarie Elloisa P. Acero *(Texas A&M University)*	Monitoring of Base Excision Repair in Living Cells Using Chimeric D/L-DNA Molecular Beacons
93	Ruibin Liang *(Texas Tech University)*	Elucidating Photochemical Structure-Activity Relationships in Photopharmacology via Multiscale Simulations
94	Rutendo S. Nyamadzawo *(Texas A&M University)*	Targeting ASH1L AND TRIM28 Bromodomains for the Development of Anti-Cancer Agents
95	Sahar Heidari *(The University of Texas at Dallas)*	Structural Basis for Lithium Inhibition of Eukaryotic Fluoride Channel
96	Samson J. Joseph *(Baylor University)*	Characterizing O-Glycoproteinases in Opportunistic Pathogens with Chemoproteomics
97	Sandeep Atla *(Texas A&M University)*	From Nicotine to SARS-CoV-2 Antivirals with Potent in vivo Efficacy and a Broad Anti-Coronavirus Spectrum
98	Sarthi Polara *(The University of Texas at Dallas)*	Computational Study of Cytarabine Effects on DNA Elongation in DNA Polymerase λ and Nucleosome-Bound Pol λ

Poster Session

Poster #	Presenter Name	Poster Title
99	Scott Elmore *(The University of Texas at Dallas)*	Utilizing a Hyaluronan-Binding Peptide for Interspecies Neuron-Specific Targeting and Molecule Delivery
100	Sebin Abraham *(Texas A&M University)*	Selective Targeting of RhoA G17V Oncogenic mutant by Macrocyclic Peptides Identified Through Phage Display and Structural Mapping
101	Seye J. Oladeji *(Rice University)*	Structural Basis and Rational Engineering of a Thermophilic Cas13a for Robust Nucleic Acid Detection
102	Shreestika Pradhan *(The University of Texas at Austin)*	On-Site Portable Lithium Detection in Mining and Recycling Industries Based on a DNAzyme Fluorescent Sensor
103	Shria Chatterjee *(The University of Texas at Austin)*	DNA-Activated Peptide Assembly as a Strategy for Supramolecular Therapeutics
104	Slade Lee *(Texas Christian University)*	Improved Synthesis of Small Molecule Antioxidant OH-PyN3
105	Sophea Pa *(Texas A&M University)*	Deorphanizing NR4A1: Phage Display for Ligand Discovery
106	Sophia Sliter-Hays *(The University of Texas Southwestern Medical Center)*	Mechanisms and Targeting of LRPPRC-RNA Interactions in Mitochondrial Disease and Cancer
107	Stephanie Hernández *(The University of Texas Rio Grande Valley)*	Identifying High-Priority Zones for Lyme Disease in Northeastern Mexico through Geospatial Analysis of P. leucopus and P. maniculatus
108	Sydney S. Barnes *(The University of Texas at Dallas)*	Identifying Defluorinases through a Latent Generative Landscape

Poster Session

Poster #	Presenter Name	Poster Title
109	Tahmina Afroz *(Texas Christian University)*	Can a Biologically Relevant Hydroperoxyl-Iron Intermediate also Generate C-C Bonds?
110	Taylor Hays *(The University of Texas at Austin)*	Selective Permeation of Cancer Model Membranes by NAF1
111	Tharaka Amarasekara *(Texas A&M University)*	Characterizing the Interactions between Thymine DNA Glycosylase (TDG) and RNA
112	Tong Lin *(The University of Texas at Austin)*	Engineering Modular Polyketide Synthases for the In Vitro Biosynthesis of Leptomycin Derivatives
113	Tosin Oladosu *(The University of Minnesota Duluth)*	Design, Synthesis, and Computational Evaluation of Novel Alkyl Sulfur-Linked Pomalidomide CRBN Recruiters
114	Tracy Cobblah *(Baylor College of Medicine)*	Investigating the Cellular Consequences of Targeted Protein Degradation (TPD)
115	Ummy Habiba Sweety *(The University of Texas at El Paso)*	Mechanisms of Interfacial Interactions Between Engineered Nanoplastics and Biological Systems
116	Uyen Huynh *(The University of Houston)*	Calcium Modulates Growth and Biofilm Formation of Intestinal Lactobacillaceae
117	Vanesa Calvillo-Fernandez *(The University of Texas Rio Grande Valley)*	NASA VITAL-AI-Driven Biodegradable Sensors for Environmental Vector-Borne Diseases Monitoring
118	Veerabhadra R Vulupala *(Texas A&M University)*	Nicotine-Inspired, De Novo Designed SARS-CoV-2 Main Protease Inhibitors Reveal Unique Chemistry for Covalently Conjugating both Cysteine and Histidine Residues in the Catalytic Dyad

Poster Session

Poster #	Presenter Name	Poster Title
119	Vicente Rubio *(Texas A&M University)*	Design of Blood Brain Barrier Penetrating Peptide Macrocycles for Central Nervous System Drug Delivery of Therapeutic Proteins
120	Victoria Shearer *(Texas A&M University)*	Generation of Optimized Cross-Chiral Afnity Reagents for Structured RNA
121	Xiangli Shao *(Rice University)*	Novel Chemical Biology Tools to Investigate RNA Modifications and their Roles in Disease
122	Xiaoding Jiang *(The University of Texas at Austin)*	Direct and Selective Activation of Glycolysis using a Covalent PFK1 Ligand
123	Xin Li *(Baylor College of Medicine)*	Structure-Guided Discovery of Covalent Inhibitors Targeting SARS-CoV-2 Proteases with Potent Antiviral Activities
124	Xinming Zhang *(Rice University)*	In situ Profiling of GlycoRNA-Protein Interactome in Living Cell
125	Xuejiao Shirley Guo *(Texas A&M University)*	Small Molecule Inhibition of the ENL YEATS Domain Suppresses Acute Myeloid Leukemia
126	Yaamini Subramanian *(The University of Texas Dallas)*	Copper Stoichiometry Drives the Conformational Dynamics in P1-B-type ATPase Revealed by Hydrogen Deuterium Exchange Mass Spectrometry (HDX-MS)
127	Yining Wang *(The University of Texas at Dallas)*	Enzyme-Catalyzed Stereoselective C(sp3)-S Bond Formation via a Dichotomic Carbene Transfer Mechanism

Poster Session

Poster #	Presenter Name	Poster Title
128	Yonghong Zhang *(The University of Texas Rio Grande Valley)*	The School of Integrative Biological and Chemical Sciences at UT Rio Grande Valley: a unique school offering diverse and flexible master's degrees in chemistry, biology, and in between
129	Yougant Airan *(Yale University)*	Synthesis and Biological Evaluation of Colibactin Derivatives
130	Yuanjie Sun *(The University of Texas at Austin)*	Discovery of Surface-Engineered Nanoparticles That Boost Enzyme Activity
131	Yugendar R. Alugubelli *(Texas A&M University)*	A Refined Search of SARS-CoV-2 Main Protease Inhibitors as COVID-19 Antivirals
132	Yusif I. Gyasi *(Texas A&M University)*	Regioselective multicomponent synthesis of α-boryl ureas: discovery of a potent main protease inhibitor
133	Yuting Wu *(The University of Texas at Austin)*	DNAzyme-Based Tools to Probe Metal Chemistry in Neurodegeneration and Cancer
134	Zhenglin Yang *(The University of Texas at Austin)*	Programmable DNAzyme Probes Illuminate Metal Ions in Human Health and Diseases
135	Zhenyu Xi *(Texas A&M University)*	Conformational Pattern and Aggregation of GLP-1 Analogs

2026 SynthX Texas Chemical Biology Young Investigator Award

Brian Belardi

Assistant Professor, UT Austin

Sponsored By:

Synth center at Rice University

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SARTORIUS

TECAN.

SB SinoBiological

Journals

RSC Chemical Biology

DBC Division of Biochemistry and Chemical Biology

Poster Number	Title, Author(s), Contact, Affiliation, Abstract
1	**Center for High-Throughput Reaction Discovery & Synthesis** https://ht-rds.utdallas.edu The University of Texas at Dallas
2	**Advancing Drug Discovery Through DNA-Encoded Library Technologies: Innovations, Applications, and Future Directions** jordan.lachance@medchemexpress.com, william.zhang@medchemexpress.com MedChemExpress DNA-Encoded Library (DEL) technology has transformed drug discovery by enabling ultra-high-throughput screening through DNA barcoding. Furthermore, DEL screening requires little sample, minimal assay development, and no specialized instrument. Despite its advantages, first-generation DEL often suffers from low hit rates, off-target interactions, and poor drug-like properties. To overcome these limitations, we developed the next-generation DELs: Covalent DEL (CoDEL) and Focused DEL (FoDEL). CoDEL employs electrophilic warheads to form irreversible bonds with nucleophilic residues in target proteins, offering an alternative strategy for traditionally undruggable targets. For example, EGFR inhibitors such as Afatinib and Osimertinib covalently bind Cys797. Drug resistance caused by C797S mutation, however, has prompted exploration of alternative nucleophilic sites beyond cysteine. We assessed the bioreactivity of 17 warheads against 9 nucleophilic residues in FGFR2 and constructed a CoDEL comprising 24.8 million compounds targeting cysteine, lysine, arginine, or glutamic acid, significantly broadening the landscape of covalent inhibitor development. FoDEL leverages structural insights to improve hit rates. For example, cyclic peptides offer enhanced compound stability, as well as enhanced binding specificity and affinity to targets. We developed eight cyclic peptide DELs, utilizing different cyclization strategies, including oxidative disulfide bond formation or thiol-electrophile cross-linking with various bifunctional linkers, to explore broader chemical space. Each cyclic peptide DEL contains ~154 million molecules. Innovations in DEL are driven by advancements in synthetic methodology, structural integration, and library design. MedChem Express (MCE) supports this evolution with a broad portfolio of building blocks for constructing advanced DELs to accelerate drug discovery.
3	**Development of Small-Molecule YEATS4 Inhibitors for Lung Cancer** Abdalrahman Khalifa, Logan Herring, Lai Hoang Son Le, Xuejiao Guo, Satyanarayana Nyalata, Sandeep Atla, Yugendar Reddy Alugubelli, Wenyue Cao, Joshua Trae Hampton, and Wenshe Liu akhalifa@tamu.edu Texas A&M University YEATS4 is an epigenetic reader protein that regulates gene expression programs associated with lung cancer progression, making it a promising yet underexplored therapeutic target. To discover selective small-molecule inhibitors, we employed a computationally guided design strategy integrated with the development of a robust AlphaScreen assay optimized for high-throughput screening (HTS). Screening a 30,000-compound library led to the identification of multiple chemically tractable hits with IC_{50} values around 1 µM. Direct target engagement of these hits was confirmed using biolayer interferometry (BLI). Selected compounds were further evaluated in lung cancer cell lines (A549 and H1299), demonstrating encouraging antiproliferative activity, supporting their potential as therapeutic leads. Ongoing structure–activity relationship (SAR) studies focus on improving potency, selectivity, and oral bioavailability. This work highlights an integrated approach combining computational design, multistep organic synthesis, assay development, HTS, hit validation, and SAR optimization to advance YEATS4-targeted small-molecule therapeutics. These findings provide a foundation for chemical biology-driven drug discovery and contribute to the development of targeted therapies addressing epigenetic drivers of lung cancer.

4 **Molecular Dynamics Simulation Study of Unphosphorylated B-RAF: Wild-Type and Cancer-Associated Mutations**

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B-RAF is a serine/threonine kinase that occupies a central position in the MAPK signaling cascade, regulating cell proliferation, survival, and differentiation. Oncogenic mutations in BRAF are among the most prevalent driver mutations in human cancers, occurring in approximately 59% of melanomas, 18% of colorectal cancers, and 14% of liver cancers. These mutations are classified into three mechanistic classes based on their dependence on RAS signaling and dimerization state: Class 1 mutations (e.g., V600E) act as constitutively active monomers; Class 2 mutations (e.g., G464E) drive RAS-independent dimerization; and Class 3 mutations (e.g., D594H) impair intrinsic kinase activity and signal through C-RAF in a RAS-dependent manner. In this work, we present an extensive molecular dynamics (MD) simulation study of full-length human BRAF (residues 1-766) encompassing wild-type and six cancer-associated variants across all three mutation classes, as well as three functionally unclassified variants. Two complementary sets of simulations are performed: (i) systems with phosphorylation of the activation segment at Thr599 and Ser602 (PTM systems, performed by D. Pearson), encompassing monomer, homodimer, and heterodimer assemblies; and (ii) systems in the unphosphorylated (no-PTM) state (performed by A. Shamma), providing the unphosphorylated baseline necessary to isolate the contribution of phosphorylation to kinase activation across all mutation classes. Each system is simulated with three independent 200 ns replicates using the AMBER ff14SB force field. A comprehensive set of analyses is applied, including root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), dynamic cross-correlation matrices (DCCM), principal component analysis (PCA), essential dynamics analysis (EDA), dynamic network analysis, and key salt-bridge monitoring. Together, these simulations provide a detailed atomistic picture of how each mutation class perturbs BRAF structural dynamics and allosteric communication, with and without activation-segment phosphorylation.

5 **MCM8/9 Ensures Genomic Continuity during Mitotic Progression**

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High levels of replication stress are a common feature of cancer cells, slowing or stalling DNA replication during S-phase. This stress arises from several factors, including DNA damage and difficult-to-replicate regions such as fragile sites, oncogene activation, and altered metabolism, including nucleotide pool depletion. MCM8 and MCM9 are recent additions to the minichromosomal maintenance (MCM) family of DNA helicases. This alternative heterohexameric helicase, conserved in higher eukaryotes, plays a protective role at stalled replication forks, contributing to the repair of inter-strand crosslink lesions through homologous recombination. However, MCM8/9's functions outside of S-phase remain poorly understood, particularly during mitosis, where genomic integrity is ensured prior to the production of daughter cells. Common fragile sites are frequently under- replicated, leading to collisions between the replication and transcription machinery. Mitotic DNA synthesis (MiDAS) is a replication-rescue mechanism that resolves under- replicated regions prior to chromosome segregation. However, attenuation of MiDAS promotes mutagenesis and chromosome abnormalities, which are subsequently inherited by daughter cells. In cancer, dysregulation of mitosis results in an expanded population of genetically unstable cells with chromosome loss, rearrangements, or missegregations. We find that the absence of MCM9 results in profound suppression of MiDAS activity when replication stress occurs, allowing under-replicated regions to persist into the subsequent cell cycle. Furthermore, knock-out of MCM9 elevated chromosome mis- segregation, accompanied by defects in centromeres and overall chromosome integrity. Together, these findings establish

that MCM8/9 regulates replication stress and preserves chromosome stability to ensure proper cell-cycle progression during mitosis in addition to its reported role in S-phase.

6 **Tag and Trash: A Mechanism-Guided Discovery Platform Identifies ELAVL1 Degrader**

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Approximately 90% of the human proteome is considered “undruggable” with traditional small- molecule inhibitors due to the absence of suitable binding pockets. Molecular glue degraders (MGDs) address this barrier by recruiting target proteins to an E3 ligase, leading to target ubiquitination and degradation. However, MGD discovery remains largely serendipitous and is commonly guided by either cell-viability screening (which can miss non-lethal degraders) or global proteomics (which can mis-assign indirect downstream changes as direct targets). To enable more mechanism-anchored discovery, we developed a scalable chemoproteomics platform that directly reports on essential early steps in MGD mechanism. We developed TRUE (Target Recruitment and Ubiquitination Enrichment), a high-throughput in- cell platform that integrates two complementary proximity-labeling assays to measure MGD activity at two essential nodes: (i) target recruitment to an E3 ligase and (ii) subsequent target ubiquitination. TRUE was established in HEK293T cells and benchmarked with two well- characterized MGDs: lenalidomide and CC-885. Following this, an E3 ligase cereblon (CRBN)– directed MGD library was synthesized and screened using the TRUE platform to identify targets. Functional degradation of identified targets was validated using global proteomics via data- independent acquisition mass spectrometry (DIA-MS). Benchmarking TRUE platform in HEK293T cells using lenalidomide and CC-885 yielded significant recruitment and ubiquitination of their known targets, CK1α and GSPT1, respectively, indicating the sensitivity of the platform. Screening of the CRBN-directed MGD library identified multiple hits, including ELAVL1, with significant recruitment and ubiquitination. ELAVL1 (Embryonic lethal abnormal vision–like protein 1) is an oncogenic RNA-binding protein whose overexpression correlates with poor clinical outcomes, and it lacks an FDA-approved inhibitor or degrader. Further assessment of our hit compound (NGT-21-1) by DIA-MS and immunoblotting showed selective, dose-dependent degradation of ELAVL1. Structural evaluation revealed that ELAVL1 possesses the canonical G-loop—a structural "hook" that CRBN-directed MGDs use to grab and degrade specific proteins within the cell. We identified two putative G-loops in ELAVL1, which structural aligns with CK1α G-loop in the CRBN–lenalidomide complex. By requiring evidence of both recruitment and ubiquitination, TRUE platform provides a stringent, mechanism-informed filter that reduces false positives and captures targets missed by current discovery methods. Using TRUE, we identified NGT-21-1 as a potent and selective ELAVL1 degrader, opening a tractable route to pharmacologically suppress an important oncogenic driver. Ongoing work will optimize NGT-21-1 via structure–degradation relationship and evaluate its anti- tumor efficacy in xenograft models.

7 **Deciphering the Neddylation Pathway through Advanced Proteomic and Drug Discovery Methods**

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Ubiquitination is one of the key post-translational modifications in the human body, and is carried out by the Ubiquitin protein. Like Ubiquitin are Ubiquitin-like Proteins (Ubls), which share similar chemistry and parallel processes. One of these Ubls is Neural precursor cell expressed, developmentally downregulated 8, or NEDD8, which is found to be closely linked to hepatocellular carcinoma. While studies have been performed previously on NEDD8, this project aims to further explore the neddylation pathway through advanced methods. Both current and next-generation activity based probes will be deployed in numerous cell lines, both cancerous and non-cancerous (HepG2, Hep3B against THLE-2, LO2) to find new enzyme related to the pathways. Enzymes related to neddylation and deneddylation that will be obtained can then in turn be used to find new inhibitors that can target these enzymes through the usage of a high-throughput screening workflow. This HTS workflow will also employ fluorogenic probes developed by the Liu Lab for detection of enzymatic activity and inhibitor efficacy. Then, modern biology methods will be used to find further biological implications of neddylation, knocking down identified enzymes and using combination therapeutic treatments to understand the pathway better. Altogether, this project will allow for a better understanding of NEDD8 while also building a platform to treat diseases and cancers related to this pathway, such as hepatocellular carcinoma, and pathways of other Ubiquitin-like proteins.

8 **Exploring the Impact of Asymmetrically Modified CpGs and Nucleosome Sequence on TDG Activity in Chromatin**

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Epigenetic modifications are driven by fundamental chemical processes that shape the landscape of the genome, governing the intricate processes of development and proper biological function. These modifications encompass a wide array of molecular changes, all of which orchestrate important gene expression patterns during developmental stages and throughout an organism's life. One of the most studied epigenetic modifications is 5-methylcytosine (5mC). Primarily residing within the context of CpG dinucleotides in DNA, it has historically been regarded as a static modification. However, 5mC is now recognized as a dynamic player in the gene regulation, particularly in the formation of heterochromatin and the suppression of gene expression. The reversal of 5mC, a process known as DNA demethylation, has emerged as a pivotal contributor to various biological pathways, including those critical for developmental and transcriptional regulation. Through a cascade of events, 5mC is oxidized and later excised from the DNA by thymine DNA glycosylase (TDG), initiating the base excision repair (BER) pathway. TDG plays a critical role in this step, as it is the only know enzyme to remove the most oxidized forms of 5mC from the DNA. Therefore, TDG has an essential role in maintaining a proper DNA methylated landscape, controlling epigenetic states, regulating transcriptional activation sites, and minimizing tumor formation. A notable knowledge gap persists in understanding the regulation of TDG accessibility and activity across the genome. Higher-order chromatin structure, which influences DNA accessibility, has emerged as a critical determinant of the activity of DNA-binding enzymes. However, the intricate relationship between chromatin structure and TDG activity remains largely unstudied. This work will focus on unveiling the molecular interactions of TDG and chromatin structure, and the influence of the other has on shaping DNA methylation patterns across the genome. This research endeavors to bridge existing gaps in our comprehension of TDG's activity regulation, the influence of chromatin structure on TDG, and the broader implications of these findings for our understanding of the regulatory mechanisms governing the DNA (de)methylation processes. Through an integrated investigation,

we aim to shed light on the multifaceted mechanisms that underlie proper epigenetic regulation and their potential impact on human health and disease.

9 **FloDisMod: Community Outreach Project for Vector-Borne Diseases Prevention in the Rio Grande Valley**

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The transboundary region of the United States with Mexico is characterized by a high flow of people, and these unique environmental and social conditions increase the vulnerability to diseases carried by vectors, such as mosquitoes, kissing bugs, and ticks. Vectors act as carriers for pathogens, including bacteria, viruses, and protozoa, which can infect humans and create serious consequences for public health, where the vector will take the pathogen from a human and transmit it to another human in a cycle of disease. Favorable environmental conditions of humidity, precipitation, and sun exposure alter the life cycles of both the vectors and the pathogens' development, enhancing their reproduction rates and hence transmission. This project is part of the FloDisMod framework, a collaborative initiative integrating flood modeling and infectious disease dynamics to better understand and predict health risks associated with extreme weather events, intending to create accessible bilingual (English/Spanish) educational outreach materials to create better awareness of vector-borne diseases in the border region. Outreach strategies include videos, interactive activities (e.g., educational games), and community engagement with vulnerable populations, including children, the elderly, and individuals in socioeconomically disadvantaged areas with poor water management. Surveys are being created to measure the effectiveness of these interventions in improving knowledge and awareness. Ongoing analysis will evaluate the reach and understanding of the materials in promoting public health awareness and reducing risk factors associated with vector-borne diseases in the U.S.–Mexico border region.

10 **Assembly and Structural Characterization of the Hsp90-Hsp70-HOP-MAPKAPK2/RAF1**

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The Hsp90 chaperone system plays a critical role in the folding, stabilization, and activation of client proteins. This includes kinases involved in stress response and signaling pathways. HSP90 facilitates the folding, stability, and activation of mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2; MK2), preventing its degradation and ensuring efficient cellular stress responses. In this study, we investigate the assembly of a multi-chaperone complex composed of Hsp90, Hsp70, HOP, and the kinase MK2. MK2 gets partially denatured under controlled thermal conditions before its incorporation into the chaperone complex to promote client recognition. The assembly process was optimized by sequential addition of components and modification of temperatures and pH, allowing pre-formation of the Hsp90–Hsp70–HOP complex before client introduction. The resulting complexes were analyzed using size exclusion chromatography (SEC), dynamic light scattering (DLS) and are currently awaiting the cryo-electron microscopy data collection. DLS analysis revealed time-dependent changes in particle size distribution, indicating progressive complex formation and stabilization. Optimal incubation conditions resulted in a predominant species consistent with a higher-order assembly. Negative stain grid screening confirmed the presence of assembled complexes, although particle aggregation was still observed under certain conditions. These results demonstrate successful *in vitro* assembly of a chaperone–client complex and provide a foundation for future structural characterization using cryo-EM. We hypothesize that partial denaturation of MAPKAPK2 promotes its recognition as a client protein by the Hsp70–Hsp90–HOP chaperone machinery, leading to the formation of a stable multi-protein complex. The research goal for this project is to assemble and characterize the Hsp90-Hsp70-HOP-MK2 and Hsp90-Hsp70-HOP-RAF1 complex for structural analysis by cryo-EM.

11 **Developing Cancer-Relevant Genomic Mutations of U1 snRNA Using CRISPR/Cas9 with Circular Single-Strand Donors from the pScaf Phagemid System**

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U1 small nuclear ribonucleoprotein (U1 snRNP), a key component of the spliceosome, plays a critical role in pre-mRNA splicing and prevents premature cleavage and polyadenylation through telescripting. Recurrent mutations in non-coding U1 snRNA have been identified in several cancers; however, their functional consequences remain poorly understood. Progress in studying these mutations has been limited by the lack of efficient strategies to introduce precise genomic mutations into endogenous *RNU1* loci. To address this challenge, we developed a CRISPR/Cas9-based genome editing approach using circular single-stranded DNA (cssDNA) donors generated by the pScaf phagemid system to engineer cancer-relevant U1 snRNA mutations. As a model system, we targeted the g3A>C mutation, frequently observed in chronic lymphocytic leukemia, in HCT116 cell. sgRNA candidates were selected using in silico tools, and CRISPR/Cas9-mediated double-strand breaks were validated using T7 endonuclease I assay, confirming efficient cleavage at the target locus. In parallel, we produced cssDNA repair templates using the pScaf phagemid system. Clonal cell lines are currently being established through single-cell isolation and will be screened by Single Nucleotide Polymorphism (SNP) genotyping to confirm successful editing. These models will enable us to determine how mutant U1 snRNA alters snRNP biogenesis and contributes to cancer development.

12 **Sol-moiety: Discovery of a Water-Soluble Prodrug Technology for Enhanced Oral Bioavailability of Insoluble Therapeutics**

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Solubility remains a significant challenge for medicinal chemists striving to develop potent, selective molecules with increasing hydrophobicity. To address this issue, we present a novel platform for enhancing the solubility of drug prototypes featuring diverse functional groups. Our sol-moiety design incorporates a benzyl scaffold substituted with a phosphate group at the para position relative to a carboxylate or phosphonate group. Upon conjugation to drug candidates, the sol-moiety undergoes hydrolysis by alkaline phosphatases in the intestine or plasma, releasing the active drug via a subsequent 1,4-elimination reaction.In exploring the modulation of phosphate cleavage rates, we hypothesized that modifications to the phosphate environment could influence the enzyme's conversion rate, thereby enhancing oral bioavailability. To test this, we synthesized four sol-moiety conjugates with the commercial drug enzalutamide. In vitro screening confirmed that the sol-moiety prototypes were ideal substrates for alkaline phosphatase. An in-vivo cassette study demonstrated nearly a 2-fold increase in bioavailability (92%) compared to the standard carboxymethylcellulose (CMC) formulation of enzalutamide. Modifying the phosphate group environment also altered the rate of cleavage, further supporting our hypothesis. Moreover, we demonstrated the versatility of this platform with significant pharmacokinetic improvements for both enzalutamide and paclitaxel. To our knowledge, we developed the first water-soluble, orally administered paclitaxel prodrug, exhibiting enhanced efficacy in a mouse BxPC-3 tumor model. This sol-moiety platform offers a promising alternative to complex formulation strategies, addressing solubility challenges for poorly bioavailable drug candidates or marketed therapeutics, and providing a more convenient administration route for potent drugs.

13 **Thymine DNA Glycosylase Binds to R-loops and Excises 5-Formyl and 5-Carboxyl Cytosine from DNA/RNA Hybrids**

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R-loops: DNA/RNA hybrids structures with a displaced single-stranded DNA – have immerged as regulators of active DNA demethylation. Yet the underlying mechanism remains unclear, including whether the associated proteins bind or function on R-loops. Here, we showed that thymine DNA glycosylase (TDG), a critical enzyme in active DNA demethylation pathway, binds synthetic R-loop substrates in vitro and excises DNA methylation intermediates 5-formylcytosine (5fC) and 5-carboxycytosine (5caC) from DNA/RNA hybrids. We also provided mechanistic insight into hybrid duplex base excision using 19F NMR. We further showed that R-loops can direct strand selectivity – potentially explaining the asymmetric distribution of 5fC/5caC at gene promoter. Lastly, we showed that TDG might interact with R-loops in mammalian cells. Together, these findings establish a biochemical mechanism for R-loop-mediated DNA demethylation and suggest that TDG-R-loop interactions may be relevant in mammalian cells.

14 **Breakdown of Biotin: Bacterial Catabolism of Vitamin B7**

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Vitamin B7, also known as biotin, is a cofactor necessary in all domains of life. It serves as a carboxylate carrier in biochemical carboxylation reactions. Biotin-dependent CO2 metabolism is well-studied. Similarly, much is known about the biosynthesis of biotin. However, it is still unknown how biotin is broken down into primary metabolites. Our work uncovers a catabolic operon in Ochrobactrum sp. that serves as the first known gene cluster responsible for the biochemical breakdown of biotin. This gene cluster has been isolated, and the genes were assigned functions based on sequence. Using chemical logic, a catabolic pathway was proposed starting from biotin-sulfoxide and resulting in pyruvate and acetyl-CoA as the final metabolites. The enzymes in the catabolic gene cluster were overexpressed and purified in E. coli. Enzymatic reactions were studied through in vitro biochemical assays. Synthetic standards of enzyme substrates were used in the reconstitution of the pathway. In cases where the synthesis of substrates proved complex, substrate analogs were used as preliminary substitutes. The initial steps of the pathway shortening the side chain of biotin have been reconstituted. The end of the pathway producing the final primary metabolites has also been reconstituted, revealing that a hydantoin ring is formed and broken down in the intermediate steps. This highlights an unusual rearrangement from the biotin bicyclic core to the hydantoin heterocycle. The majority of the biotin catabolic pathway has been reconstituted, with several key steps that remain to be studied. As biotin is a required cofactor for fatty acid biosynthesis, understanding this highly specific degradation could serve as a foundation for biotin-targeted weight loss therapeutics. Once the full pathway is completed, this work will write a new chapter in vitamin and cofactor metabolism.

15 **Development of Quinoxiline-Containing Inhibitors of the Protein−Protein Interactions between Transcription Coactivator AF9/ENL and DOT1L/AF4: Design, Synthesis, Structure−Activity Relationships, and Antitumor Activity**

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Mixed lineage leukemia (MLL) gene rearrangements cause ∼75% of acute leukemia in infants and 5−10% in children and adults with poor clinical outcomes. Protein−protein interactions (PPI) between frequent MLL fusion partners AF9/ENL and AF4 or histone methyltransferase DOT1L are drug targets for MLL-rearranged (MLL-r) leukemia. Sixty-seven quinoxaline compounds were synthesized and tested for their ability to inhibit such PPIs. Compounds 16, 17, 59, and 63 were found to be potent inhibitors with IC50 values of 0.35−1.5

μM. Structure–activity relationships are discussed. Potent inhibitors can suppress the expression of MLL target genes Myc and Meis1 and selectively block the proliferation of MLL-r and several other leukemia cells with EC50 values as low as 0.84 μM. Compound 17 exhibited significant antitumor activities in a mouse model of MLL-r leukemia without overt toxicities. It also showed favorable pharmacokinetics in mice. These results indicate that compound 17 is a promising pharmaceutical lead for the treatment of MLL-r leukemia.

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16 **LipiX-MS: A Novel Crosslinking Mass Spectrometry Strategy for Studying Lipid-Protein Interactions**

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Lipid-protein interactions regulate essential biological processes, including membrane organization, signal transduction, and metabolism, and their dysregulation is implicated in metabolic disease, neurodegeneration, and cancer. Despite their importance, these interactions are difficult to characterize due to their transient nature and the structural diversity of lipids. Existing approaches, including structural biology techniques, biophysical assays, and lipidomics-based enrichment, often lack site-specific resolution or fail to capture weak and dynamic interactions. Mass spectrometry offers high sensitivity and molecular specificity, yet current MS-based strategies typically infer lipid binding indirectly and rarely localize lipid binding sites on proteins. Here, we introduce LipiX-MS, a cross-linking mass spectrometry strategy that directly captures and maps lipid–protein interactions. Chemically modified lipids are designed to introduce a reactive handle for subsequent cross-linking with lipid-binding proteins, enabling site-specific identification of lipid-binding residues within a single MS workflow.

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17 **Molecular Dynamics Simulations of BRAF Kinase Mutant Complexes Reveal Variant Effects and Activation Mechanisms**

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RAF proteins are serine/threonine kinases within the MAPK signaling pathway that regulate cell growth and division. Among them, BRAF is often mutated in cancer, and its kinase activity is associated with specific conformational states and dimerization behavior. There are three classes of BRAF missense mutations that result in distinct signaling pathways through different mechanistic routes, necessitating a framework to explain how sequence variation alters kinase regulation. In this work, we use Molec- ular Dynamics (MD) simulations with the AMBER ff14SB force field to investigate how oncogenic mutations affect structural and dynamical features in BRAF activa- tion. Specifically, BRAF monomers, BRAF–BRAF homodimers, and BRAF–CRAF heterodimers are simulated to characterize mutation-dependent effects on stability, flexibility, correlated motions, and domain interactions in the kinase region. Each type of assembly is simulated with three independent PTM 500 ns replicates; a complemen- tary set of 200 ns replicates of the non-phosphorylated PTM state is performed by A. Shamma to help understand the contribution of phosphorylation to kinase activation across all mutation classes. Our goal is to determine whether computational methods can distinguish the known classes of BRAF mutations based on their structural and dynamical properties. We include representative mutations from each established class: V600E (Class 1, RAS-independent active monomers), G464E (Class 2, constitutively active dimers), and D594H (Class 3, kinase-impaired, RAS-dependent). Additional mutations with less well-defined behavior, including G469A, G469E, and R384G, are analyzed to test whether these signatures can be used to classify variants of unknown mechanism. For each system, an extensive comparative analysis set is performed, ulti- mately providing a detailed picture of how each mutation class affects BRAF structural dynamics and allosteric communication.

18 **Biomolecular Condensates Formed by Designer Antimicrobial Peptides**

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Biomolecular condensates formed through liquid-liquid phase separation (LLPS) of intrinsically disordered proteins (IDPs) have significantly advanced our understanding of cellular organization. However, the contribution of molecular ordering in regulating phase behaviour remains insufficiently explored. In this work, we systematically investigate the role of secondary structures in LLPS using modularly designed multidomain peptides (MDPs) as a tunable model system. These MDPs are designed on the principle of molecular frustration, comprising a central β-sheet forming domain flanked by cationic arginine residues that promote disassembly. Spectroscopic analyses reveal a structural transition from random coils to partially folded β-sheet conformation and ultimately to fully ordered hydrogel structures. Peptides adopting partially folded β-sheet conformations undergo LLPS to form dynamic, liquid-like condensates. Fluorescence recovery after photobleaching (FRAP) confirms the liquid-like behaviour of these condensates, while confocal Raman spectroscopy suggests that hydrophobic interactions and hydrogen bonding involving aromatic residues contribute to phase separation. Furthermore, the MDPs can form stable complex condensates with anionic polymers at reduced critical concentration, exhibiting enhanced droplet stability. Finally, phosphorylated MDPs were developed that undergo alkaline phosphatase-triggered *in situ* condensate formation in bacterial cultures, highlighting their potential for antimicrobial therapeutic applications.

19 **Site-Specific Immobilization of ZNRF3 Reveals the Importance of Target Structural Integrity on Macrocyclic Peptide Selections**

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Phage display of macrocyclic peptide libraries has proven highly effective for ligand discovery, yet the impact of target immobilization and structural integrity on selection outcomes has not been systematically examined. Using the ZNRF3 ectodomain as a model, we incorporated p-azidophenylalanine (AzF) at three phenylalanine residues with distinct solvent exposures (F217, F85, F156) to enable selective perturbation of the protein's structure via site-specific strain-promoted azide- alkyne cycloaddition (SPAAC) immobilization. Biochemical evaluation of the mutants confirmed efficient conjugation and structural disruption of the protein, with the F156AzF mutant displaying the most significant reduction in activity. Phage selections using a CX12C macrocyclic library demonstrated that enrichment efficiency and sequence diversity correlated with structural preservation: F217AzF and F85AzF yielded robust and overlapping peptide pools, while F156AzF produced few and modestly-enriched sequences. Biophysical characterization of top hits indicated that peptides derived from structurally intact immobilizations were most likely to bind wild-type ZNRF3, with the highest-affinity ligand, 85-2 (KD = 124 nM), emerging from the shared pool. This work reports a technique to selectively disrupt protein domains during phage selections, while also demonstrating that the structural integrity of immobilized targets is a primary determinant of phage display success. Not only does the necessity to maintain structural integrity influence sequence composition and affinities of peptides toward native protein targets, but also the overall enrichment efficiency of the selection itself. While disruptive immobilization may still yield useful ligands, strategies that preserve native folds enhance phage enrichment and maximize the identification of biologically relevant binders.

20 **Phage-Assisted Discovery of Anti-Cancer Peptides for Histone Deacetylase (HDAC) Proteins**

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Epigenetic regulators such as Histone Deacetylases (HDACs) represent a promising class of drug targets due to their involvement in gene expression and carcinogenesis. Human HDACs are categorized into four classes with 18 members. HDACs catalyze the removal of acetyl groups from lysine residues on histone proteins, resulting in chromatin condensation and transcriptional repression. Abnormal HDAC expression promotes cancer by silencing genes involved in cell cycle arrest, DNA repair, and apoptosis, underscoring the need for targeted therapies. This study aims to identify, optimize, and validate peptide binders for HDAC2 isoform of histone deacetylases using phage display method. Peptide therapeutics have rapidly evolved into one of the most promising frontiers in modern drug discovery, due to improved target specificity, potency, cell permeability, and cost-effective production. Phage display is a high throughput technique that enables screening of large peptide libraries (>10^9 variants). However, traditional phage display is limited by its reliance on *E. coli*, restricting chemical diversity to the 20 canonical amino acids and often yielding unstable, low-affinity peptides. To address these limitations, we employ phage-assisted active site-directed ligand evolution (PADLE) technique, which incorporates noncanonical amino acids (ncAAs) to enhance peptide diversity, stability, and binding affinity. We utilize an evolved amber suppression system based on pyrrolysyl-tRNA synthetases (PylRS) from Methanosarcina species enabling genetic incorporation of ncAAs into phage-displayed peptides. The ncAA-containing phage library have been utilized for selection against HDAC2 protein, enabling discovery of high-affinity peptide binders. Following peptide selection, binding assays such as Alpha Screen and Biolayer Interferometry (BLI) will be employed to assess interaction kinetics, affinity, and specificity. Finally, structural optimization and cellular engagement studies will support the development of selective inhibitors in cancer therapy.

21 **The U1 snRNP-Specific Protein U1C Is a Key Regulator of SMN Complex–Mediated snRNP Formation**

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The stability and abundance of spliceosomal small nuclear ribonucleoproteins (snRNPs) are determined by the assembly of an Sm protein ring (Sm core) on each snRNA, a process orchestrated by the survival of motor neurons (SMN) complex. While the role of the SMN complex as a chaperone is well-established, the mechanisms that regulate its activity remain poorly understood. In this study, we identify U1C, a U1 snRNP-specific protein, as a key regulator of the SMN complex. Using *in vitro* Sm core assembly and protein binding assays, we demonstrate that U1C is essential for Sm core assembly on all snRNAs. In the absence of U1C, Sm core formation on U1 snRNA is disrupted, impairing the SMN complex's ability to facilitate Sm core assembly on other snRNAs. Furthermore, we show that U1C interacts with the SMN complex *via* post-translational arginine methylations at its C-terminal region, a site distinct from its interaction with U1-70K. Notably, we demonstrate that a prevalent cancer-associated mutation in U1 snRNA, located near the U1C binding site, not only disrupts Sm core assembly but also sequesters the SMN complex, thereby inhibiting canonical snRNP formation. These findings provide important mechanistic insights into how snRNP-specific proteins regulate the SMN complex and suggest that U1 snRNA mutations in numerous cancers may contribute to dysregulation of RNA metabolism by impairing SMN complex activity.

22 **Development of a Red Fluorescent Biosensor for Nitrate**

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The consumption of nitrate has been linked to enhanced human wellness, including improved cardiovascular health and increased muscular performance. While the study of nitrate supplementation on a systems level is a rapidly growing field, the subcellular mechanisms remain underexplored. Current methods to measure nitrate rely on *ex vivo* techniques, such as the Griess assay or N^{15}-radiolabeling, and thus lack spatial and temporal resolution. Genetically encoded fluorescent biosensors can act as complimentary tools to such methods by providing real-time monitoring. To this end, the most recent advance is NitrOFF – a chimeric indicator based on the green fluorescent protein EGFP and the nitrate binding domain NreA. While NitrOFF exhibits micromolar sensitivity, it is inherently pH sensitive, limiting cellular applications. To overcome this, we engineered a red-shifted nitrate biosensor named rFLINT. In this presentation, I will describe the design and directed evolution, photophysical properties, and cellular application of rFLINT.

23 **Predicting the Northward Expansion of the Central American Locust (Schistocerca piceifrons) Using Machine Learning and Citizen Science**

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The Central American Locust (CAL - Schistocerca piceifrons) poses a critical threat to agricultural stability, having previously caused extensive crop losses and economic instability across South America. The extreme weather pattern is creating potential distribution shifts for CAL and an imminent distribution into the USA is expected. The objectives of this project are dual: (1) to use AI machine learning to predict suitable locations for the expansion of CAL and (2) to conduct community outreach and engagement to create a citizen science monitoring network in the Lower Rio Grande Valley (LRGV). Preliminary findings indicate that portions of the LRGV are becoming climatically suitable for permanent breeding, with models showing a steady northward encroachment toward Texas. These results establish a framework for a predictive early-warning system, enabling stakeholders to implement proactive mitigation strategies to reduce agricultural losses in border regions.

24 **Improving Heterochiral Aptamer Interactions through 2'OMe Modified SELEX**

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L-aptamers, composed of mirror-image L-nucleotides, bind structured D-RNA targets with exceptional affinity and minimal off-target activity, making them promising therapeutic agents. However, conventional SELEX is performed using unmodified D-DNA/RNA libraries, which often leads to reduced affinity and stability once chemical modifications are introduced post-selection. To address this limitation, we are investigating the incorporation of 2’-O-methyl (2’OMe) nucleotides directly into the SELEX process. Because 2’OMe enhances nuclease resistance, structural rigidity, and biocompatibility, selecting aptamers within this chemically stabilized environment is expected to improve heterochiral recognition and streamline downstream therapeutic development. Our approach aims to generate L-aptamers with higher binding affinity, increased biological stability, and reduced toxicity while shortening development timelines by eliminating modification-induced affinity losses. This work establishes a framework for a more streamlined and clinically relevant route to high-performance heterochiral aptamers.

25 **The C-Terminal Region Tunes Nitrate Binding Affinity in Nitrate Sensors from Staphylococcus**

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Nitrate is an essential oxyanion for microbes. It can be transported and metabolized to serve as a source for nitrogen and terminal electron acceptor for anaerobic respiration. Given this need, microbes have evolved mechanisms to sense nitrate in their environments. One such example is the two-component NreABC system from *Staphylococcus carnosus*, in which the NreA protein from the GAF superfamily serves as the sensor for intracellular nitrate levels. While this sensor is widely annotated, it remains biochemically understudied. Motivated by this gap, we sought to understand how sequence level differences could contribute to nitrate sensing. Detailed bioinformatic analysis reveals that more than 736 putative NreAs are found across diverse commensal and pathogenic Staphylococcal strains. In this presentation, I will describe the biophysical characterization of a sub-selection of these homologues, uncovering that the non-coordinating C-terminus tunes nitrate binding affinity in these sensors.

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26 **Influences of Native ESI Buffers on Protein Structure Captured by Native Mass Spectrometry**

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In native mass spectrometry (nMS), buffers ammonium acetate (AmAc), ethylenediamine diacetate (EDDA) and triethylammonium acetate (TEAA) are commonly used. EDDA and TEAA are both known to reduce the average charge (Zavg) of ions relative to AmAc, raising questions about their effects on protein conformation. To investigate this, intact hydrogen-deuterium exchange mass spectrometry (HDX-MS) and ion mobility mass spectrometry (IM- MS) were employed, using transthyretin (TTR), a 56 kDa homotetramer sensitive to solution conditions, as a model system. HDX-MS results revealed that wild-type TTR exhibited similar deuterium uptake in AmAc (45.0%) and TEAA (46.1%) after 96 hours, while significantly lower uptake was observed in EDDA (40.4%). This trend was consistent across multiple TTR mutants (V30M, L55P, T119M, V122I), suggesting that the presence of EDDA reduces the number of solvent-accessible hydrogens. This could be due to the structure of EDDA, where two ammonium groups may interact with the protein at multiple sites simultaneously, thereby blocking residues from interacting with the surrounding solvent. HDX-MS also provided insight into TTR tetramer dynamics. Evidence of tetramer disassembly and reassembly was observed in AmAc and TEAA through the emergence of a higher-mass species over time. This process was markedly reduced in EDDA, indicating enhanced tetramer stability along with the overall reduction of HDX. Complementary IM-MS measurements showed buffer-dependent differences in average collision cross section (CCSavg) of TTR, with values of 3705 Å² in AmAc, 3635 Å² in EDDA, and 3588 Å² in TEAA. These findings all together demonstrate that buffer composition significantly impacts the dynamics, stability, and structure of TTR in solution.

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27 **Citizen Science: Establishing a Community-Based Monitoring Network for the Central American Locust in the Rio Grande Valley**

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The Rio Grande Valley faces an escalating agricultural threat from the Central American locust (*Schistocerca piceifrons*), a species capable of forming dense, synchronized swarms that consume vast amounts of vegetation in a short period of time. These outbreaks can devastate staple crops such as corn, cotton, and citrus within hours, placing regional food systems and local economies at significant risk. To address this gap, this project developed a community-centered citizen science network that transforms local residents into

active participants in pest monitoring efforts. The initiative emphasizes culturally relevant outreach by incorporating familiar and engaging educational tools, including interactive lotería games and youth-focused coloring materials. These resources are paired with accessible digital reporting platforms that enable participants to identify and report locust sightings, contributing real-time geospatial data for analysis. The results demonstrate that integrating community engagement with user-friendly technology significantly improves early detection capabilities while expanding the reach of conventional monitoring systems. In addition to strengthening surveillance, this approach promotes public awareness and fosters a shared sense of responsibility for protecting regional agriculture. By bridging scientific research with community participation, this project highlights the effectiveness of citizen science as a scalable and cost-efficient strategy for mitigating invasive species threats and enhancing long-term agricultural resilience in the Rio Grande Valley.

28 **Structural Insights into the DapC, DapD, DapE, and DapF: Key Enzymes of the meso-Diaminopimelate (mDAP) Pathway**

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The lysine/meso-diaminopimelate (mDAP) biosynthetic pathway is essential for bacterial survival, contributing to both lysine production and peptidoglycan precursor synthesis. Due to its absence in mammalian systems, the mDAP pathway constitutes a promising high-value target for antimicrobial development. The enzymes DapC, DapD, DapE, and DapF catalyze key sequential steps within this pathway and are indispensable for maintaining metabolic flux and cell wall biosynthesis. Recent studies propose that enzymes within central metabolic pathways can form transient, spatially organized complexes known as metabolons, that facilitate substrate channeling, enhance catalytic efficiency, and enable coordinated regulation. In this context, we hypothesize that DapC, DapD, DapE, and DapF exhibit structural complementarity that supports their assembly into a functional multi-enzyme complex. This project aims to characterize the structural interfaces and functional interactions among these enzymes using biochemical and structural techniques. By elucidating their potential organization into a metabolon, we seek to define the mechanistic basis of substrate transfer, catalytic coupling, and pathway regulation within the mDAP biosynthetic network.

29 **Molecular Dynamics Reveal Mechanistic Divergence Between the Two Pores of Fluc**

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The introduction of fluoridated water has been one of the most impactful public health interventions, contributing not only to bone health and dental protection but also functioning as a potent antimicrobial agent. The effectiveness of fluoride has been challenged by the discovery that microorganisms possess specialized transport systems to eliminate intracellular fluoride. Identified about a decade ago, the two key players are CLCF and Fluc, which represent distinct structural solutions to the same evolutionary problem. While CLCF shares structural and mechanistic features with the well-studied CLC family of chloride channels and antiporters, Fluc represents a completely novel protein family that has captivated the scientific community with its unique properties. Fluc is the fastest and most selective ion channel reported to date; even a modest reduction in its selectivity for fluoride over chloride would compromise membrane potential. Remarkably, its extraordinary performance arises from an antiparallel homodimeric assembly that creates two independent, asymmetric fluoride-conducting pores rather than a central shared pore. Crystal structures have also revealed a central cation, most likely sodium, whose precise role in channel stability or function remains unresolved. In this work, we employed long- timescale electrophysiology-based molecular dynamics simulations to investigate the molecular mechanism of fluoride permeation in Fluc. Our results reveal a

striking functional asymmetry between the two pores, each operating through a distinct mechanistic pathway. Furthermore, we observed dynamic movement of the central sodium ion, suggesting it may play a critical role in modulating conductivity. To our knowledge, this is the first demonstration that a single Fluc dimer can support two mechanistically distinct transport routes. These findings not only provide new insight into the enigmatic features of Fluc but also suggest strategies for designing transporters with dual selectivity by exploiting structural asymmetry.

30 **Structural Understanding of Protein Interactions that Regulate Ca^{2+} Homeostasis in *Arabidopsis Thaliana***

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CAX1 is a tonoplast Ca^{2+}/H^{+} exchanger involved in plant calcium homeostasis. Under high-calcium conditions it can be regulated by the CBL3–CIPK9 complex. We are investigating CAX1 WT, a constitutively active mutant CAX1-T33D, and its regulatory partners CBL3/CIPK9. We aim to restore activity *in vitro* through liposome reconstitution and explore the structural constraints behind this interaction. This work will help us better understand how the N-terminal regulatory region controls CAX1 activity. SDS-PAGE and Western blot confirmed protein expression, while DLS analysis revealed predominantly monodisperse populations with particles near 9–10 nm. Ongoing studies include Ca^{2+} transport activity assays, and Cryo-EM data collection.

31 **A General Strategy for Photostable and Bioconjugatable Pentamethine Cyanine Fluorophores**

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Pentamethine cyanine (Cy5) fluorophores are widely used in biological imaging but are often limited by rapid photobleaching under prolonged illumination and oxidative conditions. Here, we report a general strategy to enhance the photostability of pentamethine cyanines through electronic modulation of the indolenine scaffold. Specifically, we introduce electron-withdrawing substituents, including sulfonate groups on the benzene ring for aqueous solubility and difluoro- or trifluoroethyl groups at the *N*-alkyl position, to get SAT-Cy5-s-F2 and SAT-Cy5-s-F3. Importantly, incorporation of these electron-withdrawing groups preserves the photophysical properties of the dyes while significantly reducing photooxidative degradation under continuous irradiation and in reactive oxygen and sulfur species-rich environments compared to commercial standards, including Alexa Fluor 647. Additionally, our strategy can be modulated to incorporate bioconjugation handles for biomolecule labeling. We demonstrate that bioconjugatable versions of SAT-Cy5-s-F2 and SAT-Cy5-s-F3 can be conjugated to mAbs at a range of labeling densities and retain their enhanced photostability. Overall, this work demonstrates that tuning the electronic properties of indolenine building blocks provides a general and effective approach to designing pentamethine cyanine fluorophores with improved photostability for advanced biological imaging applications.

32 **Development of Sulfated Flavonoids as Selective Allosteric Inhibitors of Plasmin**

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Plasmin, is the key serine protease responsible for fibrinolysis, the degradation of fibrin clots. Beyond clot dissolution, plasmin regulates extracellular matrix remodeling, cell migration, inflammation, and cancer progression, reflecting a broader physiological role. Thus, plasmin inhibition represents not only an important therapeutic strategy for stabilizing hemodynamic clots but also a means of intervening in other pathological settings arising from dysregulated plasmin- mediated proteolysis. Despite this profound clinical relevance, there are currently no FDA- approved direct plasmin inhibitors. The only approved antifibrinolytics, tranexamic acid and ε- aminocaproic acid, act indirectly by blocking plasminogen activation upstream rather than inhibiting active plasmin. This reduces their potency and overall effectiveness under conditions of excessive fibrinolysis. This underscores the critical need for novel, selective, direct plasmin inhibitors. We previously reported sulfated flavonoid-based, non-saccharide glycosaminoglycan mimetics as allosteric inhibitors of plasmin. Building on this foundation, we sought to enhance inhibitory potency and further define structure–activity relationships by designing and synthesizing a focused library of sulfated flavonoids that incorporated systematic variations in sulfation density, linker architecture, and valency. Compounds were evaluated using a chromogenic substrate hydrolysis assay, and mechanisms of inhibition were characterized through Michaelis–Menten kinetics together with competition and salt-dependence studies. Our studies identified molecule 6, a dodeca-sulfated flavonoid trimer, as the most potent inhibitor reported in this class to date. The compound inhibits plasmin with an IC50 of 3.0 μM (Ki = 1.1 μM) and is 2– 35-fold more potent than corresponding inhibitors from the previous generation. Kinetic analyses indicate an uncompetitive, salt-dependent mechanism. Inhibitor 6 is >300-fold selective for plasmin over thrombin and Factor Xa, two serine proteases in the coagulation cascade. Despite extensive sulfation, approximately 80% of its calculated binding affinity arises from nonionic interactions, which may account for its specificity. The compound partially competes with unfractionated heparin, further supporting its allosteric mechanism. Collectively, these findings position molecule 6 as a proof-of-concept candidate for evaluation in animal models of fibrinolysis-related disease.

33 **Working Towards Energy Transfer Near IR Chemiluminescence Probe**

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Chemiluminescence is light emission from an excited state product formed in a chemical reaction, which has been widely used for molecular and ion detection. Since it does not require an exogenous excitation light source, thus effectively eliminating the autofluorescence, photobleaching, and light scattering of fluorescent probes, as well as providing an extremely high signal-to-noise ratio. Among the chemiluminescent molecules, Schapp's dioxetanes have been extensively researched as these dioxetanes can provide tunable emission wavelength by adding different appendage and more importantly the ability to cage the protecting group with cleavable substituent which provides the specialty for the detection. These dioxetanes are thought to undergo triggered chemiluminescence by way of a chemically initiated electron exchange luminescence (CIEEL) mechanism. In this study, we present our chemiluminescent probe design which contains two parts: 1. A 1,2 dioxetane phenol is modified by acrylic acid group with the chemiluminescence emission wavelength of 530 nm. 2. An Aza-BODIPY dye modified by the appendage of piperazine to give an excitation emission wavelength of 700 nm, which acts as a chemiluminescence resonance energy transfer acceptor. The two parts can be coupled together using HBTU coupling. The energy transfer in a single molecule construct should enable NIR chemiluminescence in vivo imaging. Previous study shows the EDC coupling through ester bond

does not provide energy transfer. This study may provide more evidence for the piperazine as more suitable linker for the design of the energy transfer chemiluminescent probe.

34 **Synthesis and Analysis of Host-Activated Prodrugs**

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Pyrazinamide is a first-line treatment for tuberculosis. It is a prodrug that requires conversion into its active form, pyrazinoic acid, by a bacterial enzyme known as pyrazinamidase under inflammatory conditions. However, due to mutations, pyrazinamide has become resistant, resulting in an urgent need for new antimycobacterial agents capable of bypassing this mechanism. In this study, we designed and synthesized a pyrazinoate prodrug via amide coupling to overcome this resistance. The prodrug successfully inhibited the growth of *Mycobacterium smegmatis* and *Mycobacterium marinum*, whereas pyrazinamide showed no activity under the same conditions. Furthermore, a positive Wayne assay confirmed pyrazinamidase-independent activation of the prodrug through the release of pyrazinoic acid. These findings demonstrate the potential of this molecule to circumvent pyrazinamide resistance and highlight its promise as a lead compound for developing new antimycobacterial therapies.

35 **Influence of Intramolecular Epistasis on Catalytic Promiscuity and Enzyme Specificity among Protein Homologs**

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One of the key challenges in enzyme engineering is rewiring intramolecular protein interactions to engineer highly specific and efficient enzymes with novel functions. Insights from natural evolution can help address this by revealing how enzymes are able to catalyze different reactions using a conserved structural scaffold. To explore this, we analyzed the evolution of *N*-succinylamino acid racemase (NSAR) activity from an ancestral *o*-succinylbenozate synthase (OSBS) via catalytically promiscuous enzymes that possess both activities. An aromatic-to-aliphatic mutation in the active site was identified as a potential specificity determinant, as it led to an increase in NSAR activity of *Alicyclobacillus acidocaldarius* OSBS from undetectable to a modest 1.2 x 10^2 $M^{-1}s^{-1}$. However, introducing the equivalent mutations in two other homologs required a second substitution to elicit an increase in NSAR activity. These findings suggest that non-additive intramolecular amino acid interactions (epistasis) influenced the molecular mechanisms for evolving NSAR activity. This underscores the complexity of sequence-function relationships and highlights the role of epistasis in enzyme evolution. Future studies, including deep mutational scanning, are underway to elucidate how enzymes acquire new functions while preserving structural integrity, providing valuable insights for engineering robust and versatile biocatalysts.

36 **Design and Application of Genetically Encoded Phage-Derived Peptide Probes for High-Throughput Screening of Bromodomain Protein 9**

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Acetylation is the most dynamic protein translational modification often associated with increased DNA accessibility and transcription. These acetylated histones recruit transcription and remodeling factors, and their deregulation could result in aberrant expression of survival and growth-promoting genes. Recognition

of acetylated lysine is principally mediated by bromodomains (BRDs). Recent studies have shown that BRD9 is preferentially used by cancers that harbor SMARCB1 abnormalities such as malignant rhabdoid tumors and sarcomas. BRD9 is an essential component of the SWI/SNF chromatin remodeling complex, and a critical target required in acute myeloid leukemia. As the biological function of BRD9 in tumorigenesis becomes clear, bromodomain of BRD9 has become a new hot target for effective tumor treatment method. BRD9 has a different architecture than other bromodomains. Due to larger hydrophobic cavity of BRD9, it can recognize longer propionyl and butyryl marks on lysine. Thus, N-butyryl-lysine (BuK) can selectively bind to BRD9. Our group specializes in the amber suppression-based noncanonical amino acid (ncAA) mutagenesis technique. Herein (Fig 1), we propose to extend this technique using phage-displayed ncAA-containing peptide libraries for the identification of high- affinity and highly selective BRD9 inhibitors. Phage display is a technique for rapid screening of potential ligands. It is facilitated through the creation of a genetic fusion between a randomized peptide sequence and pIII, a phage coat protein. This direct link between genotype and phenotype allows for peptide screening. We utilized Phage- assisted, Active site Directed Ligand Evolution (PADLE) approach to target BRD9. To identify the binders, we choose 7mer phagemid library which generates 1.5x1010 randomized possible peptides displayed on PIII of bacteriophages. Iterative rounds of selection and enrichment yielded a lead peptide with a dissociation constant (Kd) of approximately 800 nM, representing a substantial improvement over the micromolar affinities typical of histone-based probes. Incorporation of this peptide probe into biochemical assay enabled the development of a highly sensitive and cost- effective screening platform.

37 Methodology for Functionalized Enneamethine Cyanines Enables Synthesis of Diverse Fluorophores above 850 nm

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The near-infrared region (NIR: 750-1000 nm) holds immense potential in biomedical imaging due to low autofluorescence and maximum tissue penetration. Heptamethine cyanine dyes (Cy7s) are the most common near-infrared absorbing fluorophores. There have been intense efforts to develop synthetic strategies to access polymethine- and indolenine-substituted Cy7s. However, most Cy7 derivatives remain limited to absorption below 800 nm and do not take advantage of the further NIR-I spectra (800-1000 nm). Therefore, there is a need for new design strategies that retain polymethine functionalization while enabling red-shifted cyanines with absorption beyond 800 nm to maximize the use of the NIR region. To address these limitations, we report a general two-step strategy for the synthesis of functionalized enneamethine cyanines (Cy9s) from commercially available precursors. These Cy9s have absorbance above 850 nm. The strategy involves ring opening of electrophilic pyridinium benzoxazole derivatives utilizing a powerful enolate nucleophile to give 7-carbon merocyanine-like intermediates (Mero-C7s). The Mero-C7 synthesis is high-yielding and has broad functional group tolerance, including aliphatic, aromatic, and heteroatom-pyridines. Subsequent Knoevenagel condensation with diverse indolenines led to the development of a highly diverse compound library consisting of multiple polymethine- and heterocycle-substituted Cy9 fluorophores (SAT-NIR dyes; 21 derivatives in total). The SAT-NIR fluorophores are the most comprehensive Cy9 library reported to date. The polymethine and indolenine substitutions impact both photophysical and photochemical properties. Notably, this work allows for the modulation of functional groups on the polymethine chain that was originally not possible for Cy9 compounds. The lead candidate, SAT-NIR-853, was encapsulated in PEGylated nanoliposomes, which provided superior NIR-II imaging as compared to ICG in tissue-mimicking phantoms. This platform provides a robust synthetic pathway to generate deep tissue penetrating Cy9 compounds, which could lead to the development of photostable and bio-conjugatable NIR fluorophores.

38 **GlueMiner: Powering Next Generation Molecular Glue Discovery through Data Integration, Templated AI Folding and High-throughput Virtual Screening**

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Molecular glues represent a promising class of targeted protein degraders that function by inducing protein-protein interactions between an E3 ubiquitin ligase and a neo-substrate. This interaction facilitates polyubiquitination and subsequent proteasomal degradation of the target protein. Rational design of these degraders requires extensive Structure-Activity Relationship (SAR) data and precise ternary structures of the E3-ligase-target complex. However, much of the available SAR data remains buried within disparate proteomics datasets and library screenings, often under-analyzed in original publications. Furthermore, traditional structural biology methods, such as X-ray crystallography and Cryo-EM, frequently struggle to resolve structures for low-affinity lead compounds. To address this, we developed GlueMiner, an integrated online database and discovery tool for molecular glues. We curated and reanalyzed molecular glue screening data from diverse sources, including ubiquitinomics, global proteomics, immunoprecipitation (IP) pull-down, and flow-based mutation screenings. GlueMiner enables medicinal chemists to cross-reference historical studies, focusing on specific chemical scaffolds or targets of interest. Beyond data integration, we performed large-scale structural predictions across the human proteome. Focusing on previously identified G-loop degrons, we performed structural alignments using AlphaFold2 (AF2) predicted domain structures against Cryo-EM resolved ternary structures. These models were further refined using Boltz-2 templated folding, yielding 6,930 high-confidence hits from an initial pool of 39,402 G-loop structures. These structures are integrated into the GlueMiner platform to provide actionable structural insights. Further analysis is being conducted for high-throughput screening with these strong hits and molecular glue libraries from different vendors. By combining comprehensive data curation, AI-driven templated folding, and high-throughput screening, GlueMiner serves as a powerful bioinformatics ecosystem to accelerate the discovery and optimization of novel molecular glue degraders.

39 **Phospholipid Bilayer Fatty Acid Composition Controls Membrane Electrostatics and Fluidity**

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Piezophiles have adapted to thrive in high pressure environments, such as the bottom of the ocean where pressure can reach up to 100 MPa. These organisms have been found to have a higher percentage of fatty acids within their membranes. This adaptation is believed to help the organisms prevent pressure-induced membrane rigidity, although little is known about how the membrane's physical properties are affected by increased fatty acid concentration. Membrane fluidity and electrostatics play an important role in maintaining membrane ion concentration gradients and membrane-protein interactions. Here, I employ lanthanide-shifted 31P Nuclear Magnetic Resonance and vibrational Stark effect FTIR on 50 nm and 100 nm DOPC vesicles respectively to examine changes to membrane fluidity and surface potential for six different fatty acids at ambient pressure. At higher fatty acid concentration, unsaturated and branched fatty acids were found to significantly increase the membrane fluidity. Additionally, adding fatty acids to the vesicles increased the membrane surface potential while having little to no change to the membrane dipole electric field. These changes to membrane fluidity and electric field strength at ambient pressure conditions give us the first insights into how piezophiles have adapted their membranes to better survive their environment. I aim to continue this work at a variety of pressures to quantify changes to membrane physical properties at high pressure.

40 **Breaking the Keap: Unlocking Nrf2 for Neuroprotection in Alzheimer's Disease**

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Oxidative stress plays a significant role in the progression of Alzheimer's disease, making cellular antioxidant pathways attractive therapeutic targets. The Keap1–Nrf2 signaling pathway regulates the cellular response to oxidative stress, and inhibition of the Keap1 protein can activate Nrf2, promoting neuroprotective antioxidant responses. In this study, a series of quinoline-modified macrocyclic compounds were designed and synthesized to evaluate their potential as Keap1 inhibitors. Computational and experimental approaches were employed to investigate the interaction of these compounds with the Keap1 protein. In-silico studies were conducted to analyze the binding affinity of the synthesized compounds using molecular docking, molecular dynamics simulations, and machine learning–based prediction of IC_{50} values. These analyses provided insight into the stability of the ligand–protein complexes and the structural features that influence binding interactions. The computational results indicate that compounds containing polar substitutions on the upper synthon exhibit stronger binding affinity and form more stable complexes with the Keap1 protein. Additionally, modification of the macrocyclic scaffold with quinoline substitution on the side nitrogen was found to enhance interactions with the protein binding pocket, suggesting a favorable structural motif for Keap1 inhibition. Together, these findings provide insight into structure–activity relationships for this class of compounds and highlight promising molecular features for the development of Keap1 inhibitors as potential therapeutic leads for Alzheimer's disease.

41 **GlycoRNA and Cell Surface RNA Biogenesis Study Through Flow-Cytometry Based CRISPR Screen**

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Glycosylated RNA (glycoRNA) is a newly identified class of RNA localized on the cell surface, with emerging roles in immune regulation; however, its biogenesis remains poorly understood. In addition, the relationship between glycoRNA and cell surface RNA (csRNA) remains unclear. Here, we establish a flow cytometry–based CRISPR screening platform to enable unbiased identification of genetic regulators of glycoRNA and csRNA. By integrating orthogonal click chemistries, we further develop a multiplex labeling strategy that allows simultaneous detection of diverse glycan types and RNA species. This approach enables systematic dissection of glycoRNA and csRNA biogenesis at a systems level.

42 **Stereochemically Defined Cyclohexylamide Scaffolds as Chiral Peptidomimetics for Mimicking α-Helical Surfaces**

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α-Helix-mediated protein–protein interactions (PPIs) are challenging to inhibit because it is difficult to reproduce the exact side chain orientation and spacing necessary for effective molecular recognition. To date, α-helix mimetics, such as aromatic scaffolds, stapled peptides, and foldamers, have shown notable conformational rigidity but often lack systematic stereochemical control and tunable side chain positioning. In contrast, the chiral cyclohexylamide scaffolds we designed uniquely combine enhanced structural rigidity with precise stereochemical control side chain positioning. This dual advantage allows accurate replication of side chain arrangements found in α-helices and overcomes limitations of previously reported helix mimetics. This is a new class of peptidomimetics engineered to present side chains found at the *i, i+4, i+7,* and *i+11* positions of three helical turns. They comprise stereochemically defined, tri-substituted cyclohexanecarboxylic acids, serving as modular building blocks. Through regio- and stereoselective bromo-lactonization, eight distinct cyclohexane stereoisomers were synthesized and efficiently assembled into cyclohexylamide oligomers. These combinations of rigid three-dimensional structure and stereochemical diversity expand the design space of α-helix mimetics, enabling more selective disruption of PPIs.

43 **An Integrated Platform for High-Throughput Native Mass Spectrometry Screening and Thermodynamic Profiling**

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Protein–ligand interactions are central to biological function and are of broad importance in drug discovery and biotechnology. Native mass spectrometry (native-MS) has emerged as a versatile and powerful method for probing non-covalent protein–ligand complexes, providing direct access to stoichiometry and binding affinity under near-physiological conditions. Despite these advantages, its application in drug-discovery screening remains constrained by low throughput and limited access to thermodynamic parameters efficiently within a single experimental workflow. Here, we report an integrated platform that enables high-throughput screening while simultaneously supporting quantitative affinity measurements and temperature-dependent thermodynamic analysis within a single native MS experiment, advancing native MS toward screening-grade applicability in drug discovery. The platform combines a programmable microplate positioning stage with a fused-silica capillary assembly that enables concurrent sample aspiration and electrospray directly from each well. Sample transport is driven by MS inlet vacuum and capillary action, while an inline high-voltage interface applies spray potential to the flowing solution. An integrated temperature-control module maintains well temperatures from -5 to 65 °C with ± 0.1 °C precision, enabling thermodynamic measurements during acquisition. Using this platform, discrete native MS measurements were acquired in 5–10 s per sample with minimal inter-sample dead time. The platform produced native mass spectra across a broad mass range from ubiquitin (9 kDa) to GroEL14-mer (801 kDa), with sensitivity and charge-state distributions comparable to conventional nanoelectrospray ionization. Preservation of non-covalent complexes was demonstrated using lysozyme with tri-N-acetyl-β-glucosamine (NAG_3) and carbonic anhydrase II with multiple ligands. Titration curve experiment using lysozyme–NAG_3 enabled dissociation constant determination, while temperature-dependent binding data supported Van't Hoff analysis to extract ΔG, ΔH, and - TΔS, yielding values consistent with nESI, ITC, and SPR. Carryover studies showed no detectable left-over signal between adjacent wells containing different proteins. Plate-based reproducibility, evaluated across 60 wells containing premixed lysozyme and NAG_3 at a 1:1 molar ratio, gave a coefficient of variation (CV) of 7.17% for complex fraction. To further demonstrate screening throughput, we performed pooled-ligand analysis by incubating carbonic anhydrase II with a 20-compound mixture containing 7 binders with distinct affinities and 13 non-binders. Because each bound ligand generates a unique mass shift, multiple ligands can be screened simultaneously within a single well without binding ambiguity, provided sufficient spectral sensitivity is maintained. All seven binders were clearly detected, while no binding peaks were observed for the non-binders. Notably, the relative intensities of the protein–ligand complex peaks reflect ligand binding affinity, with stronger binders producing higher-intensity complex signals. These results demonstrate the feasibility of pooled native MS screening on the integrated platform and enable high-throughput screening (>10,000 compounds per day).

44 **Visible Light 3D Printing of Microneedles**

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Commercially available acrylate and alkene-functional monomers along with co-initiators and a photoredox catalyst (PRC) were used in a one-pot system to generate defined polymeric microneedle arrays. Although the acrylate-functional system had exclusively been applied to 3D printing of varying forms, our novel approach set out to utilize the photoresin system in our Digital Light Processing (DLP) fluorescence microscope to generate microneedles. Trimethylolpropane triacrylate (TMPTA) served as the tri-functional acrylate ester to crosslink with co-monomer N,N-dimethylacrylamide (DMA). The polymerization was photoinitiated by Rose Bengal, which participated in a catalytic cycle in reaction with co-initiators H-Nu 254 and Borate V. Blue light exposure successfully facilitated photoresin activation, resulting in 3D patterned microneedle arrays that propagated in the z-direction with distinct feature quality. Overall dimension control of the microneedles was achieved through variation of LED exposure of the photoresin, with a direct relationship emerging between exposure time and needle length. Shape sizes within the projected patterns also afforded control over size and shape of the polymeric microneedle arrays. Complementary fluorescence studies revealed dye loading capacity within the microneedles. These results demonstrated achievable coating of the polymeric needles and subsequent release of dye to the surrounding media, with observable dependence on incubation time. The findings from this loading model provided evidence these microneedles could be successfully implemented in drug delivery systems.

45 **Selective Inhibition of HAT1 Using AB Oligomers: A Tunable Platform for Targeting Enzymes**

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Histone acetyltransferase 1 (HAT1), an enzyme that catalyzes the acetylation of lysine residues on histone H4 tails, remains a challenging therapeutic target due to the poor cell permeability of peptide-based inhibitors and the lack of specificity in small molecule inhibitors. Here, we present a novel class of compounds, AB oligomers, as selective and synthetically diverse inhibitors of HAT1. AB oligomers are composed of two groups of building blocks, amino acid (A) and functionalized aminobenzoic acid (B) alternating in sequence. They can be readily synthesized in solid-phase, which enable rapid construction of small but focused chemical libraries. AB oligomers exhibit structural diversity, metabolic stability, outstanding cell permeability, making them useful for developing potent and selective inhibitors through extensive structure-activity relationship (SAR) studies. B21-2, an AB pentamer, demonstrated selective inhibition of HAT1 with an IC50 value of approximately 1 µM. It appears to act as a substrate-based inhibitor and effective biochemical probe. The ease of synthesis, coupled with the potential for AI-guided design and library screening, positions AB oligomers as a promising platform for targeting various proteins and pathways in biomedical studies.

46 **Electronically Tuned Quinone Methide Probes Enable Functional Profiling of Carbohydrate Metabolism in the Gut Microbiome**

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Understanding enzyme activity in complex microbiomes remains a central challenge in chemical biology, where genomic potential often fails to reflect functional metabolism. Activity-based protein profiling (ABPP) offers a direct route to enzyme activity, yet probe performance is frequently dictated by poorly controlled reactivity. Quinone methide (QM)-based probes offer versatile electrophilic capture following enzyme-triggered activation, but their utility is often limited by the "neighborhood effect," where diffusion of reactive intermediates leads to off-target labeling. Here, we introduce electronically tuned carbohydrate-based ortho-quinone methide (oQM) probes that transform this limitation into a controllable design feature, enabling deliberate modulation of labeling radius and functional specificity. Applying these probes across biological scales—from a model gut bacterium to a defined fiber-degrading community and human stool—we demonstrate that electronic tuning directly rewires chemoproteomic outputs, selectively enriching distinct networks of glycoside hydrolases, transporters, and carbohydrate metabolism pathways. Notably, probe performance is context-dependent, with broader-reactivity probes enabling target capture in highly complex microbiomes, while tuned probes enhance specificity in defined systems. This work establishes reactive intermediate control as a generalizable strategy for designing next-generation ABPP tools and highlights electronic tuning as a key component for understanding carbohydrate metabolism in complex biological systems.

47 **Discovery of a Color and Chloride Tuning Hotspot in a Red Fluorescent Protein**

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Chloride is the most abundant biological anion and is essential for cellular physiology, supporting processes such as innate immunity and cell-cycle progression. Disrupted chloride gradients contribute to diseases including cystic fibrosis and kidney stones, motivating interest in restoring or modulating chloride transport. Genetically encoded indicators are needed to visualize when and where chloride fluxes occur. Although most chloride indicators derive from green/yellow fluorescent protein lineages, red-shifted sensors remain scarce, limiting multiplex and deep-tissue imaging. Here, we explored this possibility with the red fluorescent protein mGrape1 and applied directed evolution with sequential anion screening to identify de novo halide responsiveness. Surprisingly, we uncovered a variant with two mutations displaying halide-dependent fluorescence quenching; however, the emission was shifted from red to green. Mutational deconvolution identified a single mutation as the driver of both properties. Anion profiling revealed responses to multiple halides and selected oxyanions, consistent with a pocket that accommodates chemically diverse anions. Computational modeling using molecular dynamics (MD) and quantum mechanics/molecular mechanics (QM/MM) simulations reveal how altered interactions within the chromophore and anion binding pocket give rise to the observed photophysical properties. Together, these findings underscore the persistent challenge of achieving robust chloride sensitivity without compromising red emission, indicating that anion responsiveness and stable red fluorescence may be difficult to achieve simultaneously in this scaffold and motivating exploration of other red fluorescent proteins to unlock red-shifted chloride sensing.

48 **Development of New Antibacterial Candidates against Helicobacter pylori: Rational Design of an Initiation Factor 1 derived Peptide based on IF1 Structure and Function and Identification of New Inhibitory Compounds**

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Helicobacter pylori (*H. pylori*) is a gram-negative microaerophilic bacterium that colonizes the human gastric mucosa and is associated with peptic ulcer, gastritis, and gastric cancer. The treatment of *H. pylori* infections presents a growing clinical challenge due to the prevalence of antibiotic resistant strains. Bacterial protein synthesis is a validated antibiotic target, and translation initiation factor 1 (IF-1) plays a vital role in this process by binding to the 30S ribosomal subunit for translational initiation. However, the three-dimensional structure of *H. pylori* IF1 (Hp- IF1) remains unknown. This study aims to determine the three-dimensional structure of Hp-IF1 by Nuclear Magnetic Resonance (NMR) spectroscopy, evaluate the antibacterial activity of a synthetic Hp-IF1 derived peptide against H. pylori, and investigate the antibacterial effects of erythromycin combined with caffeic acid as well as the Hp-IF1-derived peptide combined with caffeic acid against H. pylori. Hp-IF1 protein was expressed in an E. coli expression system using recombinant plasmid pET24b- Hp-IF1 and purified by His-tag affinity chromatography followed by ion exchange chromatography. The purified proteins were used to conduct NMR experiments and allowed NMR assignments and structural determination. The complex structure of Hp-IF1 and the 30S ribosome was modeled and guided the rational design of Hp-IF1-derived peptide for inhibitory test against H. pylori growth in this study. H. pylori strain NCTC 11637 was cultured under microaerophilic conditions in the lab and used for antimicrobial susceptibility testing by broth microdilution assay using resazurin as a viability indicator. The minimum inhibitory concentrations (MIC) of trans-caffeic acid, caffeic acid, erythromycin, and their combinations were determined. The combinations of caffeic acid and trans-caffeic acid with erythromycin yielded the lowest MIC values, representing an approximately 32-fold reduction compared to caffeic acid and trans-caffeic acid alone, indicating an additive antibacterial interaction. MIC testing of the Hp-IF1 derived peptide showed that it inhibits the growth of H. pylori but does not interfere with the bacterial membranes, supported by Scanning electron microscopy (SEM). This result suggests that the peptide likely acts on an intracellular target, which may have synergistic effect with caffeic acid. This research provides structural insight into Hp-IF1 and demonstrates that combining caffeic acid with erythromycin substantially enhances antibacterial efficacy against H. pylori. These findings support the further exploration of caffeic acid-antibiotic combinations as a strategy to combat antibiotic resistance, while ongoing peptide studies allow the identification of novel antimicrobial candidates derived from the Hp-IF1 sequence.

49 **The Chemistry and Enzymology of Riboflavin (Vitamin B2) Catabolism**

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Riboflavin (vitamin B_2) is a redox cofactor involved in the catalysis of a wide diversity of biological oxidation reactions, and flavoenzymology is now a well-studied area. In contrast, very little is known about the enzymes involved in riboflavin catabolism. We have previously isolated a strain able to catalyze the oxidative cleavage of ribose from the isoalloxazine heterocycle, to form lumichrome. We then characterized a strain able to catabolize lumichrome, identified the responsible gene cluster, and characterized the enzymes involved. Given the general insolubility of lumichrome in water (4.8 mg/L), the first step of the catabolism involves lumichrome solubilization. This is accomplished by the oxidation of the C7 methyl group by a cytochrome P450, producing 7-carboxylumichrome. From here, a series of oxidative and hydrolytic enzymes open the three core flavin rings of lumichrome. One of these enzymes is a novel thiamin pyrophosphate (TPP)-dependent decarboxylase. The resulting heterocycle is involved in a Rieske dioxygenation reaction followed

by a catechol dioxygenase cyclization. The final steps include a retro-aldol reaction to yield pyruvate and acetoacetate. To elucidate this pathway, each of the enzymes was overexpressed and purified, and the reaction products were characterized using synthetic standards, NMR, and LC-MS.

50 **A Split Intein Reaction to Modulate Dynamics of Protein Condensates**

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Emerging research show that many proteins can self-assemble into condensates within living cells, which are micrometer-sized protein clusters. Protein condensates are involved in normal cellular processes and mis-regulation in the assembly process and dynamics of protein condensates have led to various diseases. Extensive prior studies mainly focused on the effects of protein sequences on condensate properties and functions. In contrast, the effects of molecular topology of proteins remain elusive, which hinders progress using protein condensates for biomaterial and biomedical applications. Using a split-intein reaction to circularize proteins, we expressed condensate-forming proteins in either linear or circular topologies in mammalian cells. While linear chains exhibit liquid-like dynamics, circular proteins in contrast display unexpected gel-like properties. Additionally, circular proteins have a higher tendency to assemble condensates compared to their linear counterparts. These differences between linear and circular protein are observed across various proteins, including FUS, EWS, TAF15, TDP-43, hnRNPA1, and LAF1. In some co-condensates composed of both linear and circular proteins, we found that the dynamics of linear proteins can slow down, resembling the behaviors of circular proteins. Additionally, we showed that linear and circular proteins have differential abilities in recruiting their binding partner proteins. For example, adenovirus packaging protein L1 52K, when circularized, can no longer effectively recruit minor capsid protein pIIIa into L1 52K condensates. In contrast to the prevailing methods that tune condensates through sequence optimization, this work highlights an intein-based strategy to modulate molecular topology and shows that non-linear topologies represent a novel parameter in protein condensates. The findings identify the effect of topological structure on biophysical properties of protein condensates and can create new opportunities to modulate protein-based biomaterials properties and chemical biology processes.

51 **Rapid Biocatalysis of Stereocomplex Polyketides by in vitro Reconstituted Assembly Lines**

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While strategies are increasingly available to engineer modular polyketide synthases (PKSs) that yield desired products from diverse chassis organisms, titers are usually suboptimal. *In vitro* reconstituted PKS systems could help study the responsible phenomena as well as be developed into complementary biocatalytic platforms to access desired polyketides. The few PKSs that have been reconstituted have yielded mixed results, with a refactored, 7-module erythromycin PKS measured to operate at an apparent k_{cat} of 1.1 min^{-1} and the 3-module venemycin PKS at 36 min^{-1}. Here, we reconstitute, study, and harness the 7-module pikromycin PKS and engineered variants thereof. Polypeptides too large to be expressed well in *E. coli* were divided with docking domains. Through optimizing docking domains, relocating histidine tags, and supplying the editing thioesterase PikAV, a refactored pikromycin PKS was observed to produce narbonolide at an apparent k_{cat} of 92 min^{-1}. Malonyl-CoA, methylmalonyl-CoA, and NADPH can be converted into narbonolide with 94% efficiency. From a 5-mL reaction conducted over 2 hours at room temperature using extender unit, NADPH, and ATP regeneration systems (the Extender unit to PolyKetide, or EPK, platform), 5 mg pure narbonolide was obtained, enabling the crystal structure of this iconic, stereocomplex macrolactone to be reported for the first time.

52 **Biochemical Basis of the Regulation of the SCF(Met30) E3 Ubiquitin Ligase by Sulfur Metabolism and Cadmium**

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The bZIP transcription factor Met4 is the master regulator of genes involved in sulfur metabolism in *Saccharomyces cerevisiae*, and its activity is strictly controlled by the SCF(Met30) ubiquitin ligase in response to sulfur metabolite availability. While cadmium is also known to inhibit Met4 ubiquitination, the underlying biochemical mechanisms by which Met30 senses sulfur metabolites and heavy metals have remained elusive. In this study, we developed a minimal, fully recombinant *in vitro* system—utilizing Uba1, Cdc34, and a modular SCF(Met30) complex—to dissect the mechanics of this regulatory switch. Our assays successfully reconstituted polyubiquitination of Met4, which was potently inhibited by micromolar concentrations of Cd^{2+}. To investigate the role of metal coordination, we engineered a "cysteine-less" (All C-to-S) Met30 mutant and discovered that it remains fully sensitive to Cd^{2+}, challenging the prevailing model of direct Met30 thiol-mediated inhibition. Unexpectedly, interaction assays revealed that Cd^{2+} enhances the physical association between Met30 and Met4 within the holo-SCF complex. These findings suggest that Cd^{2+} does not disrupt substrate recognition but instead acts as a molecular "brake," trapping the SCF(Met30)-Met4 assembly in a catalytically inactive state. This work aims to advance our understanding of E3 ligase regulation by small molecule metabolites and heavy metals, providing a biochemical framework for how cells achieve rapid metabolic recalibration through the stabilization of master regulators under heavy metal stress.

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54 **Advancing Drug Discovery Through DNA-Encoded Library Technologies: Innovations, Applications, and Future Directions**

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DNA-Encoded Library (DEL) technology has transformed drug discovery by enabling ultra-high-throughput screening through DNA barcoding. Furthermore, DEL screening requires little sample, minimal assay development, and no specialized instrument. Despite its advantages, first-generation DEL often suffers from low hit rates, off-target interactions, and poor drug-like properties. To overcome these limitations, we developed the next-generation DELs: Covalent DEL (CoDEL) and Focused DEL (FoDEL). CoDEL employs electrophilic warheads to form irreversible bonds with nucleophilic residues in target proteins, offering an alternative strategy for traditionally undruggable targets. For example, EGFR inhibitors such as Afatinib and Osimertinib covalently bind Cys797. Drug resistance caused by C797S mutation, however, has prompted exploration of alternative nucleophilic sites beyond cysteine. We assessed the bioreactivity of 17 warheads against 9 nucleophilic residues in FGFR2 and constructed a CoDEL comprising 24.8 million compounds targeting cysteine, lysine, arginine, or glutamic acid, significantly broadening the landscape of covalent inhibitor development. FoDEL leverages structural insights to improve hit rates. For example, cyclic peptides offer enhanced compound stability, as well as enhanced binding specificity and affinity to targets. We developed eight cyclic peptide DELs, utilizing different cyclization strategies, including oxidative disulfide bond formation or thiol-electrophile cross-linking with various bifunctional linkers, to explore broader chemical space. Each cyclic peptide DEL contains ~154 million molecules. Innovations in DEL are driven by advancements in synthetic methodology, structural integration, and library design. MedChem Express (MCE) supports this evolution with a broad portfolio of building blocks for constructing advanced DELs to accelerate drug discovery.

55 **Investigating Eph Receptor Endocytosis in Cancer and Model Cells: A TIRF Microscopy Approach**

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Eph receptors regulate cell–cell interactions and migration, yet the mechanisms governing their endocytosis remain incompletely understood. This research investigates the endocytic mechanism of Eph receptors by using Total Internal Reflection Fluorescence (TIRF) Microscopy. COS7 and SUM159 cells were transfected with EphA2 wild type (WT), and EphA2 LS mutants, and EphA3 WT and treated with ephrin-A1 (EA1) ligand to track receptor internalization. EphA2 WT shows minimal colocalization with Adapter Protein Complex-2 (AP-2), suggesting that internalization occurs via a non-clathrin-dependent mechanism. Similarly, EphA3 WT exhibited a similar non-clathrin internalization pattern. These findings indicate that Eph receptors employ a clathrin independent endocytic route in cancer cells, potentially affecting their role in tumor biology. In the future, we will examine the alternative endocytic pathways of Eph receptors, including caveolin-mediated endocytosis, to better elucidate the processes that regulate Eph receptor function in cancer cells.

56 **Structural Regulation and Dynamic Chaperone Activity of Hsp27 in Cellular Stress Responses**

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Small heat shock proteins (sHsp) are classified as molecular chaperones that assist in the folding of denatured or misfolded proteins within the cell. Hsp27 is involved in the functional role of stabilizing the dynamic cytoskeleton, anti-apoptotic activity, redox stress, and stress resistance. It plays a vital role in axonal transport of neurofilament proteins, making it essential for neuronal function. Mutations in Hsp27 are associated with motor neuropathies such as Charcot-Marie-Tooth Disease Type 2F (CMT2F) and distal hereditary motor neuropathy (dHMNIIIB), both characterized by axonal degeneration of peripheral nerves and motor neurons. Structurally, sHsp's are characterized by a conserved alpha-crystallin domain that aids in the formation of dimers which further assemble into oligomeric complexes. Stress-induced phosphorylation converts these complexes into active dimeric forms that enable rapid cellular response without need for new protein synthesis. Here we show Hsp27 and MAPKAPK2 efficiently expressed and purified with high yield using both ion exchange and size exclusion chromatography techniques for downstream functional analysis. This project aims to further investigate the functional chaperone state of Hsp27 utilizing MAPKAPK2 to induce phosphorylation, promoting the transition from inactive, oligomeric complexes into smaller, active dimeric units. This approach enables investigation into the chaperone activity of Hsp27 using model substrates. Understanding how molecular chaperones such as Hsp27 shift between active and inactive states provides insight into how cellular stress responses are modulated in biological systems. More broadly, this research highlights significant implications for neurodegenerative diseases that are associated with protein misfolding and aggregation.

57 **Characterization of MctB: a Copper Transporter of the Mycomembrane**

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Worldwide, Tuberculosis disease is the second leading cause of death due to an infectious pathogen. The World Healthcare Organization estimates that one quarter of the global population is infected by *Mycobacterium tuberculosis* (*Mtb*). Hence, the need to further investigate Mtb and its virulence factors when infecting the human body. Analysis of the Mtb's genome also led to the discovery of the mycobacterial copper transport protein B (MctB), which is present in the outer membrane (mycomembrane) of *Mtb*. Studies on MctB indicated its role as a virulence factor pivotal for copper homeostasis. However, the general principles controlling copper translocation across Mtb cellular membranes remain elusive. The aim of this study is to elucidate the metal selectivity and translocation mechanism of the transmembrane protein MctB. We have

established a platform to recombinantly express, purify, and reconstitute MctB in artificial lipid bilayer vesicles (proteoliposomes), in which fluorescent probes responsive to diverse stimuli (metals, pH, transmembrane potential) can be encapsulated in the lumen to study translocation events in real-time. The study of MctB in the proteoliposomes model proved that the protein acts a Cu^{2+} transporter with a channel-like function, having the capacity of transporting Co^{2+} and Ni^{2+} too. These results provide novel understanding of the molecular mechanism underlying Mtb resilience towards immune systems responses.

58 **Evaluation of αGal-Liposomes on Macrophage Polarization**

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Macrophages play a central role in wound healing, and shifting them toward a pro-regenerative (M2-like) phenotype can improve tissue repair. Large traumatic and burn wounds often heal slowly, are highly prone to infection, and frequently result in scarring and long-term functional loss. Approaches that can accelerate healing while reducing complications and supporting restoration of high-quality, functional skin remain a clinical priority. Inspired by earlier findings that alpha-galactosyl (alpha-Gal) liposomes can trigger macrophage-driven regeneration through interactions with natural anti-alpha-Gal antibodies, we developed fully synthetic alpha-Gal-decorated liposomes as a translational path toward pro-regenerative immunotherapy. These materials use a chemically defined alpha-Gal glycolipid rather than inhomogeneous animal-derived mixtures, enabling precise control over composition, purity, and scalability. Synthetic alpha-Gal liposomes were prepared by thin film hydration and characterized for size and polydispersity. Their ability to bind anti-alpha-Gal antibodies was confirmed by ELISA, and antibody–liposome complexes interacted with Fcγ receptors on macrophage-differentiated human U-937 cells. Ongoing work focuses on how these complexes influence macrophage activation and polarization toward regenerative phenotypes. Finally, the secretion of the cytokine IL-10 and the vascular endothelial growth factor (VEGF), both associated with M2 macrophage polarization, was assessed by ELISA, demonstrating slightly higher levels in macrophages exposed to the LPs-αGal/Abs complexes. This platform may provide a controlled, scalable strategy to modulate macrophage behavior, accelerate healing, and improve outcomes in traumatic skin injuries at high risk of infection and potential functional loss.

59 **Carbon Quantum Dots as a Neuroprotective Platform Against Environmental Neurotoxicant-Induced Neurodegeneration**

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Neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) have been increasingly associated with chronic exposure to environmental toxicants, including herbicides and pesticides. Among these, paraquat is a widely used herbicide known to selectively induce dopaminergic neurodegeneration in the substantia nigra. Despite growing evidence linking environmental contaminants to neurodegeneration, effective therapeutic strategies capable of crossing the blood–brain barrier (BBB) remain limited. In this study, we report the development of polyphenolic carbon quantum dots (CQDs) synthesized via a green, hydrothermal approach using naturally derived precursors, including caffeic acid, quinic acid, and chlorogenic acid. The synthesized CQDs were extensively characterized using spectroscopic techniques to confirm their physicochemical properties. Functional analyses demonstrate that these CQDs effectively modulate protein misfolding by inhibiting the soluble-to-toxic transition of the amyloidogenic model protein Hen Egg White Lysozyme (HEWL), as evidenced by pulse-chase fluorescence and Thioflavin T (ThT) binding assays. Importantly, the CQDs exhibited significant free radical scavenging capacity, attributed to their sp^2-rich polyphenolic structure, and demonstrated the ability to penetrate the BBB. In vitro studies using the human neuroblastoma SH-SY5Y cell line revealed pronounced

neuroprotective effects against oxidative stress. Furthermore, in vivo evaluation in the Caenorhabditis elegans model of Parkinson's disease showed that treatment mitigates paraquat-induced dopaminergic neuronal damage. Collectively, these findings highlight the therapeutic potential of green-synthesized polyphenolic CQDs as multifunctional nanomaterials for mitigating neurodegeneration associated with environmental toxicant exposure. This study provides a promising foundation for the development of BBB-permeable nanotherapeutics targeting environmentally induced neurodegenerative disorders.

60 **Using Variable-Temperature Native Mass Spectrometry to Probe the Role of Hydration in Thermodynamics for Multi-Ligand Protein Complexes**

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Protein–ligand interactions are governed not only by direct contacts but also by the surrounding solvent, with growing evidence that hydration plays a central role in binding energetics and mechanism. However, experimentally isolating the contribution of water remains challenging, and much of our understanding comes from computational studies. Here, we use native mass spectrometry (nMS) combined with variable-temperature electrospray ionization (vT-ESI) to directly probe how temperature and hydration influence ligand binding to the GroEL single-ring mutant (SR1), a model chaperonin system. By comparing measurements in H_2O and D_2O, we further assess how changes in hydrogen-bonding properties and solvent dynamics impact binding. We find that ADP binding to SR1 exhibits distinct temperature-dependent thermodynamic behavior across sequential binding events. Analysis of the temperature-dependent average charge state, which reflects changes in solvent-accessible surface area, together with van't Hoff analysis, reveals a shared inflection near ~20 °C. This transition corresponds to a shift in protein behavior in which hydration-driven cold unfolding dominates at lower temperatures, while thermally activated ("hot") unfolding and increased conformational dynamics prevail at higher temperatures. Consistent with this, low temperatures favor enthalpy-driven binding associated with structured hydration and strong protein-solvent interactions, whereas increasing temperature enhances entropic contributions, reflecting water release and increased flexibility. The fully bound SR1$(ADP)_7$ complex shows the greatest sensitivity to temperature and deviates from trends observed for intermediate binding states, suggesting enhanced cooperativity and coupling between ligand binding, hydration, and conformational change. Comparisons between H_2O and D_2O amplify these effects, highlighting the influence of hydrogen- bonding differences and solvent structure on binding thermodynamics. Overall, these results demonstrate that nMS can directly resolve how hydration and temperature shape protein–ligand binding thermodynamics in large protein complexes.

61 **Confusion Matrix Analysis of Machine Learning Models for Crop Pest Prediction**

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This study applies AI and machine learning approaches to predict the potential distribution of the Central American Locust (CAL), an invasive crop pest threatening agriculture systems in the USA. Random Forest, Neural Network, and XGBoost models were implemented to analyze species distribution patterns. Model performance was evaluated primarily using confusion matrices, which provide a statistical framework for assessing classification accuracy, including true positives, false positives, and misclassification rates. The confusion matrix plays a critical role in supporting model selection by allowing scientists to directly compare model performance and identify the most robust output for species distribution predictions. This evaluation indicates that the XGBoost model achieved the highest classification performance, followed by Random Forest, demonstrating greater reliability in distinguishing between the presence and absence of the species' suitable habitat. This robust model selection can guide field-based decision-making and help establish

effective monitoring and management programs to prevent locust outbreaks and food security in vulnerable agricultural regions.

62 **Propagation of Alpha-Synuclein Misfolding Is Tuned by Proteostasis Activity**

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The aggregation of alpha-synuclein is a hallmark of many neurodegenerative diseases such as Parkinson's Disease and Multiple System Atrophy. Alpha-synuclein aggregates have been shown to adopt varying conformations often termed polymorphs, which can have different biological activities. For example, polymorphs vary in the propensity to propagate additional misfolding of new monomers in cells. While this variation has been observed repeatedly, the mechanism by which polymorphs gain propagation efficiency remains incompletely understood. We hypothesize that propagation efficiency is governed by interactions between alpha-synuclein aggregates and other proteins within the cell. To address this, we map the interactomes of polymorphs with varying propagation efficiency. Our results shed light on the potential role that the proteostasis network has on the propagation efficiency of alpha-synuclein polymorphs.

63 **In silico Design of Disulfide-Stabilized Macrocyclic Peptides with Ligand-Directed and Site-Selective Targeting Moieties for Protein Engagement**

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Cyclic peptides, especially those with disulfide linkage, offer various advantages (increased affinity, stability, and cellular permeability) over linear counterparts in chemical biology research due to their constrained conformation. In this study, we developed a novel computational design workflow tailored for disulfide-stabilized macrocyclic peptides for protein engagement. The initial complex could be derived either from experimental structures in the Protein Data Bank or from computational prediction using a deep learning platform named ColabFold. Downstream computational analyses mainly relied on Rosetta and GROMACS to select the top peptides for experimental testing. This general protocol of designing, synthesizing, testing, and optimizing has been applied to two different targets (YEATS4 and ZNRF3) to generate peptide-based protein binders with corresponding experimental validation. YEATS4 is an epigenetic reader that has been associated with various cancer types. However, only a few chemical probes and inhibitors for the YEATS4 domain has been discovered. The computational peptide design framework identified an 11-mer peptide named 0453, the first-ever disulfide-stabilized cyclic peptide with a novel sequence shown to bind to YEATS4 with higher affinity than any currently known histone peptides, confirmed by both bio-layer interferometry (Kd = 1.599 μM) and AlphaScreen assay (IC50 = 1 μM). This peptide was approximately 700 times more potent than the template peptide (Kd = 788 μM). Peptide 0453 was then chemically modified to develop a chemical probe for a YEATS4 high-throughput screening system used to screen and test the activity of small molecule libraries and various 0453-derived peptides. Peptide 0453 was subsequently modified through rational design, from which peptide 0453-CrK was discovered (IC50 = 319 nM). Positive control showed that 0453 bound to the recognition site YEATS4 with the ligand-directed moiety AcK. ZNRF3 is a transmembrane E3 ubiquitin ligase that is targeted for regenerative therapy. Although peptide binders that promote ZNRF3 clearance and reinitiate organoid renewal have been identified, their poor pharmacokinetic properties limit practical application. The same framework has successfully designed and optimized at least seven high-affinity disulfide-stabilized cyclic peptides and related variants towards ZNRF3 engagement. The computational workflow used a hybrid approach (deep learning-based and physics-based) to generate new peptides from initial FASTA sequences of ZNRF3 and a 14-mer template peptide 30-2 (Kd = 376.9 nM), avoiding the need for explicit complex structures. Top-hit peptides (11-mer and 14-mer peptides) with nanomolar Kd values (1.3-600 nM) were comparable, if not better, than the template peptide 30-2 with various optimization strategies:

physicochemical property enhancement, peptide truncation, non-canonical amino acid incorporation, bicyclic peptide formation, diversifying the structure of ZNRF3-binding peptides. These findings proved the success of computational design for peptides with disulfide linkage, laying a foundation for further application in other protein targets.

64 **Frustration in Coiled-Coil Pairing Promotes Biomolecular Condensate Assembly**

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Proteins can assemble into micrometer-scale clusters in living cells known as biomolecular condensates which underlie many membraneless subcellular structures and are implicated in various diseases. Here, we show a coiled-coil peptide can spontaneously assemble condensates in cells. Instead of a classical expectation of a side-by-side binding that stops at coiled-coil dimers or oligomers, our modeling reveals that open ends created through heptad-shifted binding accommodate additional proteins for cluster growth. The peptide sequence can be designed to promote condensate assembly when interaction in heptad-shifted configuration is energetically favorable. Furthermore, different spatial arrangements of two orthogonal coiled-coil heterodimer pairs lead to distinct condensate assembly outcomes: condensate formation is inhibited when the heterodimeric coiled-coils match perfectly side-by-side; condensates turn gel-like when heterodimeric coiled-coils interact in geometrically-frustrated pairing. This work highlights that frustrated or imperfect matching from protein interactions between structured domain can be readily engineered to modulate biomolecular condensate assembly and dynamics.

65 **Structural and Functional Insights into the ΦEL-Encoded Chaperonin gp146**

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Bacteriophage EL (ΦEL) is a massive phage infecting *Pseudomonas aeruginosa* whose genome encodes a Group I chaperonin, gp146. It is structurally related to bacterial GroEL and mitochondrial Hsp60 but functionally distinct in several key aspects. Unlike GroEL, gp146 operates without a GroES-type co-chaperonin, relying on a more open terminal structure and an expanded folding chamber to encapsulate substrates. Biochemical and structural studies have shown that gp146 can support folding of viral and non-viral proteins, suppress aggregation and fibrillation of a-synuclein, and act as a general folding aid in vitro. This work summarizes current knowledge on ΦEL biology and massive phage chaperonins, outlining expression and purification strategies used to obtain gp146 and related gene products. The review also highlights emerging applications of ΦEL-encoded proteins in protein folding, antimicrobial development, and modulation of protein aggregation. Finally, we discussed outstanding questions regarding the client repertoire, mechanistic basis of co-chaperonin independence, and potential biotechnological and biomedical exploitation of gp146.

66 **Development of Potent and Selective YAP-1 Inhibitors towards Cancer: Lead Optimization and in vitro Proof-of-Concept Studies**

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YAP1 has been discovered as a potent oncogene that drives tumorigenesis and metastasis in various cancers. YAP1 is dispensable for the homeostasis of most adult tissues as evidenced by the relatively mild phenotypes It is observed to be regulated by proteasomal-mediated degradation which directed us to develop the compounds that promote YAP1 degradation. From high-throughput screening, we identified several compounds with a core structure that degrade YAP1 protein. Structure Activity Relationship (SAR) studies followed by extensive validation identified a lead molecule, RL-77, which degrades YAP1 at nanomolar concentrations. RL-77 inhibited the proliferation of YAP1-dependent cell lines in vitro and reduced tumor

growth in a xenotransplantation mouse model. Further, isothermal calorimetry (ITC) and Surface Plasmon Resonance (SPR) assays provided initial evidence of the binding of RL-77 to purified YAP1 protein. I*n silico* modeling study supported RL-77 binding to YAP1. We synthesized PROTACs using RL-77 and identified two potent PROTACs, RLP-88 and RLP-89 that degrade YAP1 at low nanomolar concentration. RL-77 has excellent stability in the plasma in vitro, however preliminary pharmacokinetic analysis suggested that RL-77 is rapidly cleared (T1/2 = 19 min) in mice. Considering this, we further synthesized small molecules and PROTACS around RL-77 and RLP-88 aiming to develop lead molecules with improved potency, pharmacokinetic properties and selective YAP1 protein degradation activity. Our aim is to develop novel small molecules that can be further developed into clinical compounds for the inhibition of YAP1 in cancers that depend on this potent oncogene and provide novel insights into mechanisms of YAP1 function in a variety of cancers. The lead optimization strategies, potency and selectivity (structure activity relationship, SAR), *in vitro* data of the novel compounds will be presented in the meeting.

67 **Investigating the Effects of Peptide Mimics on the Binding Interaction between BRCA1 and PALB2**

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BRCA1 plays an important role in the DNA damage response pathway by promoting the facilitation of homologous recombination with its binding partner, Partner and Localizer of BRCA2 (PALB2). Inherited loss-of-function BRCA1 variants disrupt this highly conserved and stabilized protein-protein interaction, preventing the complex from repairing double-stranded breaks in DNA. Hereditary breast cancers have been treated using well-established methods, such as PARP inhibitors and DNA-damaging agents. However, nonhereditary breast cancers that retain BRCA1 function are not susceptible to these treatments because they are able to effectively repair their DNA, leading to a proliferation of the cancer cells. We investigated whether small peptide-mimicking molecules, such as stapled peptides and macrocycles, can disrupt the BRCA1 and PALB2 interaction. We designed a short sequence of amino acids that mimicked the coiled coil region of BRCA1, the area that binds to PALB2. This sequence was then “stapled” with a short hydrocarbon linker between sidechains to create a stapled peptide. The macrocycles were designed by targeting amino acids necessary for the BRCA1/PALB2 interaction. Binding interactions between the peptide mimics and PALB2 were measured using isothermal titration calorimetry (ITC). This method is widely used and reliable for sensing the heat changes upon binding to predict protein interactions. Our results suggest that macrocycles do not inhibit the BRCA1/PALB2 interaction, while the stapled peptides may be competing with BRCA1 for the binding site of PALB2. Our findings indicate that, due to the high specificity and conservation of the BRCA1/PALB2 interaction, finding a molecule to completely disrupt this interaction would require high-throughput screening methods to test multiple compounds at once. Further refinement of the peptide length, sequence, staple placement, and staple chemistry, as well as different macrocycles, may also be useful to effectively inhibit this interaction. Based on our findings, targeting the BRCA1/PALB2 interaction remains a promising strategy for treatment of nonhereditary breast cancers.

68 **Interactions between Insulin-Like Growth Factor 1 Receptor and EphA2 and their Relevance to Cancer**

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Insulin-like growth factor 1 receptor (IGF1R) and EphA2 are two receptor tyrosine kinases (RTKs) that play important roles in regulating cell proliferation, migration, and survival. These pathways have been linked to a variety of conditions, including cancer, cardiovascular disease, and neurodegeneration. Here, we test the hypothesis that EphA2 and IGF1R directly interact at the plasma membrane and that this interaction contributes to cellular processes associated with cancer. To address this, we used pulsed interleaved excitation fluorescence cross-correlation spectroscopy (PIE-FCCS) to quantify receptor interaction and diffusion in COS7 and HEK293T cells under multiple conditions. Our results show that stimulation with ephrin-

A1 (EA1), a natural ligand of EphA2, induces significant changes in EphA2 mobility and enhances its interaction with IGF1R. Analysis of the correlated fraction (Fc) and diffusion coefficients indicates that ligand stimulation alters the multimerization state of EphA2 in the presence of IGF1R. Together, these findings provide mechanistic insight into how EphA2–IGF1R interactions may regulate signaling pathways associated with cancer. This work highlights receptor co-organization as a potential target for modulating RTK signaling in cancer.

69 **Time-Resolved Secretome Tracking of Intracellular, Cell Surface, and Extracellular Glycoconjugates with a Mini-Tetrazine N-Acetylglucosamine**

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Glycosylation is instrumental in governing essential biological processes. Herein we describe a mini-tetrazine *N*-acetylglucosamine (HTz-GlcNAc) that is incorporated into *N*-linked glycans and, through rapid live-cell labeling with *trans*-cyclooctene (TCO) reagents, enables real-time visualization and evaluation of glycoconjugate trafficking in living cells. We utilize cell-permeable and impermeable TCO-fluorophores to perform time-resolved, multicolor live labeling of cell-surface glycoconjugates, as well as intracellular and internalized glycoconjugates. We observe intracellular glycoconjugate trafficking throughout the secretory pathway of live cells in real-time, as well as cell surface glycan turnover and extracellular vesicle secretion across three days. In the toolkit of probes for metabolic oligosaccharide engineering, HTz-GlcNAc brings the capability of precise interrogation of intracellular and extracellular glycoconjugate trafficking, while providing a handle for the purification and enrichment of glycans for immunoblot and proteomic analyses.

70 **Mitigating PFAS-Induced Protein Damage Using Carbon Quantum Dots: Insights from BLG Interactions**

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Per- and polyfluoroalkyl substances (PFAS), particularly perfluorodecanoic acid (PFDA), are persistent environmental contaminants associated with significant health risks, including protein dysfunction and neurotoxicity. Despite widespread exposure, especially through dietary sources such as milk, the molecular mechanisms underlying PFDA–protein interactions remain poorly understood. In this study, β-lactoglobulin (BLG), a major milk protein, was used as a model system to investigate PFDA-induced structural alterations. Fourier-transform infrared (FTIR) spectroscopy revealed that increasing PFDA concentrations promote conformational changes in BLG, characterized by enhanced β-sheet and cross-β structures, indicating protein aggregation and destabilization. To mitigate these effects, carbon quantum dots (CQDs) synthesized via a green hydrothermal method from caffeic acid and citric acid were introduced. CQDs demonstrated a concentration-dependent protective effect, partially restoring native protein structure and reducing aggregation. These findings suggest that CQDs can act as effective nanomaterial-based mitigators against PFDA-induced protein damage through binding interactions and antioxidant properties. This study provides new insight into PFAS–protein interactions and highlights the potential of sustainable nanomaterials for reducing PFAS toxicity.

71 **Histological and Immunohistochemical Responses to Sertraline Exposure in Goldfish: Evidence of Nitrative Stress and Proteasome Regulations**

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Anthropogenic activities enhance environmental pollution. Freshwater aquatic organisms are impacted by pharmaceuticals, mainly by antidepressant medications (e.g., sertraline). Controlling the use of antidepressants and reducing pollution are the most public health concerns. Adverse effects of antidepressant drugs are well documented in aquatic freshwater organisms, and sertraline effects on animal fish models are known. The use of model organisms, such as goldfish (*Carassius auratus*), is used in a variety

of research that greatly improves knowledge regarding the biological sciences. The recent experiment was mainly concerned with the effect of sertraline, which was exposed to low dose at 1.0 µg/L and high dose at 5.0 µg/L for 2 weeks. Histopathological study indicated widespread damage in both gills and kidneys. In addition, histopathological analysis in goldfish kidneys showed widespread tissue disarray (e.g., shrinking of Bowman's capsule, deposition of melanin pigment, etc.). Furthermore, sertraline exposure changes the morphology of the gill architecture and mucus production on the gill tissues. Immunohistochemical analysis provided insight into the expression of molecular biomarkers in tissue. Sertraline-treated fish showed a significant (P<0.05) change in 26S proteasome expression in both tissues. Overall, these results show that sertraline exposure causes changes in the morphology of goldfish tissues, which may lead to impaired physiological functions.

72 **Connecting protein function to phenotype: investigating nucleosome ubiquitylation by BRCA1 in *C. elegans***

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BRCA1 protects genomic stability by signaling for the homologous recombination pathway, DNA repair, and transcriptional regulation. A pathogenic mutation in BRCA1 causes a higher predisposition to the development of breast and ovarian cancer. BRCA1 acts as a scaffold for many dynamic protein complexes, as well as functions as an E3 ligase towards various substrates. We do not know which if these interactions and substrates are tied to the many phenotypes associated with BRCA1 disfunction. Our lab is exploring the importance of BRCA1 E3 ligase activity toward the substrate histone H2A. Using structural and biochemical assays we designed a BRCA1 mutant that maintains other critical BRCA1 interactions and substrates but specifically eliminates nucleosome ubiquitylation. This mutant allows us to connect this specific BRCA1 function to downstream phenotypes at an organismal level. A homolog of BRCA1 is conserved in *C. elegans* as BRC-1. We propose that nucleosome monoubiquitylation is a key mechanism contributing to some cellular functions of BRC-1, including DNA damage accumulation and transcriptional regulation of cytochrome p450 genes. We have generated a *C. elegans* mutant strain with these two specific point mutations that alter the ability of BRC-1 protein to interact with the nucleosome and ubiquitinate histone H2A while retaining all other functions. We hypothesize this mutation increases DNA damage accumulation and disrupts transcriptional regulation to establish nucleosome ubiquitylation as a necessary precursor for these, but likely not all, BRC-1 functions. We compare three strains of *C. elegans* (wildtype, *brc-1* knockout, and our nucleosome monoubiquitylation-deficient mutant) in different conditions designed to induce cellular stress or DNA damage accumulation. We find that BRC-1 nucleosome ubiquitylation contributes to embryonic survival under standard conditions as well as DNA damage-inducing conditions. Preliminary results also indicate an intermediate response regarding the role of nucleosome ubiquitylation in transcription regulation of cytochrome p450 genes. These findings help us better connect specific BRCA1 activity with downstream functions in the organism. We hope this project can be used as a blueprint for how protein structure-function relationships can be explored with the powerful *C. elegans.*

73 **Platform-Based Discovery of New degraders as Therapies: Targeting ecDNA driven Drug Resistance in Aggressive Cancers**

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We have developed a chemistry-driven, target-agnostic discovery platform that enables phenotypic screening of small-molecule degrader libraries to uncover novel cancer dependencies. Our collaborators have identified KAT7 as a critical regulator of extrachromosomal DNA (ecDNA) maintenance, a major driver of oncogene amplification, tumor evolution, and therapy resistance. While small-molecule inhibition produces only partial effects, complete loss of KAT7 leads to collapse of ecDNA and reduced tumor viability. Leveraging this

biological insigh, employing our platform, we developed KP-162, a first-in-class small-molecule degrader that induces selective ubiquitination and proteasomal degradation of KAT7, phenocopying genetic knockout and driving loss of oncogene amplification. This work establishes both a novel therapeutic strategy for ecDNA-driven cancers and a scalable platform for the discovery of additional degradation-based therapies.

74 **In-Cell Assembly of Stapled Peptides for Targeting Protein-Protein Interactions**

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Macrocyclic peptides have emerged as a promising modality in drug discovery. In particular, the size and conformationally constrained structure of cyclic peptides make them attractive scaffolds for selective and potent interaction with proteins and for targeting protein-protein interactions. Although many approaches have been developed for peptide cyclization, peptide stapling has only been conducted using synthetically derived peptides, limiting their use for the generation of combinatorial libraries and, therefore, the discovery of novel peptide drug candidates. This work highlights the development of a methodology to generate stapled peptides in bacterial cells (*E. coli*) utilizing commercially available thiol-reactive cross-linkers. For proof of concept, model peptide constructs were tested against an array of twenty different commercially available cross-linkers, resulting in eleven cross-linkers that displayed efficient cyclization in cells. Moreover, to demonstrate the applicability of this strategy toward targeting protein-protein interactions, it was applied to generate stapled peptide inhibitors of calpain-1, with the different linkages providing a means for tuning the biological activity of the stapled peptides. This strategy is expected to expand opportunities toward developing stapled macrocyclic peptides for targeting and modulation of protein-protein interactions.

75 **Targeting Structured RNA: Modified L-DNA Aptamers Against pre-miR-155 and Small-Molecule Discovery for Therapeutic Development**

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The development of structure-specific RNA-binding reagents remains a central challenge in RNA biochemistry and drug discovery, limiting our ability to selectively target functional RNA motifs. Here, we present a strategy that leverages nucleobase-modified L-DNA aptamers to recognize structured RNA elements with high affinity and specificity. Using miR-155 as a model target, we employed a selection strategy to evolve L-DNA aptamer candidates with the ability to bind RNA through structure-dependent interactions. Incorporation of chemically modified nucleobases expands the interaction repertoire of the aptamers, enabling enhanced engagement with RNA structural features such as loops and bulges. In addition, aptamers can serve as functional probes to define druggable RNA motifs. We demonstrate that aptamer–RNA complexes can be utilized in competitive displacement assays to screen for small molecules that target the same structured regions. This approach establishes a direct link between aptamer-based recognition and small-molecule discovery, providing a generalizable framework for identifying ligands that can mimic or replace aptamer–RNA interactions. In this study, we screened a library of 18,000 small molecules to displace the aptamer–RNA complex. Among these, five compounds were able to interfere with aptamer binding. Further experiments are required to confirm whether these small molecules bind directly to the RNA rather than the aptamer.

76 **Impact of a Cancer-Associated Mutation and Post-Translational Modifications on Poly(ADP-ribose) Polymerase 2 Inhibition**

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Poly(ADP-ribose) polymerase 2 (PARP2) is a key regulator of genomic stability in human cells and plays an essential role in DNA damage recognition and activation of multiple DNA repair pathways, including single- and double-strand break repair. PARP has emerged as an important therapeutic target, since its inhibition leads to the accumulation of DNA damage and selective cancer cell death. Talazoparib is among the most potent PARP inhibitors and disrupts DNA repair and replication by blocking the catalytic active site and trapping PARP on damaged DNA. PARP2 has been implicated in multiple cancer types. In previous work from our group, a hypothesis-driven SNP search identified a common variant in the PARP2 gene, rs3093921, strongly associated with pancreatic cancer and marginal zone lymphoma. This variant gives rise to a D235G missense mutation located in the conserved helical domain of PARP2, with the potential to disrupt protein function and alter drug response. In addition to genetic variation, PARP2 activity is regulated by post-translational modifications. Phosphorylation at serine residues S226, S232, and S353 has been identified in PARP2. Although these modifications have not been directly linked to disease, studies on the related protein PARP1 show that phosphorylation enhances enzymatic activity, suggesting a possible regulatory role in PARP2. Prior studies from our group demonstrated that while a cancer-associated variant in PARP1 (V762A) does not markedly alter inhibitor binding affinity, talazoparib uniquely induces pronounced structural and dynamical changes in the mutant protein. In a separate study on PARP2, we showed that the D235G mutation disrupts normal function, whereas phosphorylation at S226, S232, and S353 can partially mitigate the deleterious effects of the mutation and shift protein behavior toward the wild-type state. In the present project, we investigate how the D235G mutation, together with phosphorylation at S226, S232, and S353, influences PARP2 inhibition and the response of mutant PARP2 to pharmacological treatment. The results and implications for PARP2 function will be presented.

77 **Cu(I) P-type ATPases function as electrogenic uniporters of Pt(II)-drugs**

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Cu(I) P-type ATPases are central transmembrane transporters that regulate cellular copper homeostasis by catalyzing Cu(I) ion export across cellular membranes against electrochemical gradients, thereby acting as primary-active transmembrane ion pumps. Overexpression of Cu(I) pumps in tumor cells is associated with pre-target drug resistance to Pt(II)-based chemotherapy, suggesting that they may also facilitate the vesicular sequestration and/or cellular efflux of Pt(II)-complexes. However, the ability of Cu(I) P-type ATPases to translocate Pt(II)-drugs across cellular membranes, their selectivity towards Pt(II)-complexes, and the Pt(II)-cargo translocation mechanism remain elusive due to the complexity in monitoring *in-vitro* turnover Pt(II)-translocation events with purified pumps in membrane-mimetic systems. In this study, we developed supramolecular mercaptosuccinic acid-capped CdTe core-type quantum dot- encapsulated proteoliposomes (MSA-CdTe QD PLs) to study the translocation of Pt(II)-complexes by Cu(I) P-type ATPases in real-time. Since Cu(I) P-type ATPases couple ATP hydrolysis to substrate transport, Pt(II)-complex stimulated ATPase activity was compared with real-time translocation of Pt(II) complexes to validate the developed MSA-CdTe QD PLs platform. Furthermore, by incorporating pyranine and oxonol VI fluorescence detector probes in proteoliposome lumen, which are responsive for pH and membrane potential, respectively, we demonstrated that Cu(I)-pumps are primary active electrogenic Pt(II)-drug uniporters. Additionally, selective activity towards Pt(II)-complexes with *cis*- configuration (like cisplatin and carboplatin) compared to *trans*- Pt(II)-complexes (like transplatin) reveals a characteristic stereoselectivity of Cu(I)-pumps. This work also validates

the transmembrane sulfur ligand exchange translocation pathway for Pt(II)-complexes by performing studies on an inactive mutant lacking the key conserved cysteine and methionine residues at the transmembrane high-affinity binding site. Overall, this work unravels the Cu(I) P-type ATPase selectivity towards Pt(II)-complexes and their translocation mechanism and establishes the MSA-CdTe QD–encapsulated proteoliposome platform as versatile tool to study Pt(II) transport across lipid bilayers for other Pt(II) transporter classes.

78 **Direct Cellular Screening of Pd-Mediated Arylation of Cyclic Peptide Binders Targeting Ubiquitin Chains: Toward Modulating NEMO Liquid–Liquid Phase Separation**

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Ubiquitination is a critical post-translational modification that regulates key cellular processes such as protein degradation and DNA damage repair. Targeting a specific type of ubiquitin chain (e.g., Lys48 or Lys63-linked ubiquitin chain) via cyclic peptides presents a new strategy to modulate biological processes with therapeutic potential for different diseases. However, such a strategy remains challenging due to the obstacles of cell permeability and bioactivity. Here, we report a new approach to directly examine these parameters by combining palladium-mediated Cys arylation with *in situ* cell-based screening. Using CP4, a previously identified cyclic peptide modulator of Lys63-linked ubiquitin chains, we generated a focused library of arylated analogues and optimized the Pd-mediated arylation for cell-based screening. We discovered a new analog, CP-P12-$Ar^{H,}$ that demonstrated enhanced binding affinity and robust bioactivity, as evidenced by increased γ-H2AX phosphorylation and apoptosis induction in cancer cells. This work establishes a generalizable platform for the rapid optimization of cyclic peptide therapeutics targeting protein-protein interactions

79 **Bench-stable Boryl Thianthrenium Dication Enables Aziridinyl Boronate Synthesis via Metal-free Late-stage Aziridination with Diverse Nitrogen Nucleophiles**

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Organoboron compounds are pivotal in both synthetic organic chemistry and drug discovery due to their versatile reactivity and favorable physicochemical properties. In this work, we report the first synthesis of a bench-stable boryl dicationic intermediate through chemical or electrochemical thianthrenation of vinyl MIDA boronates. The MIDA boryl moiety plays a crucial role in directing the transformation, suppressing deborylation and promoting selective mono-adduct formation via a formal [4+2] cycloaddition. This novel boryl dication serves as a key intermediate in a transition-metal-free, chemo- and diastereoselective synthesis of aziridinyl boronates, leveraging a wide range of nitrogen nucleophiles. This methodology exhibits broad substrate scope, high functional group tolerance, and practical applicability, particularly for late-stage functionalization of drug-like molecules. Additionally, an electrochemical one-pot protocol and multiple downstream derivatizations demonstrate the potential for synthetic streamlining and molecular diversification. These findings open new avenues for accessing boron-containing pharmacophores, providing a powerful platform for medicinal chemistry applications, including structure–activity relationship studies and the development of novel therapeutic agents.

80 **Dense DNA Functionalization of Lactoperoxidase Enhances Antimicrobial Potency against Drug-Resistant Wound Pathogens**

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infects thousands of Americans annually, generating $3-4 billion in healthcare costs driven by reinfection rates of 20-30% even after aggressive treatment. Resistance to mupirocin, the first-line topical therapy, has been documented in nearly one in four clinical MRSA cases. Mupirocin functions by targeting a single bacterial enzyme, isoleucyl-tRNA synthetase, a mechanism bacteria can readily circumvent through mutation. When mupirocin fails, clinicians must turn to intravenous vancomycin. Vancomycin targets peptidoglycan synthesis in the bacterial cell wall but now alarmingly also faces emerging resistance, creating a cycle of recurrence and escalating risk of life-threatening conditions including cellulitis and sepsis. The vulnerability of these single-target therapies underscores the urgent need for a fundamentally different approach. In this work, our laboratory has developed Nano-Lac, a DNA-decorated nanoscale formulation of lactoperoxidase. Lactoperoxidase is an enzyme central to the bodies innate immune response against bacteria. Unlike single-pathway antibiotics, it kills bacteria by simultaneously disrupting membrane integrity, halting energy production, and collapsing internal defenses, a multi-target mechanism to which no bacterial resistance has been documented. In its native form, lactoperoxidase degrades rapidly in wounds and cannot penetrate skin. The engineered DNA shell of Nano-Lac addresses both limitations, yielding a construct that is more stable and capable of reaching bacteria beneath the skin surface. Compared to native lactoperoxidase, Nano-Lac exhibits 4-fold greater catalytic activity, 3-fold greater MRSA killing efficacy, and 1.5- fold greater disruption of protective biofilms. Proof-of-concept efficacy has been demonstrated in a murine topical MRSA wound model. Notably, Nano-Lac has also shown efficacy against multidrug-resistant Escherichia coli, suggesting broader utility in the treatment of polymicrobial wounds where multiple resistant pathogens co-exist. This work represents a fundamental shift in how bacterial infections can be treated, moving beyond conventional antibiotics toward immune- inspired nanoscale therapeutics.

81 **A Manganese CAT/SOD Mimic Attenuates H_2O_2-Driven Oxidative Stress in Immortalized Human Keratinocytes**

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EUK-134 is a manganese-salen complex widely used in anti-aging skincare formulations due to its potent antioxidant activity resulting from catalytic decomposition of reactive oxygen species. Despite its popularity, the fundamental kinetic properties that govern its efficacy and recyclability are not well understood, limiting its optimization in skincare products. As a result, the study presented here investigates the efficiency, sustained activity, and selectivity of EUK-134 in comparison to the Green lab ligand library by evaluating its turnover number (TON), turnover frequency (TOF), and reaction rate. Results indicate that while EUK-134 demonstrates high catalase-type activity and selectivity, the activity decreases with continuous exposure to H_2O_2, suggesting a need for re-application in real-world scenarios to achieve long-term protection. Additionally, selectivity studies show that peroxidase activity was observed, which may impact the stability of sensitive ingredients in formulations. Finally, we propose a new 13 membered (DML10) macrocycle that protects Human Keratinocyte cells (HaCaT) from hydrogen peroxide induced damage. Furthermore MTT cell viability results prove DML10 is the less cytotoxic than EUK-134. These findings provide essential kinetic benchmarks to compare future small molecules and optimize EUK-134's use in antioxidant skincare products. Without a clear understanding of these fundamental properties, we lack benchmarks to compare future small molecules that compete with EUK-134.

82 **Overcoming Oxygen Limitations: Method Development for the Anaerobic Expression of ZapNIR1 in E. coli Top10 Cells**

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Zinc is an essential metal for all living organisms and is involved in many biological processes including catalysis, structural stabilization, and cell signaling. Zn^{2+} ions function as key regulators of host- microbe interactions in the human gut, where Zn^{2+} availability shapes the diversity and composition of gut bacteria. The underlying molecular mechanisms remain unclear, however, especially for commensal microbes. To gain insight into these mechanisms, we aim to develop fluorescent protein-based sensors to monitor zinc uptake in bacteria. Many existing fluorescent protein-based Zn^{2+} sensors, however, are based on oxygen-dependent green fluorescent proteins, and cannot be applied to anaerobic microbes that do not grow with oxygen. To this end, we developed a near-infrared (NIR) Förster resonance energy transfer (FRET)-based Zn^{2+} sensor, ZapNIR1. ZapNIR1 binds to biliverdin IXα (BV) for fluorescence in a reaction that does not require oxygen. In bacteria, ZapNIR1 is often co-expressed with heme oxygenase (HO1) to produce sufficient levels of BV for the sensor. This co-expression system, however, is unsuitable for the anaerobic gut environment because HO1 requires oxygen to function. To overcome this limitation, we hypothesized that supplying commercially available BV could bypass the need for HO1 and enable anaerobic production of fluorescent ZapNIR1. When ZapNIR1 was expressed for 24 hours in LB media at 18 °C, followed by adding biliverdin and reducing the temperature to 25 °C, there was an increase in fluorescence intensity that rapidly declined over time. We hypothesized that fluorescence degradation could result from noncovalent binding of biliverdin to ZapNIR1. Given that ZapNIR1 binds BV via cysteine residues through a thioether linkage, covalent attachment of ZapNIR1 could be hindered by disulfide bond formation. Inclusion of a cell- permeable reducing agent resulted in a stable fluorescence intensity over time. To further facilitate BV uptake from the media, which is another challenge that could reduce production of fluorescent ZapNIR1, we switched the carbon source in the media from 0.4% glycerol to fructose. As a better energy source that enables higher metabolic activity in E. coli cells, fructose increased the fluorescence of ZapNIR1. After optimizing ZapNIR1 production in anaerobic E. coli, we used this sensor to visualize real-time Zn2+ uptake kinetics and detect exogenous Zn^{2+} under anaerobic conditions. ZapNIR1 is the first NIR genetically encoded and oxygen-independent sensor for Zn^{2+} ions and our demonstration of its utility for tracking real- time Zn^{2+} uptake in E. coli under oxygen-free conditions is a crucial step to understanding bacterial growth and survival in the gastrointestinal tract.

83 **Reversible Protein Assembly via Light-Responsive β-Strand Interfaces and Chromophore–Driven Conformational Coupling**

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Achieving reversible, stimuli-controlled protein assembly with molecular precision remains a key challenge in chemical biology. Here, we present a light-regulated protein assembly system in which oligomerization is governed by residue-specific interactions at a β-strand interface coupled to chromophore isomerization. We engineer a fusion protein (DELP) by embedding a photoswitchable Dronpa145N domain within an elastin-like polypeptide (ELP) scaffold. At the molecular level, a Lys145→Asn (K145N) substitution on β-strand 7 reprograms the protein's intermolecular interface, enabling light-dependent oligomerization. Upon 400 nm illumination, chromophore cis–trans isomerization induces conformational rearrangement of the β-barrel, promoting inter-protein β-strand interactions (TENLYV region) and driving tetramer formation. This tetramer acts as a multivalent crosslinking node, resulting in rapid hydrogel assembly. In contrast, 500 nm illumination alters chromophore protonation and flexibility, destabilizing the β-strand interface and triggering tetramer dissociation into monomers, leading to complete material disassembly. This system establishes a direct

structure–function coupling between chromophore photophysics and protein quaternary structure, enabling reversible supramolecular assembly without covalent chemistry. The resulting protein network exhibits tunable viscoelasticity and maintains high cytocompatibility. Leveraging this reversible crosslinking mechanism, we demonstrate light-gated cell encapsulation and release, preserving cell viability while enabling spatiotemporal control over cellular microenvironments. Overall, this work introduces a chemically defined strategy for programming protein–protein interactions through light-responsive residues and secondary structure interfaces. By linking chromophore dynamics to β-strand-mediated oligomerization, this platform expands the toolkit of chemical biology for designing adaptive biomaterials, optically controlled protein assemblies, and dynamic cell–material systems.

84 **Bicyclic MOrPHs: Leveraging Genetic Code Expansion for the High-Throughput Discovery of Functional Bicyclic Peptides**

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Bicyclic peptides have garnered significant attention in recent years as a promising class of bioactive molecules and new drug modality. Endowed with unique conformational and functional features, bicyclic peptides have facilitated the discovery of potent inhibitors of various biomolecular targets, including 'undruggable' protein-protein interactions (PPIs). Inspired by these properties, we report a novel platform for the biosynthesis of genetically encoded bicyclic peptides of arbitrary sequence in bacterial cells. Specifically, we have designed and developed a novel, genetically encodable unnatural amino acid bearing a bis-electrophilic functional handle on its side chain and identified a promiscuous AARS/$tRNA_{CUA}$ pair for its efficient incorporation into proteins *via* amber stop codon suppression. Using this system, we demonstrate its utility for directing the generation of bicyclic peptides *in cellulo*. We further show that this general biosynthetic platform can be integrated with phage display to devise a powerful, high-throughput screening method for the accelerated discovery of bioactive bicyclic peptides against therapeutically relevant proteins.

85 **Engineering Entry-Competent DNA-Encoded Libraries for Gram-Negative Bacteria: Design, Assembly, and Screening**

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The rise and spread of multidrug-resistant bacterial populations, particularly Gram-negative species, pose an increasing threat to human health as treatment options are limited and the drive to innovate new antimicrobial classes wanes. Despite the relative ease of identifying small molecules that target bacterial proteins, a significant hurdle in drug discovery is the limited antibacterial activity of these antibiotic candidates due to poor accumulation across the outer membrane of Gram-negative species. Prior studies have uncovered a set of physicochemical properties that promote membrane permeability, notably low globularity, high rigidity, and a sterically unhindered primary amine. However, these permeability guidelines have only been used to adapt the limited existing inventory of compounds with activity against Gram-positive and Gram-negative bacteria. Screening a collection of compounds already displaying these features would maximize targeted drug development, but synthesizing such compounds individually is challenging and labor-intensive. We propose leveraging combinatorial chemistry- based DNA-encoded chemical libraries (DECLs) designed to follow the entry rules to promote bacterial entry. This approach will allow us to efficiently access and screen diverse chemical spaces with a better chance of identifying compounds that accumulate in Gram-negative bacteria. These libraries will be screened against both periplasmic and cytoplasmic bacterial targets, including carbapenemases (OXA-48, NDM-1), BamA, and DXR, using standard in vitro affinity selection methods. Hits will be evaluated for antibacterial activity with minimum inhibitory concentration (MIC) growth assays in parallel with assessment of compound accumulation in bacteria via LC/MS analysis. For lead optimization, structure-activity relationship (SAR) studies will be performed on hit compounds to

systematically explore how variations in chemical structure affect potency, specificity, and permeability. Toxicity of optimized compounds will be assessed with stability and cytotoxicity assays. Crystallographic studies will elucidate important binding interactions between these optimized compounds and their bacterial targets. By utilizing entry-focused library design in a high-throughput screening method, our approach aims to generate highly potent, membrane-permeable inhibitors against Gram-negative bacteria that can overcome existing resistance mechanisms.

86 **Identification and Characterization of a Putative Fe^{2+}-ZIP Transmembrane Transporter in the Human Brain-Eating Amoeba**

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Naegleria fowleri, also known as the brain-eating amoeba, causes a brain infection that leads to fatal meningoencephalitis. While colonizing the brain the pathogen hijacks host cellular pathways to acquire essential micronutrients allowing pathogen survival and replication. During infection iron is a critical micronutrient and catalytic cofactor for key metabolic processes which must be uptaken from the host, but the molecular processes involved in these nutritional immunity responses remain elusive. In this work, by bioinformatic approaches, we identified a novel putative iron transmembrane transporter (*Nf*FiT, ferrous iron transporter) belonging to the ZIP (Zrt-/Irt like protein) family as a mediator of iron uptake in *N. fowleri*. The ZIP transporter family is known for facilitating the influx of biologically essential divalent metal cations including Zn^{2+}, Mn^{2+}, Fe^{2+}, and Cd^{2+} in all domains of life. However, the structure and function of Fe^{2+}-transporting ZIPs, in particular from unicellular eukaryotic protozoan pathogens, remains largely unexplored. To address this gap, we developed a platform to express, purify, and reconstitute in artificial lipid bilayers *Nf*FiT, to provide mechanistic insights into its cargo selectivity, promiscuity, and mechanism of metal transport. By developing real-time metal proteoliposome-based transport assays followed by stopped-flow spectroscopy we defined cargo selectivity and kinetic parameters associated with metal translocation. Upon encapsulating in the proteoliposome lumen fluorescent probes responsive to diverse stimuli (metals, pH, and transmembrane potential) we establish that *Nf*FiT is a highly-selective electroneutral $Fe^{2+}/2H^{+}$ antiporter, with very fast translocation kinetics and high affinity allowing for competition with the host labile iron pool. Mutagenesis established residues involved in cargo selection and translocation across the lipid bilayer. These findings expand the current understanding of Fe^{2+} homeostasis in *N. fowleri* and provide mechanistic insight into Fe^{2+} translocation by the ZIP family, offering novel pathways to combat this lethal pathogen.

87 **G-Quadruplex-Dependent and dCas9-Mediated Stalling Leads to Transcriptional Blockage**

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Non-canonical DNA structures beyond the classical double helix, such as G- quadruplexes (GQ), have emerged as critical regulatory hubs. G-quadruplexes have been identified in the promoters of genes associated with the etiology of multiple diseases, including cancer and neurodegeneration. We investigated the mechanistic aspects of catalytically inactive CRISPR- associated protein 9 (dCas9) on gene expression regulation and modulating transcription through sequence-specific DNA, without any permanent mutations. We used GQs proximal to the transcriptional start site in the tyrosine hydroxylase (*TH*) gene as a working model. A series of guide RNAs targeting distinct positions along various DNA templates encompassing or surrounding the GQs were employed to assess effects of RNP complex on transcriptional progression. We performed *in vitro* ensemble and single-molecule investigations to study whether GQ structures and/or dCas9 impede T7 RNA polymerase (RNAP) mediated transcription process. Denaturing gel analysis showed truncated transcription product at various time points, indicating transcriptional stalling at defined positions. Our results demonstrate that dCas9 is more likely to block RNA polymerase progression when the non-template strand

is targeted. The GQ in the *TH* promoter was effectively destabilised when the dCas9 target site partially overlapped with the GQ-forming sequence. We also determined that a minimum separation between the transcription start site and the dCas9 target site is required for effective stalling of RNAP by dCas9. This study suggests that transcriptional outcomes in dCas9-based systems arise from the interplay between intrinsic nucleic acid structure and protein-mediated obstruction. This work provides a quantitative and mechanistic framework for understanding and predicting dCas9-mediated transcriptional regulation.

88 **A Focused Set of Biochemical Assays for Characterizing Small Molecule Inhibitors of eEF-2K/CaM Binding**

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Eukaryotic elongation factor 2 kinase (eEF-2K) is a Ca^{2+}/calmodulin (CaM)-dependent kinase and an important regulator of translational elongation and protein synthesis. Abnormal eEF-2K activity plays a role in a variety of diseases such as cancer, depression, and dementia. eEF-2K activity is dramatically enhanced by CaM binding, and this interaction is unique among the kinome. Therefore, targeting this protein-protein interaction (PPI) with small molecules is a potential strategy for selective and clinically useful eEF-2K inhibition. To promote selectivity, we sought to identify inhibitors that prevent CaM binding by targeting eEF-2K in a non-ATP-competitive manner. To this end, we previously conducted a PPI-based AlphaScreen of ~60,000 compounds and identified 18 strong hits that disrupted the eEF-2K/CaM interaction with high potency (IC_{50} <10 µM). We validated that these compounds also blocked the ability of eEF-2K to phosphorylate a substrate peptide in the presence of CaM. To gain further insight into how the hits prevent CaM binding, we employed a series of additional biochemical assays. First, to filter compounds that may act on the ATP-site, we used ADP-Glo kinase assay technology to evaluate eEF-2K ATPase activity in the absence of substrate and CaM. We also performed a fluorescence polarization-based assay to rule out inhibitors that directly interact with CaM. In advanced stages of hit characterization, we employed differential scanning fluorimetry (DSF) and NanoBit PPI assays in cell lysates. After filtering the 18 hit compounds through our validation assays, we found one lead compound (T1-11) that fit our desired profile. T1-11 inhibited eEF-2K activity in the presence of CaM, but did not have an effect on ATPase activity, suggesting it is not ATP-competitive. It showed minimal effects in the polarization assay, which suggests it does not function by directly targeting CaM. Using DSF, we confirmed that T1-11 interacts with eEF-2K. Furthermore, T1-11 disrupted eEF-2K/CaM binding in HEK293 lysates. From these results, we predict this compound may interact with eEF-2K at the CaM binding interface. When coupled with other structural, cellular, and biophysical studies, the assays presented here offer useful support in validating mechanisms of eEF-2K inhibition.

89 **Nature's Redox Machines: Engineering Proteins for Self-Powered Biosensors and Energy Harvesters**

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Nature has evolved remarkable redox-active proteins, such as cytochromes and microbial nanowires, that enable efficient electron transfer across biological membranes and long molecular distances. These protein architectures inspire new paradigms in sustainable energy conversion and biosensing, but their integration into functional devices remains a challenge due to limited stability, orientation control, and poor electronic coupling with materials. In this poster, I will present a materials-driven strategy to rewire these natural electron transfer systems by embedding heme-containing proteins into colloidosomal organic frameworks. These soft-matter architectures mimic membrane-like environments while enabling hierarchical assembly, enhanced structural stability, and tunable redox accessibility. We demonstrate that such hybrid assemblies retain protein activity and enable electron flow, paving the way for self-powered biosensors and energy harvesters. This interdisciplinary platform bridges protein engineering with nanomaterials design, offering a new route to programmable, long-lived, and environmentally responsive redox systems.

90 **Microfluidic Assessment of Gold Nanoparticle-Induced Platelet**

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Engineered nanoparticles (NPs) are increasingly used in biomedicine for drug delivery, imaging, and therapy, but their small size allows entry into the circulatory system, where they can disrupt hemostasis by promoting or inhibiting platelet aggregation. Gold nanoparticles (AuNPs), particularly smaller ones (≤50 nm), have shown pro-thrombogenic effects in vitro, accelerating clot initiation at higher doses (5 nM). However, conventional assays like thromboelastography (TEG) operate under static or low-shear conditions, failing to replicate physiological shear rates (15–10,000 s^{-1}). To address this, we developed a low-cost microfluidic system integrated with fluorescence microscopy to investigate the thrombogenic potential of AuNPs and gold nanostars under flow. Both particle types induced strong platelet activation (PE-CD62P fluorescence) and aggregate formation at all concentrations tested. At low concentrations (0.5 ug/ml), platelet distribution was uniform with minimal clustering, while the highest concentration (50 ug/ml) produced extensive dense aggregates. Higher flow rate (20 µL/min) increased adhesion and aggregation due to elevated shear, whereas lower flow (10 µL/min) resulted in more dispersed aggregation. Aggregate analysis confirmed that maximum clot sizes occurred at 50 ug/ml, with AuNPs exhibiting the highest thrombogenic risk.

91 **A 1,2-dDioxetane-Based Chemiluminescent Probe for *in vivo* Copper Imaging**

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Copper is involved in healthy physiology and disease with prominent roles in Wilson's and Menkes disease. Tracking its reactivity in biological systems is crucial to understand its roles and helpful in identifying targeted therapies. We developed a turn-on chemiluminescent probe CuCL which was designed by linking the picolinic acid moiety to the phenolic substituent of 1,2-dioxetane. Reaction of CuCL with copper results in formation of copper complex intermediate that releases the phenolate upon hydrolysis. The latter generates a chemiluminescent light after being initiated by chemically initiated electron exchange luminescence (CIEEL) mechanism. The probe showed excellent selectivity for Cu^{2+} compared to other competitive metal ions. The limit of detection of CuCL was calculated to be 360 nM. The mechanism was studied using initial rate kinetics to provide an estimated second order rate constant of $5.18 \pm 0.383 \times 10^{-5}$ s^{-1} and copper binding constant of K_{eq} = 69,627 ± 2,213 M^{-1}. The probe has been tested in living mice, demonstrating that it can be used for selectively detecting copper *in vivo*.

92 **Monitoring of Base Excision Repair in Living Cells Using Chimeric D/L-DNA Molecular Beacons**

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Base excision repair (BER) is a key DNA repair pathway responsible for repairing single- strand breaks and single-base damages to maintain genome stability. One of its essential enzymes, apurinic/apyrimidinic endonuclease 1 (APE1), incises abasic sites generated by DNA glycosylases, initiating downstream repair that restore DNA integrity. APE1 dysregulation has been implicated in numerous diseases, making it both a critical biomarker and promising therapeutic target for modulating DNA repair. Traditional strategy for studying BER enzymes often rely on nucleic acid-based molecular beacons; however, these constructs suffer from nuclease degradation and unwanted intracellular interactions, limiting their use in live-cell applications. To overcome these, we developed a series of chimeric D/L-DNA probes that combine a natural D- DNA substrate region for target recognition with flanking nuclease-resistant L-DNA segments. This design takes advantage of the superior biostability of L-DNA while retaining the ability to target native BER enzymes. Using a probe containing a tetrahydrofuran (THF) abasic site mimic, we detected robust, APE1-dependent fluorescence in live cells, showing that the probe accurately reports APE1 activity in its native environment. The optimized chimeric probe can differentiate APE1 levels between cancerous and normal cell lines, can be functionalized

with photoactivatable elements for spatiotemporal control, and support multiplexed assays for BER inhibitor screening. Altogether, this platform provides a versatile toolkit for probing BER dynamics in live cells, offering valuable insights into DNA repair mechanisms, drug discovery, and therapeutic development.

93 **Elucidating Photochemical Structure-Activity Relationships in Photopharmacology via Multiscale Simulations**

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Molecular photoswitches enabling precise photocontrol of protein function. Their performance in photopharmacology depends critically on how substituents and protein environments modulate excited-state dynamics, quantum yields, and the light-responsive difference in binding affinity between their isomeric forms. Yet, the photochemical structure-activity relationships underlying these effects remain poorly understood. Our recently developed multiscale simulation framework aimed at addressing this challenge. Using an integrated computational framework that combines docking, classical and QM/MM molecular dynamics, excited-state enhanced sampling, first- principles non-adiabatic dynamics, and alchemical free-energy calculations, we investigated a diverse series of photostatin (PST) derivatives bound to tubulin. Our results reveal how protein electrostatics and steric confinement reshape excited-state free-energy landscapes, influencing non-radiative decay rates, excited-state lifetimes, and photoisomerization quantum yields. We identify the directional alignment of torsional motion with non-adiabatic coupling vectors and backward ground-state isomerization as key factors affecting the isomerization quantum yield. These findings align well with and explain the trends observed in ultrafast time-resolved crystallography, absorption spectra, and isomer-dependent bioactivity. Thermodynamic Integration consistently yields the best agreement with experiments, accurately capturing the effects of substituents and stereochemistry, whereas endpoint and enhanced-sampling approaches show notable limitations. Together, these studies establish a predictive multiscale platform for quantifying photochemical structure-activity relationships of molecular photoswitches in complex biomolecular environments, guiding the rational design of next-generation light-regulated drugs in photopharmacology.

94 **Targeting ASH1L AND TRIM28 Bromodomains for the Development of Anti-Cancer Agents**

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ASH1L and TRIM28 are epigenetic regulators that play important roles in gene expression and cancer progression. While ASH1L functions as a histone methyltransferase and gene activator, implicated in mixed-lineage leukemia and breast cancer, TRIM28 acts as a transcriptional co-repressor associated with breast and lung cancers. The dysregulation of these proteins leads to disease, highlighting the need for targeted therapeutic strategies. This study aims to identify, optimize, and validate peptide binders for ASH1L and TRIM28 utilizing phage display. Peptides offer a unique therapeutic niche, combining the specificity of biologics with the cell permeability and cost-effectiveness of small molecules. However, traditional phage display is limited by its reliance on E. coli, restricting chemical diversity to the 20 canonical amino acids and often yielding unstable, low-affinity peptides. To overcome these limitations, we employ phage-assisted active site-directed ligand evolution (PADLE) technique, which incorporates noncanonical amino acids (ncAAs) to enhance peptide diversity, stability, and binding affinity. We utilize an evolved amber suppression system based on pyrrolysyl-tRNA synthetases (PylRS) from Methanosarcina species to genetically encode ncAAs, including propionyl-lysine (PrK), into phage- displayed peptides. Initial bio panning using a 7-mer linear peptide library yielded enriched binders for both targets. A lead peptide for TRIM28 demonstrated binding in bio-layer interferometry (BLI) assays and is undergoing further validation. Future work includes screening a 7-mer cyclic library to improve specificity and proteolytic stability. Peptide hits will be characterized by using assays including Alpha Screen, BLI, FP. Structural optimization and cellular engagement

studies will also be conducted to support the development of selective inhibitors for ASH1L and TRIM28 in cancer therapy.

95 **Structural Basis for Lithium Inhibition of Eukaryotic Fluoride Channel**

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Fluoride is toxic to fungi, plants, and other eukaryotes, and fluoride export protein (FEX) provides a major defense mechanism by preventing intracellular fluoride accumulation. FEX activity depends on reversible Na^+ binding at a conserved cation-binding niche adjacent to the fluoride permeation pathway, but how competing cations disrupt this process remains unclear. Here, we combine functional assays, cryo-EM structures, and molecular dynamics simulations to define the mechanism by which Li^+ inhibits Na^+-dependent FEX activity. Our results show that Li^+ antagonizes fluoride export by competitively occupying the Na^+-binding site while stabilizing a distinct, transport-incompetent state of FEX. Compared with Na^+, Li^+ forms a tighter and more stable coordination environment within the cation-binding niche, reduces local hydration of the external vestibule, and promotes conformational constraints near the helical break motif. These changes alter side-chain organization and helix packing adjacent to the permeation pathway, resulting in narrowing of the phenylalanine-lined fluoride pore. Thus, Li^+ does not simply block Na^+ binding, but reshapes the conformational landscape of FEX toward a rigid, narrowed, and poorly hydrated state that is unfavorable for productive fluoride transport. Together, our findings provide a structural and dynamic explanation for lithium inhibition of eukaryotic fluoride channel and reveal how selective cation binding regulates fluoride exports.

96 **Characterizing O-Glycoproteinases in Opportunistic Pathogens with Chemoproteomics**

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Opportunistic pathogens, especially the antibiotic resistant ESKAPE pathogens (*E. faecium, S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa, Enterobacter spp*., and *E. coli*), represent a significant rising threat to global public health. Opportunistic pathogens are especially dangerous to immunocompromised individuals, where immune dysfunction can lead to increased risk of infection, disease severity, and even death. Unfortunately, the complex factors governing the activity of these pathogens are poorly understood, with many opportunistic pathogens asymptomatically constituting the natural flora of the human microbiome. By characterizing the functional activities and molecular states that lead to microbial pathogenesis, the development of mitigation strategies, prophylactics and novel therapeutics can be realized. A defining system of interactions at the host-microbe interface is between host o-glycoproteins and microbial o-glycoprotein modifying or degrading enzymes (o-glycoproteinases). On the host side, these include secreted immunoglobulins such as IgA; mucins, keystone signaling and barrier forming proteins, and antigens of the MHC complex, not to mention o-glycosylation forming an entire class of PTM. Microbes secrete enzymes such as glycoside hydrolases, peptidases, and lyases that catabolize these structures as nutrient sources, and/or as virulence factors, directly countering host immune functions and gaining access to host tissues. The dynamics of these interactions are complicated by the fact that microbial catabolism of host glycoproteins do not always equate to disease, and in some cases these functions are immunostimulatory and beneficial to the host. To uncover and characterize these mechanisms, we synthesized and applied a suite of o-glycopeptide probes across seven opportunistic pathogens with predicted or known o-glycoproteolytic activity: *E. faecium, S. aureus, P. aeruginosa, E. coli, K. pneumoniae, S. enterica,* and *S. marcescens*. By growing these microbes in a chemically defined minimal media designed to replicate conditions of the gastrointestinal tract, and including or omitting purified mucin as a defined rich o-glycoprotein source, we were able to quantify differences in o-glycoproteinase activity with culturomics, SDS-PAGE, and LC-MS/MS proteomics, unveiling key mechanistic relationships and ligandable microbial targets at the mucosal barrier.

97 **From Nicotine to SARS-CoV-2 Antivirals with Potent in vivo Efficacy and a Broad Anti-Coronavirus Spectrum**

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Anecdotal reports about smoking that might prevent SARS-CoV-2 infection inspired to search nicotine and its pyrolysis products as inhibitors for SARS-CoV-2 main protease (M^{Pro}). This effort led to the discovery of 3-vinylpyridine as an M^{Pro} inhibitor. 3-Vinylpyridine resembles part of nirmatrelvir to bind M^{Pro} but doesn't involve a critical interaction with residue E166, whose mutation has led to resistance to nirmatrelvir. Integration of the two molecules followed by a medicinal chemistry campaign, produced several molecules with better *in vitro* potency than nirmatrelvir. Two lead molecules, YR-C-136 and SR-B-103, displayed better pharmacokinetic characteristics than nirmatrelvir and much better antiviral efficacy in virus-challenged mice. Both molecules maintain high potency to inhibit M^{Pro}(E166V/L50F) that resists nirmatrelvir. They also have a broad and highly potent antiviral spectrum against most pathogenic coronaviruses. With high *in vivo* potency, both molecules are potentially standalone pan-antivirals for coronaviruses and may serve as countermeasures for future coronavirus outbreaks.

98 **Computational Study of Cytarabine Effects on DNA Elongation in DNA Polymerase λ and Nucleosome-Bound Pol λ**

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DNA polymerase lambda (Pol λ) is an X-family enzyme involved in DNA repair processes, where it facilitates gap filling during base excision repair and non-homologous end joining. A mutation in Pol λ has been reported to be associated with breast cancer and to affect important functional motions related to enzyme fidelity. In this work, the T221A and T221A/R438W mutants are studied to understand how these mutations affect enzyme behavior and interactions with inhibitors such as cytarabine. Cytarabine is a nucleoside analog used in cancer therapy and has been shown to be incorporated into DNA by Pol λ. Here, we investigate whether cytarabine incorporation leads to termination of DNA elongation. We performed 3 μs molecular dynamics (MD) simulations using AMBER on wild-type (WT), T221A, and T221A/R438W systems with either a natural primer or cytarabine at the primer terminus. The results show that cytarabine leads to differences across the systems in nucleotide addition, as well as in structural and dynamical behavior. To better represent a biologically relevant environment, we extended this work to nucleosome-bound Pol λ for WT and T221A/R438W with natural primer and cytarabine incorporation to examine how DNA packaging affects enzyme behavior and cytarabine inhibition using both MD and QM/MM. Our study provides molecular-level insight into the effects of cytarabine on DNA elongation and the impact of mutations on this process.

99 **Utilizing a Hyaluronan-Binding Peptide for Interspecies Neuron-Specific Targeting and Molecule Delivery**

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Peptide ligands that have neuron-specificity are consequential in the development of new therapeutic applications in the brain and neuroscience research. This study investigates a 15-mer peptide, named N1, which exhibits substantial *in vivo* neuronal specificity. N1 diffuses throughout the entire neuron including the cytosol, nucleus, axon, and dendritic spines. It also demonstrates neuronal labeling across multiple brain regions – cortex, striatum, hippocampus, cerebellum, and spinal cord – and multiple species – mouse, rat, treeshrew, and zebra finch. The neuronal targeting of N1 can be sustained via intraparenchymal, intrathecal, and intravenous injections after the blood-brain barrier (BBB) is made accessible through focused ultrasound

(FUS). Additionally, N1 promotes the delivery of biologically active proteins, such as Cre protein, into neurons which leads to site-specific DNA recombination. N1 is an innovative and adaptable platform for neuron-specific delivery within the central nervous system.

100 **Selective Targeting of RhoA G17V Oncogenic mutant by Macrocyclic Peptides Identified Through Phage Display and Structural Mapping**

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Oncogenic mutations in small GTPases play a pivotal role in malignant transformation through persistent activation of intracellular signaling networks. A recurrent somatic mutation, G17V, has been identified in a significant fraction of angioimmunoblastic T-cell lymphoma (AITL) cases, where it promotes aberrant T-cell receptor (TCR) signaling by stabilizing its interaction with the guanine nucleotide exchange factor Vav1. This interaction enhances Vav1 phosphorylation at Y174 by Src kinase, driving pathological T-cell activation and proliferation. Given the structural rigidity and paucity of druggable pockets in GTPases, targeting this interface with small molecules remains highly challenging. Conventional approaches such as small-molecule inhibitors or monoclonal antibodies are poorly suited to address intracellular GTPase-mediated interactions due to their lack of membrane permeability, limited surface complementarity, and difficulty engaging shallow or transient protein-protein interfaces. In contrast, macrocyclic peptides offer an emerging class of therapeutic agents that combine favorable features of both small molecules and biologics. Their constrained structure enhances proteolytic stability and conformational rigidity, while their tunable surface chemistry enables high-affinity binding to challenging targets. In the context of GTPase-driven malignancies, macrocyclic peptides represent a compelling modality for selectively disrupting oncogenic signaling complexes that have eluded conventional drug development. Following four rounds of iterative biopanning against purified, biotinylated G17V protein, we identified several candidate binders using both 10-mer and 12-mer cyclic peptide libraries. An initial top candidate, RhoA3, exhibited low micromolar affinity and partial disruption of the G17V-Vav1 interaction. To improve affinity and maintain high library diversity, we employed a regioselective cyanobenzothiazole condensation reaction with an N-terminal cysteine and the chloroacetamide reaction with an internal cysteine to generate a 12-mer cyclic library with ~1010 unique variants. This approach yielded several high-affinity binders, among which the macrocyclic peptide Z1 emerged as a lead candidate. Biolayer interferometry revealed that Z1 binds G17V with nanomolar affinity (KD 134nM), and Alpha Screen assays demonstrated functional disruption of the G17V-Vav1 interaction with an IC50 of 2. 8μM. Molecular dynamics simulations of the macrocyclic peptide with RhoA G17V reveal stable binding pocket interactions that disrupts its association with the GEF Vav1, with alanine scanning confirming the key residues identified through structural modeling. These findings establish a proof-of-concept for targeting intracellular GTPase-mediated protein–protein interactions using macrocyclic peptides. Z1 represents the first reported macrocyclic inhibitor with nanomolar affinity and in vitro functional activity against the oncogenic G17V–Vav1 complex. Ongoing work focuses on improving cellular delivery, evaluating downstream signaling inhibition in T-cell models, and assessing the therapeutic potential of Z1 analogs in preclinical systems. This platform holds promise for expanding the druggable proteome in lymphoid malignancies and other GTPase-driven diseases.

101 **Structural Basis and Rational Engineering of a Thermophilic Cas13a for Robust Nucleic Acid Detection**

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CRISPR-Cas13 systems are RNA-guided ribonucleases whose collateral cleavage activity has been widely repurposed for molecular diagnostics. However, the limited stability of commonly used Cas13 enzymes and their poor activation against structured RNA targets constrain their performance, particularly in field-deployable settings. Here, we report comprehensive biochemical profiling and structure-guided engineering of a thermophilic Cas13a from *Thermoclostridium caenicola* (TccCas13a) to overcome these limitations. Our biochemical characterization reveals intrinsic thermostability, substrate preferences, and enhanced tolerance to structured target RNA substrates. Rational engineering of TccCas13a's spacer-target RNA duplex binding channel improved target binding and enabled the determination of the cryo-electron microscopy-resolved TccCas13a ternary structure, which has been a challenge for many Cas13a systems. Furthermore, we performed extensive structure-guided engineering at the active-site proximal regions and obtained a TccCas13a variant exhibiting a 100-fold increase in target RNA sensitivity and collateral activity relative to wild-type TccCas13a in different biological matrices, supporting clinical applicability. Together, our work provides insights into TccCas13a's thermostability and activation mechanism and produced variants with improved target RNA sensitivity and collateral activity, laying the foundation for next- generation, field-deployable RNA diagnostics.

102 **On-Site Portable Lithium Detection in Mining and Recycling Industries Based on a DNAzyme Fluorescent Sensor**

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In recent years, the global demand for lithium has soared, surpassing the development of relevant technologies related to its sourcing and recycling. The identification of additional commercially valuable lithium reserves in the environment and more effective lithium recycling methods are thus in urgent need. To meet this need in lithium-driven industries, we have developed novel applications of a highly Li^+ selective DNAzyme for the detection of lithium in brine water, spodumene rock, and lithium-ion battery electrodes down to 1.4 mM (10 ppm) using portable devices. The methods developed and demonstrated in this work will allow highly selective, on-site, portable detection lithium in both environmental samples to identify new lithium resources and in battery electrodes to guide recycling strategies in order to meet the global demand for lithium.

103 **DNA-Activated Peptide Assembly as a Strategy for Supramolecular Therapeutics**

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Uncontrolled peptide self-assembly is implicated in numerous diseases. In contrast, the ability to induce peptide assembly in a programmable manner offers a promising route to functional therapeutic materials. Herein, we introduce a new chemical strategy for regulating peptide assembly through nucleic acid recognition and implement it in DNA-activated Assemblies for Responsive Therapeutics (DARTs). DARTs consist of a DNA hairpin linked at both the 5′ and 3′ termini to self-assembling amyloid-β-derived peptides. Whereas the parent peptide is intrinsically aggregation-prone, conjugation to the hairpin suppresses assembly. Upon addition of a complementary nucleic acid trigger, the hairpin is disrupted and the peptides adopt an assembly-competent state that drives rapid aggregation, affording superstructures exceeding 100 μm in size within 4 h. SEM, TEM, and AFM further reveal that these assemblies form through early fibrillar and layered intermediates that grow into larger hierarchical aggregates. Importantly, DART aggregation can

also be induced in cancer cells in response to endogenous biomarkers, where it elicits marked morphological changes indicative of cellular stress, membrane disruption, and loss of viability. DARTs thus establish nucleic acid recognition as a strategy for directing therapeutic peptide assembly and expand the scope of responsive.

104 **Improved Synthesis of Small Molecule Antioxidant OH-PyN3**

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Over seven million people are currently living with Alzheimer's disease (AD) in the United States today, with that number set to increase due to extended life expectancy. Studies have shown that amyloid-beta (Aβ) plaque accumulation, tau tangles in the brain, metal-ion dysregulation, and oxidative stress are etiological hallmarks of AD. Various treatment methods have been employed to reduce the effects of Alzheimer's disease, but these treatments aim to reduce Aβ plaque aggregates after they've formed, though this strategy focuses on symptom mediation as opposed to prevention. A different approach focuses on preventative treatment of AD to provide an antioxidant that can minimize the effects of oxidative stress through scavenging reactive oxygen species, which are known to lead to oxidative stress. Using this approach, a class of pyridinophanes has been synthesized as antioxidants and metal ion chelators to minimize the effects of oxidative stress through biomimicry of enzymes such as superoxide dismutase. The Green Group has presented multiple pyridinophanes that function as these biomimics, including OH-PyN3. Continued improvement of the synthesis of this small molecule remains a focus, with the intent of a more cost-effective synthesis to facilitate clinical translation. Here we present an improved synthetic scheme, with optimizations to the chelidamic acid esterification and protection of the chelidamic acid and diethylenetriamine moieties. Through this synthetic scheme, the total chemical yield and reduce cost were doubled to 45% and decreased by 81%, respectively.

105 **Deorphanizing NR4A1: Phage Display for Ligand Discovery**

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The nuclear receptor NR4A1 (Nur77) is an orphan receptor implicated in diverse biological processes, including metabolism, inflammation, and cancer progression. Despite its significance, the lack of well-defined endogenous ligands has limited its therapeutic exploitation. In this study, we employed phage display to identify novel ligands capable of binding NR4A1 with high specificity. A 12mer combinatorial library was screened against the ligand-binding domain of NR4A1, enabling the enrichment of high-affinity binders through bio panning strategy and iterative selection rounds. Candidate peptides were isolated, sequenced, and evaluated for binding affinity and selectivity. Several peptides demonstrated strong and specific interaction with NR4A1, suggesting potential as chemical probes or lead compounds for therapeutic development. These findings highlight the utility of phage display as a powerful platform for deorphanizing nuclear receptors and advancing ligand discovery. The identification of novel NR4A1 ligands provides new insight into receptor modulation and establishes a foundation for future studies aimed at elucidating its biological roles and druggability.

106 **Mechanisms and Targeting of LRPPRC-RNA Interactions in Mitochondrial Disease and Cancer**

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LRPPRC (leucine-rich pentatricopeptide repeat-containing protein) is a mitochondrial RNA- binding protein essential for RNA processing, stabilization, and translation. In complex with its binding partner SLIRP (SRA stem-loop-interacting RNA-binding protein), LRPPRC facilitates the delivery of mitochondrial mRNAs to the ribosome, enabling efficient translation of oxidative phosphorylation components. A single missense mutation (A354V) in LRPPRC is causative for Leigh syndrome, French- Canadian variant (LSFC) and has been associated with reduced steady-state levels of the LRPPRC–SLIRP complex. However, it remains unresolved whether disease pathology arises primarily from decreased protein stability or from altered RNA-binding function and/or gain or loss of activity. In contrast, LRPPRC is frequently overexpressed in multiple cancers and has been implicated in pro-oncogenic signaling pathways, including IL-6/JAK1/STAT3, suggesting context-dependent roles in disease. A mechanistic understanding of how LSFC-associated mutations and altered LRPPRC abundance impact RNA binding and mitochondrial transcript regulation is therefore critical for elucidating disease etiology. Moreover, given its emerging role in cancer biology, LRPPRC represents a promising therapeutic target. Here, we employ biochemical and biophysical approaches to characterize LRPPRC–RNA interactions and establish high-throughput screening strategies to identify small-molecule inhibitors that disrupt LRPPRC RNA binding activity.

107 **Identifying High-Priority Zones for Lyme Disease in Northeastern Mexico through Geospatial Analysis of *P. leucopus* and *P. maniculatus***

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The distribution of the Borrelia burgdorferi sensu lato complex, the bacteria causing lyme disease, is intrinsically linked to the geographic range of its primary tick vectors and mammalian reservoirs. While the epidemiological and molecular analysis for Lyme disease in Mexico were established through the extensive clinical and laboratory work of the research group led by Gordillo-Pérez and colleagues, there remains a need to visualize these risks through a geospatial lens. This research utilizes a primary dataset of rarefied occurrence points for the white-footed mouse and the deer mouse, primary natural reservoirs of B. burgdorferi, to analyze their distribution across Mexican territory. By synthesizing these occurrence data with the infection rates previously identified by the Gordillo group in human populations (0.3% seroprevalence) and tick vectors (8.4%–12.6%), this work identifies critical areas of overlap. The geospatial modeling provides a predictive framework for understanding where the enzootic cycle is most likely maintained. This synthesis confirms that the distribution of these reservoirs, in conjunction with the presence of B. burgdorferi sensu stricto (s.s.) confirmed in ticks, designates northeastern Mexico as a high-priority endemic zone. The results of this work can help to establish sound time-effecting monitoring of this potential areas at risk for this disease.

108 **Identifying Defluorinases through a Latent Generative Landscape**

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Anthropogenic organofluorine compounds are ubiquitous and persistent in the environment, posing toxicity concerns and driving a need for defluorination methods. Biocatalysts can serve as solutions that are mild, tunable, and scalable. However, the scarcity of defluorinases limits the understanding of sequence-level determinants underlying this chemistry, motivating approaches to learn and expand functional sequence space. To address this need, we leveraged a machine-learning model trained on homologs of the well-characterized defluorinase Q6NAM1. Through this framework, we identified extant enzymes not previously annotated with defluorination activity for biochemical characterization, leading to the discovery of a diverse set of previously uncharacterized defluorinases with a range of activity. Beyond classification, this machine-learning model can generate defluorinases outside of known sequence space, thus providing the unlimited potential to create defluorinases. Together, our experimentally validated enzymes expand the limited repertoire of known defluorinases and display the utility of the model to determine and design additional defluorinases.

109 **Can a Biologically Relevant Hydroperoxyl-Iron Intermediate also Generate C-C Bonds?**

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Iron–oxygen intermediates are widely recognized for their roles in biological and synthetic oxidation chemistry, yet their ability to support C–C bond formation remains less developed. Although high-valent iron-oxo species are often considered the dominant reactive oxidants in the catalytic reactions evaluated to date iron-hydroperoxo intermediates have recently been implicated in selective C–C bond formation in enzymatic systems such as cytochrome P450 CYP121. This observation raises a broader question: Can Fe(III)-OOH reactivity be translated into a synthetic coupling platform? In this study, phenylboronic acid derivatives are used as model substrates to evaluate Fe(III)-OOH involvement in synthetic C–C coupling. Reaction optimization identified productive iron-based conditions, and substrate-scope studies revealed broad functional group tolerance. Electron-withdrawing substituents generally improved reactivity, whereas electron- donating substituents and ortho substitution reduced coupling efficiency. Density functional theory calculations show that lower substrate LUMO energies, increased boron electrophilicity, and higher electron affinity correlate with improved yields, indicating that substrate electronics strongly influence reaction outcome. Mechanistic studies disfavor outer-sphere radical pathways and high-valent Fe(IV/V)-oxo intermediates. Instead, the data support homolytic C–B cleavage through an inner-sphere iron pathway involving an Fe(III)-hydroperoxo species. Overall, these results suggest that hydroperoxo-iron intermediates can serve as plausible oxidants in greener, earth-abundant iron-mediated C–C coupling chemistry.

110 Selective Permeation of Cancer Model Membranes by NAF1

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Cell penetrating peptides are promising therapeutic tools due to their ability to cross cell membranes independent of protein channels or pumps. NAF1 is a 24-residue cell penetrating peptide which selectively permeates cancer cells but not normal cells. Once inside cancer cells, NAF1 causes cell death. NAF1 therefore possesses unique potential as a targeted therapeutic for cancer, but a better understanding of NAF1's mechanism of selectivity toward cancer cells is needed to improve permeation efficiency and utilize NAF1 as a drug delivery tool. I address this need by using model membrane systems to determine attributes of the cancer cell environment responsible for NAF1's selectivity, elucidating the mechanism of NAF1 translocation

across the membrane, and determining the permeation efficiency of NAF1 variants. NAF1 permeation into model membranes is characterized using fluorescence spectroscopy, a mass spectrometry-based trypsin assay, and circular dichroism. Results are analyzed in conjunction with microscopy and molecular dynamics studies done by collaborators. Data show that NAF1 permeation relies on N-terminal hydrophobicity and C-terminal electrostatic interactions with membrane phospholipids. This work will elucidate the mechanism of NAF1 selectivity to enable the development of NAF1 variants with improved permeation efficiencies and drug delivery capabilities.

111 **Characterizing the Interactions between Thymine DNA Glycosylase (TDG) and RNA**

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Thymine DNA Glycosylase (TDG) is an enzyme involved in DNA repair and epigenetic regulation. TDG utilizes a base flipping mechanism to remove mismatched bases from DNA, initiating the BER pathway and is the only glycosylase known to be capable of removing 5-formylcytosine and 5-carboxycytosine from DNA, hence TDG plays an important role in maintaining DNA methylation patterns throughout the genome. Despite information available on the function of TDG, how it is regulated in cells remains unclear. Recent studies have shown a potential regulatory relationship between TDG and RNA and that TDG binds RNA *in vitro*. However, the exact mechanism of how TDG binds RNA or its involvement in recruiting TDG to the regulatory sites are yet to be explored. This study aims to better understand TDG–RNA interactions through targeted mutagenesis. Utilizing preliminary data that implicate multiple residues within the catalytic domain, a panel of TDG mutants has been generated to identify residues that directly contribute to RNA binding. In addition, mutants are being used to investigate how the intrinsically disordered N- and C-terminal domains influence RNA binding and regulate non-specific nucleic acid interactions. To further explore substrate recognition, sequencing-based hairpin libraries containing a 5-formylcytosine and randomized flanking regions are employed to define the sequence context of TDG-mediated 5-formylcytosine excision and to assess how RNA incorporation modulates substrate specificity. Overall, these findings will provide a better understanding on the role of RNA in TDG regulation and how TDG is targeted throughout the genome.

112 **Engineering Modular Polyketide Synthases for the In Vitro Biosynthesis of Leptomycin Derivatives**

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Modular polyketide synthases (PKS) are multidomain, assembly-line enzymes that can biosynthesize complex human medicines, such as the antibacterial erythromycin, the immunosuppressant rapamycin, and the anticancer agent epothilone. The correspondence between polyketide structure and PKS domain organization indicates that engineered swapping of domains within PKSs has the potential to allow the biosynthesis of desired polyketides. Leptomycin B is a natural product that covalently binds CRM1 and blocks the nucleus-cytoplasm export of proteins. Selinexor, a drug designed to target CRM1, was approved in 2019 for the treatment of multiple myeloma but is associated with significant side effects. Engineering the leptomycin PKS and its variants may enable the production of novel therapeutics with enhanced selectivity and fewer side effects. As the leptomycin TE will only recognize the features of polyketides added by the last 3 modules of leptomycin PKS, we will combinatorially swap the 4th to 9th modules from other PKS that can produce leptomycin derivatives. In vitro reactions have been applied to generate these compounds because it is more rapid and can enable us to control the parameters. After obtaining a library of leptomycin derivatives, we will test the selectivity for CRM1 and how toxic they are to fungal and cancer cells. The promising candidates will be further assessed in mouse models. This project will establish a biosynthetic platform for leptomycin derivative discovery and demonstrate the power of modular PKS engineering as a strategy for generating improved therapeutic agents.

113 **Design, Synthesis, and Computational Evaluation of Novel Alkyl Sulfur-Linked Pomalidomide CRBN Recruiters**

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Proteolysis-targeting chimeras (PROTACs) represent a powerful strategy for targeted protein degradation, enabling selective elimination of disease-associated proteins. The design of effective PROTACs relies heavily on the properties of the linker connecting the protein-of-interest (POI) ligand to the E3 ligase recruiter, as linker geometry, flexibility, and physicochemical properties can influence ternary complex formation. In this study, we designed and synthesized a focused library of sulfur-linked pomalidomide-based cereblon (CRBN) ligands containing thioether and sulfone linkers with varying linker lengths and exit vector orientations (C4 vs. C5). These ligands were developed as modular building blocks for future estrogen receptor alpha (ERα)-targeting PROTACs using toremifene as the POI ligand. The synthesized compounds were evaluated for intrinsic cytotoxicity across multiple cancer cell lines, including 4T1, 67NR, MDA-MB-231, and MIA-PaCa-2, using MTT assays. All compounds exhibited minimal cytotoxicity (IC50 > 100 μM), confirming that the sulfur-linked CRBN ligands function as non-toxic scaffolds suitable for PROTAC construction rather than standalone cytotoxic agents. To further characterize linker behavior, computational analyses were performed using RDKit-based workflows. For each ligand, multiple low-energy conformers were generated and energy-minimized to assess conformational flexibility, spatial reach from the pomalidomide core, and key physicochemical descriptors, including LogP, TPSA, molecular weight, and rotatable bonds. The analysis revealed that linker length primarily governs molecular size and flexibility, while oxidation state influences polarity, and exit vector orientation has minimal impact on overall property space. Several ligands demonstrated a balanced combination of conformational flexibility and spatial reach, suggesting favorable geometries for productive ternary complex formation. Overall, these results provide structure-property insights into sulfur-linked CRBN ligands and establish a rational framework for linker selection in PROTAC design. The identified scaffolds will serve as promising components for the future development of ERα-targeting PROTACs through conjugation with toremifene for targeted degradation studies in ER-positive breast cancer models. (MCF-7)

114 **Investigating the Cellular Consequences of Targeted Protein Degradation (TPD)**

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Targeted protein degradation (TPD) technologies are rapidly transforming therapeutic development by enabling the selective elimination of disease-causing proteins through the cell's endogenous degradation systems. By the end of 2025, over 400 TPD clinical trials had been initiated globally, representing a 25% increase from 2024, highlighting their rapid progression into the clinic. Current strategies utilize the ubiquitin-proteasome system and the autophagy-lysosome pathway, both central to maintaining protein homeostasis and regulating cellular stress responses. Importantly, protein degradation is an energetically demanding process that relies heavily on ATP. When degradation demand exceeds the intrinsic capacity of these systems, cells may experience proteotoxic stress and metabolic strain. Thus, artificially activating these pathways through TPD has the potential to disrupt both protein homeostasis and cellular energy balance. Despite their therapeutic promise, the systemic cellular consequences of artificially engaging these degradation systems remain poorly understood. This represents a critical barrier to predicting toxicity and optimizing degrader design, particularly in combination with other therapies. We aim to assess the cellular effects of TPD by examining how activation of proteasomal and lysosomal pathways influences cellular energy metabolism and protein stress responses. We hypothesize that TPD will (i) increase ATP demand and reprogram metabolic flux by altering mitochondrial and glycolytic outputs, and (ii) induce distinct proteotoxic stress responses, with proteasomal TPD elevating heat shock response (HSR) and integrated stress response (ISR) markers, and

lysosomal TPD activating unfolded protein response (UPR) pathways. To test this, we will use an exogenously expressed Bromodomain-containing protein 4 (BRD4) fusion construct as a model substrate and orthogonal proteasomal and lysosomal degraders for precise control over target expression and degradation. This approach minimizes disruption to endogenous cellular processes while allowing us to isolate pathway-specific effects, independent of intrinsic BRD4 biology. Metabolic effects will be assessed through ATP measurements, Seahorse-based bioenergetic profiling, and targeted metabolomics, while stress responses will be characterized using RNA-seq, gene set enrichment analysis, and protein-level validation. This study will determine how activating protein degradation pathways through TPD affects key aspects of cell physiology, particularly protein stress response and energy metabolism. These insights will address a critical gap in our understanding of how TPD affects cells beyond target elimination. This will also enable the prediction and mitigation of pathway-specific toxicities associated with degraders, enabling the rational design of safer, more selective, and synergistic TPD strategies for therapeutic benefits.

115 **Mechanisms of Interfacial Interactions Between Engineered Nanoplastics and Biological Systems**

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Tiny plastic particles, known as micro- and nano-plastics, have been detected in the human body and are increasingly linked to serious health concerns. However, the molecular mechanisms through which they affect biological systems remain poorly understood. In this study, we have investigated the effects of polyvinyl chloride (PVC) nanoparticles (NPs) on biologically relevant proteins and neural functions using a combination of laboratory experiments and animal models. We found that PVC NPs significantly disrupted the structure of the milk protein β-lactoglobulin (BLG), transforming its native helical shape into β-sheet structures as nanoparticle concentration increased. This conformational shift impaired BLG's ability to bind retinol (vitamin A), a vital nutrient, thereby compromising its carrier function. A similar effect was observed in lysozyme, where PVC accelerated the formation of amyloid fibrils and reduced its helical content changes typically associated with neurodegenerative diseases. In vivo experiments using the BZ555 strain of *Caenorhabditis elegans*, expressing GFP in eight dopaminergic neurons, showed that PVC exposure reduced fluorescence intensity and impaired locomotion, indicating neurotoxic effects. These findings provide new insights into the molecular toxicity of nanoplastics and underscore the potential health risks associated with chronic exposure to environmental plastic pollutants.

116 **Calcium Modulates Growth and Biofilm Formation of Intestinal *Lactobacillaceae***

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The human gut microbiota is a complex population of microorganisms in the gastrointestinal tract. These microbes help build the immune system, protect against pathogens, and synthesize nutrients. Among these, bacteria from the *Lactobacillaceae* family are well-documented to have various beneficial effects on health. *Lactobacillaceae* abundance in the gastrointestinal tract has been correlated with gastrointestinal pathologies and infection. Microbiota residents must compete for nutrients, including essential metal ions like calcium, zinc, and iron. Recent animal and human studies have revealed that dietary calcium can positively influence the diversity of the gut microbiota and abundance of intestinal *Lactobacillaceae* species. In eukaryotes, Ca^{2+} is widely used to regulate cellular processes ranging from the cell cycle to gene expression and metabolism. In prokaryotes, the requirements and roles of Ca^{2+} ions are less well defined. Here, we investigated the impacts of calcium on the growth and biofilm formation of two distinct Lactobacillaceae species found in the gut microbiota, Lactobacillus acidophilus ATCC 4356 and Lactiplantibacillus plantarum ATCC 14917. We found that calcium ions differentially affect both growth and biofilm formation of these species. Calcium ions strongly induce biofilm formation of L. acidophilus ATCC 4356 but not L. plantarum ATCC 14917. Based on bioinformatic analyses and experimental chelator studies, we hypothesize that surface

proteins specific to L. acidophilus ATCC 4356, like S-layer proteins, are responsible for Ca2+-induced biofilm formation. The ability of bacteria to form biofilms has been linked with their ability to colonize in the gut microbiota. This work shows how metal ions like Ca2+ may be important not just as nutrients for bacteria growth, but also for their ability to facilitate cell-cell interactions and possibly colonization in the gut microbiota.

117 **NASA VITAL-AI-Driven Biodegradable Sensors for Environmental Vector-Borne Diseases Monitoring**

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Mexico and Texas share a legacy of vector-borne diseases transmitted by vectors such as mosquitoes, ticks, and kissing bugs. Preventing insect bites is the primary way to stop these diseases from occurring in this transboundary region. With this in mind, the NASA VITAL project aims to create predictive maps and models of potential outbreaks for some of these diseases using NASA satellite data and AI algorithms to help prevent, control, and increase education of their spread in the Mexican-Texas region. Currently, the project is in the research phase and current vector-borne diseases such as Chagas disease, Leishmaniasis, and Rocky Mountain Spotted Fever are being identified and learned about. This is being achieved through an ongoing review paper to be published soon, which will cover current distributions to set the stage for future distributions and trends of vector borne diseases. Overall, the NASA VITAL project will enable the knowledge and outlook of future spatial distributions through NASA data and AI predictive modeling to be able to predict those trends for up to 50-100 years from now for the well-being and safety of the Rio Grande Valley. This project is aimed to find solutions to real world problems like vector-borne diseases.

118 **Nicotine-Inspired, De Novo Designed SARS-CoV-2 Main Protease Inhibitors Reveal Unique Chemistry for Covalently Conjugating both Cysteine and Histidine Residues in the Catalytic Dyad**

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Anecdotal reports about smokers with low SARS-CoV-2 infection rates prompted a search of nicotine and its pyrolysis products as SARS-CoV-2 main protease (MPro) inhibitors. From this search, 3-vinylpyridine was discovered as a weak binder for the MPro S1 subsite and was used subsequently as a de novo starting point for covalent inhibitor design that quickly yielded a highly potent inhibitor, SR-A-174 with an IC50 value of 60 nM. Representing a novel class of MPro inhibitors, SR-A-174 has a N,N-diaryl-a,a-dichloroacetamide scaffold that enabled fast exploration of alternative covalent warheads and different N-substituents, resulting in multiple inhibitors with strong antiviral potency. Eight MPro -inhibitor structures were determined, all showing covalent engagement of the catalytic Cys145 of MPro. In six determined structures, binding is dominated by the covalent bond plus van der Waals contacts, which contrasts to extensive hydrogen bond networks formed with peptidomimetic inhibitors such as nirmatrelvir. Strikingly, two N,N-diaryl- a,a-dichloroacetamide inhibitors exhibit an unprecedented dual covalent modification mode of the catalytic dyad, forming bonds to both Cys145 and His41 with concomitant loss of both chlorides and displacing the inhibitors from the S1 subsite. This dyad-targeting reactivity suggests a novel route for bioconjugation of both cysteine and histidine.

119 **Design of Blood Brain Barrier Penetrating Peptide Macrocycles for Central Nervous System Drug Delivery of Therapeutic Proteins**

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The blood–brain barrier (BBB) presents a major obstacle to the treatment of central nervous system (CNS) diseases, as more than 98% of FDA-approved therapeutics fail to penetrate the BBB. While the barrier's selective permeability protects the brain from circulating toxins, it also restricts the delivery of many promising therapeutics, particularly biologics. Receptor-mediated transcytosis (RMT) pathways have therefore emerged as an attractive strategy for transporting drugs across the BBB. Antibodies targeting BBB receptors such as transferrin receptor protein 1 (TfR1) have demonstrated success as delivery vectors; however, their large size, immunogenicity, and manufacturing complexity limit their scalability and translational potential. Macrocyclic peptides represent a promising alternative modality that combines antibody-like affinity and specificity with improved stability, reduced molecular size, and synthetic flexibility. Here, we describe a generative artificial intelligence–guided strategy to design macrocyclic peptide ligands targeting the apical domain of TfR1 for BBB drug delivery applications. Using BindCraft, we designed domain-specific peptide binders that target TfR1's apical domain. Surface plasmon resonance (SPR) binding assays demonstrated that this design pipeline can produce TfR1- binding macrocyclic peptides with low- to sub-micromolar affinities. Subsequent lead optimization strategies further improved binding affinity, yielding macrocyclic peptide ligands with markedly enhanced affinity for TfR1. These results demonstrate the feasibility of combining generative peptide design with macrocyclization strategies to create high-affinity receptor ligands suitable for BBB targeting. To evaluate their functional potential as BBB shuttle vectors, we investigated conjugation strategies enabling the attachment of these macrocyclic peptides to macromolecular therapeutic payloads (>150 kDa). As proof of concept, we explored the application in delivering a tumor cell targeted cytotoxic IgG protein whose therapeutic utility against brain tumors is limited by poor BBB penetration. Our approach aims to address this limitation by enabling TfR1-mediated transcytosis of IgG based therapeutics. Additionally, we established and characterized an in vitro BBB model to evaluate receptor-mediated peptide transport. This model enables the investigation of TfR1-dependent transcytosis and provides a platform to assess the ability of designed macrocyclic peptides to facilitate transport across brain endothelial barriers. Together, this work demonstrates the potential of AI-driven macrocyclic peptide design as a strategy to develop next- generation BBB shuttle vectors for CNS drug delivery and therapeutics for brain metastatic cancers.

120 **Generation of Optimized Cross-Chiral Afnity Reagents for Structured RNA**

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Spiegelmers have demonstrated effective RNA targeting through structure-specific recognition, making them highly promising as biostable research tools and therapeutics. Notably, all RNA-targeting Spiegelmers identified to date are G-rich and are likely to adopt G-quadruplex (G4) structures. This study exploits this G4-dependent behavior for the generation of cross-chiral aptamers. We designed a specialized DNA library pre-functionalized with an internal hairpin and enhanced G4-forming potential through the targeted insertion of consecutive guanine tracts. Selection was performed against an RNA hairpin derived from the Pseudomonas phage PP7 coat protein—a structural motif widely used in cellular imaging. To improve deep-sequencing precision and normalize for PCR amplification bias in sequence enrichment, a unique molecular identifier (UMI) strategy was implemented. Analysis of enrichment dynamics ultimately identified a highly target-specific aptamer directed against the PP7 RNA hairpin.

121 **Novel Chemical Biology Tools to Investigate RNA Modifications and their Roles in Disease**

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RNA methylation, particularly N6-methyladenosine (m6A), is a pervasive post-transcriptional modification that regulates RNA stability, localization, and translation across diverse biological systems. Despite its importance, understanding the spatial distribution and functional roles of m6A at subcellular resolution remains challenging due to the lack of sensitive and versatile imaging approaches. Here, we develop a metabolic labeling–based imaging platform to visualize m6A-modified RNA in situ with high sensitivity. Propargyl-L-selenohomocysteine (PSH) is metabolically incorporated into RNA methylation pathways, enabling selective labeling of methylated transcripts via click chemistry. This strategy is coupled with padlock probe–mediated rolling circle amplification (RCA) for robust signal enhancement and can be integrated with transcript-specific fluorescence in situ hybridization (FISH) and protein markers to simultaneously resolve RNA identity, modification status, and subcellular localization. This platform enables the investigation of spatial RNA regulation across multiple biological contexts, including neuronal local translation, RNA–protein interactions, stress responses, and disease-associated RNA remodeling. By providing spatially resolved information on RNA methylation, this approach establishes a generalizable framework to link RNA modifications with function in complex cellular environments.

122 **Direct and Selective Activation of Glycolysis using a Covalent PFK1 Ligand**

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The first committed step of glycolysis is regulated by phosphofructokinase-1 (PFK1), which catalyzes the ATP-dependent conversion of fructose 6-phosphate to fructose 1,6-bisphosphate (FBP). In mammalian systems, PFK1 is expressed as three isoforms (PFKP, PFKM, PFKL) with high sequence homology and distinct regulation and tissue-specific expression profiles. The former feature makes it challenging to target a specific isoform, which is important given that disruption of individual PFK1 proteins can produce side effects (e.g., PFKM deficiency can lead to Tarui disease). Here, we disclose a ligand that potently activates PFKL biochemical activity through covalent modification in the allosteric nucleotide effector site. Covalent engagement of PFKL with ligand in cells resulted in rapid accumulation of FBP substrate, increased glycolytic rates and potentiation of signaling in activated immune cells. Notably, these metabolic and signaling changes could be assigned to covalent modification of a single residue on PFKL with no other significantly liganded sites across thousands of quantifiable proteins, including other PFK1 isoforms, as measured by tandem mass tag (TMT) chemical proteomics. The PFKL activator represents an enabling tool that can be combined with genetically-encoded, metabolic biosensors to investigate glycolytic regulation at the subcellular and single-cell level.

123 **Structure-Guided Discovery of Covalent Inhibitors Targeting SARS-CoV-2 Proteases with Potent Antiviral Activities**

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The continued emergence of SARS-CoV-2 variants and the development of resistance to current antivirals underscore the urgent need for novel therapeutics. The viral papain-like protease (PLpro) is an essential enzyme for viral replication and host immune evasion, yet it remains an underexplored therapeutic target with only a few reported classes of small-molecule inhibitors. Here, we report the structure-guided design, synthesis, and biological evaluation of a series of small-molecule inhibitors targeting the S1′ pocket of PLpro. Structure–activity relationship (SAR) studies identified fumaramide-based compounds with potent enzymatic inhibition (IC50 as low as 16 nM). The lead compound exhibited robust antiviral efficacy in cellular assays (EC50 = 96 nM), excellent selectivity over human deubiquitinase, and no detectable cytotoxicity. Mechanistic studies and X-ray crystallographic analyses revealed that the incorporation of electron-deficient pyridine moieties significantly enhances potency by promoting favorable π–π stacking and electrostatic interactions with Trp106 in PLpro. In parallel, structure-guided efforts identified chloroacetamide- and epoxide-based covalent inhibitors of the main protease (Mpro) targeting Cys145 (IC50 as low as 490 nM) with robust antiviral activity; mechanistic and X-ray crystallographic analyses revealed that Cys145 preferentially attacks the sterically hindered epoxide carbon, while Cys44 lacks sufficient nucleophilicity for covalent targeting. Overall, this work establishes PLpro as a compelling antiviral target and provides highly potent, structurally validated lead compounds for the development of next-generation SARS-CoV-2 therapeutics.

124 **In situ Profiling of GlycoRNA-Protein Interactome in Living Cell**

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Cellular glycans play important roles in diverse biological processes and are implicated in infectious diseases and cancer. In 2021, a new type of glycosylated molecule, glycoRNAs have been discovered on the cell membranes. Emerging evidence indicates that glycoRNAs participate in diverse cellular processes, including immune cell recruitment, cell-penetrating peptide entry, immune evasion and homeostatic efferocytosis, and modulation of heparan sulfate- mediated signaling. Despite rapid progress in glycoRNA discovery, a central question remains unresolved: do cell surface glycoRNAs act merely as passive scaffolds, or do they actively instruct cellular responses through RNA sequence-encoded information? Addressing this challenge has been limited by the lack of tools capable of resolving glycoRNA-centered molecular interactions in their native extracellular context.

125 **Small Molecule Inhibition of the ENL YEATS Domain Suppresses Acute Myeloid Leukemia**

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The YEATS domain containing protein Eleven-Nineteen-Leukemia (ENL) is an epigenetic reader that recognizes acetylated histone lysine residues. Genetic studies have demonstrated that ENL is essential for leukemia maintenance, particularly in MLL-rearranged Acute Myeloid leukemia, suggesting that its pharmacological inhibition represents an attractive therapeutic strategy. Our prior research led to the discovery of a small molecule inhibitor, SR- C-107(R), that showed pronounced and specific inhibitory effects against the ENL YEAST domain. In our latest work, we designed and synthesized a structurally diverse set of ENL YEATS inhibitors and conducted a comprehensive SAR study for lead optimization. This effort yielded more than 20 compounds with strong binding affinity to the ENL YEATS domain, nine of which displayed potent inhibitory activity against AML cell lines (IC50 < 1 μM in both MOLM-13 and MV4-11 cells). Four

inhibitors, SR-D-34, NS-D-90, SR-D-105, and SR-D-129, exhibited remarkable selectivity for ENL/AF9 over YEATS2 and YEATS4, along with excellent stability in human and mouse liver microsomes, plasma, and simulated physiological fluids. Favorable cell permeability and extended in vivo half-lives supported their advancement into animal studies. In in vivo efficacy studies, SR-D-129, administered by daily intravenous injection at just 5 mg/kg in MV4-11 xenograft mice, achieved excellent tumor growth inhibition (TGI) and significantly extended median survival (24 days to 55 days). Notably, it was well tolerated, with no significant body weight loss observed throughout the studies. Collectively, this work expands the structural diversity of ENL YEATS inhibitors and advances the development of therapeutics for AML.

126 **Copper Stoichiometry Drives the Conformational Dynamics in P1-B-type ATPase Revealed by Hydrogen Deuterium Exchange Mass Spectrometry (HDX-MS)**

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Copper is an essential trace element acting as a catalytic cofactor in several cuproenzymes and central to critical cell signaling and biochemical pathways. However, its ability to redox cycle at physiological redox potentials can lead to production of free radicals and reactive oxygen species via Fenton and Haber-Weiss reactions, which are highly toxic to cells. P1B-1-type ATPases also known as Cu(I)-pumps (named CopAs in prokaryotes) are transmembrane copper exporters which, in all branches of life, play a key role in regulating cellular copper concentrations toprevent copper toxicity. The CopA pumps feature a multi- domain topology including three catalytic cytosolic domains (involved in ATP hydrolysis and auto-phosphorylation), a transmembrane core, and none to multiple soluble metal binding domains (MBD). Together, these structural elements enable transfer of Cu(I) ions from intracellular to extracellular environment through the catalytic Post-Albers cycle. Studies on Cu(I)-pumps have provided information about the topological framework by which CopAs perform their function. However, the structural and functional roles of MBDs remain still elusive, due to their structural flexibility and postulated unique functional and regulatory roles in the catalytic cycle, in particular in copper transfer events. To address this gap, we employ hydrogen-deuterium exchange coupled with mass spectrometry (HDX-MS) to study the conformational dynamics associated with copper binding in the model Cu(I) pump from *Escherichia coli* (EcCopA). By investigating the effect of EcCopA exposure to different copper stoichiometric ratios, preliminary data reveal that copper binding modulates MBDs dynamics without perturbing the transmembrane or other catalytic domains. Additionally, increased copper concentrations promote progressive MBDs metal occupancy, suggesting a concentration dependent control of MBD function. In addition, the obtained data are consistent with a potential "hand off mechanism" in which copper is bound to MBD prior to transmembrane high-affinity binding site. These findings establish the baseline for exploring the role of protein dynamics in copper transfer and loading pathways, including chaperone mediated delivery to CopAs.

127 **Enzyme-Catalyzed Stereoselective C(sp3)-S Bond Formation via a Dichotomic Carbene Transfer Mechanism**

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Asymmetric C(sp^3)-S bonds are found in many bioactive natural products and pharmaceuticals. Despite progress in the development of methods for asymmetric S-H carbene insertion reactions, this transformation remains challenging and elusive in the presence of pyridotriazoles as carbene donor reagents. Herein, we report a biocatalytic platform for the stereoselective construction of asymmetric C(sp^3)-S bonds via both a S-H carbene insertion (up to >99% ee) and a [2,3]- sigmatropic rearrangement reaction by harnessing engineered myoglobin catalysts in combination with pyridotriazole-based carbene precursors. These transformations enable the synthesis of valuable α-pyridyl sulfides with broad substrate scope, high yields, and good to excellent stereocontrol. Intriguingly, mechanistic studies show that the S-H insertion reaction

proceeds via a radical pathway, while a polar, two-electron mechanism is exploited by the enzyme for mediating [2,3]-sigmatropic rearrangement reaction, thus revealing a remarkable versatility of the hemoprotein toward operating via both a radical and non-radical pathway. This methodology provides an efficient and sustainable route to valuable pyridine-containing chiral sulfides, while unveiling a dual reactivity mode of a hemoprotein catalyst in an abiological carbene transfer reaction.

128 **The School of Integrative Biological and Chemical Sciences at UT Rio Grande Valley: a unique school offering diverse and flexible master's degrees in chemistry, biology, and in between**

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The University of Texas Rio Grande Valley (UTRGV) is a public research university with its main campus in Edinburg, Texas, and multiple other campuses throughout the Rio Grande Valley. It is the southernmost member of the University of Texas System. The School of Integrative Biological & Chemical Sciences (SIBCS) at UTRGV is dedicated to advancing scientific knowledge through cutting-edge research, transformative teaching, and impactful service to the university, the Rio Grande Valley, and the scientific community, in alignment with UTRGV's mission and core values. The challenges of our rapidly changing world present a greater need for scientific understanding, data-driven analytical skills, biotechnology innovations, and critical thinking than ever before. By exploring life and material sciences, from the fundamental building blocks of matter through the many levels of living organisms and their environment, the School offers three master's degrees in chemistry, biology, and biochemistry & molecular biology. These graduate programs' unique course offerings, research opportunities, and ethical standards provide crucial preparation for graduate students (both domestic and international) pursuing career paths in research, the health professions, industry, education, public policy, and other emerging fields.

129 **Synthesis and Biological Evaluation of Colibactin Derivatives**

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Colibactin is a pseudo-C2-symmetric gut microbiome metabolite that induces DNA interstrand cross-links and plays a causal role in colorectal cancer. Since efforts to isolate colibactin have not been successful, we developed colibactin 742 as a stable colibactin mimetic. However, colibactin 742 exists as a mixture of ring and chain isomers, which complicates analysis of its activity. We report here the discovery of colibactin 686 as a superior colibactin mimetic. Colibactin 686 is more potent than colibactin 742 and recapitulates the bacterial genotoxic phenotype. Colibactin 686 possesses a C2-symmetric structure, which will expedite its synthesis, and is incapable of ring−chain isomerization, which will simplify analysis of its biological activity. Through our SAR campaign, we discovered seven novel derivatives of colibactin and additionally establish that colibactins do not passively diffuse into cells and are substrates for monocarboxylate transporter pumps. These latter findings have implications for trafficking of natural colibactin called "Precolibactin", which remains poorly understood. Since nature produces colibactin in the form of prodrug, we have shown our efforts to hijack nature's machinery and showcasing Antibody-drug conjugates of colibactin.

130 **Discovery of Surface-Engineered Nanoparticles That Boost Enzyme Activity**

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Nanoparticles can enhance enzyme activity, but this phenomenon remains largely empirical and lacks predictive design rules. This work presents a high-throughput strategy for discovering surface-engineered nanoparticles (SENs) that modulate enzyme function through control of the local microenvironment rather than direct enzyme engineering. A library of 194 gold- and palladium-based nanoparticles functionalized with diverse peptide ligands was constructed and screened against three model enzymes: cytochrome c, lactoperoxidase (LPO), and lipase. Multiple SENs significantly enhanced enzyme activity, with the top-performing formulations producing up to ~19-fold increases. The resulting dataset enabled the training of a machine learning model that identified key ligand features associated with high-performing SENs, establishing a predictive framework for designing activity-enhancing NPs. Mechanistic studies further indicated that the ligand shell is a major determinant of the enhancement effect and that effective ligands may be transferable across nanoparticle cores. As a functional demonstration, an optimized SEN/LPO pair outperformed the native enzyme in suppressing multidrug-resistant bacterial growth and disrupting biofilms. Overall, this study establishes a scalable platform for mapping nanoscale structure-function relationships at biointerfaces and for developing nanoparticle-based strategies to enhance enzyme performance.

131 **A Refined Search of SARS-CoV-2 Main Protease Inhibitors as COVID-19 Antivirals**

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MPI8 was one of the first SARS-CoV-2 main protease (MPro) inhibitors identified with strong antiviral potency. It is a peptidomimetic aldehyde featuring P2 3-cyclohexylalanine, which binds tightly in the MPro S2 subsite, and P3 O-tert-butylthreonine, which contributes to both MPro S subsite interactions and likely cellular permeability. By fixing these two elements, analog compounds with varied functionality for binding at MPro S4 and S1' subsites and covalent warheads to engage the MPro active site cysteine were synthesized. Reveled strong S4 binders are compact N-terminal carbamates or amides bearing cyclopropane, isopropyl, or trifluoromethyl groups to fit the shallow hydrophobic pocket of S4, which were validated by crystal structures determined for three inhibitors bound with MPro. Potential S1' binders there were tested include benzothiazole-2-carbonyl, its derivatives, and acyloxymethylketone moieties, leading to analog compounds with mostly similar potency as MPI8. Crystal structure of one benzoxazole-2-carbonyl-containing inhibitor bound with MPro showed its benzoxoazole packed tightly at the S1' subsite. In parallel, nitrile and 2-amino-2-oxyacetyl warheads as alternatives to the aldehyde of MPI8 provided similar potency. Combining strong S4 binders with alternative warheads or S1' binding motifs delivered several new inhibitors with enzyme inhibition potency exceeding MPI8. Among these, MPI-131 achived an IC50 of 1.7 nM and showed substantially improved antiviral activity (EC50: 3.2 nM) reliatve to MPI8, placing it among most potent SARS-CoV-2 MPro inhibitors identified to date.

132 **Regioselective multicomponent synthesis of α-boryl ureas: discovery of a potent main protease inhibitor**

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The development of efficient synthetic methods for α-boryl ureas is of significant interest due to their potential as drug-like scaffolds in medicinal chemistry. Herein, we present a multicomponent strategy that transforms α-haloboronates, trimethylsilyl isocyanate, sodium iodide, and amines into diverse druglike scaffold α-boryl ureas under mild conditions. This protocol features broad substrate scope and great

functional-group tolerance, and enables the regioselective synthesis of previously inaccessible α-boryl ureas, including late-stage functionalization of drug molecules. Mechanistic studies suggest that a regioselective 1,2-boronate migration pathway may underlie the different regioselectivities observed with primary and secondary amines. To highlight the potential of this methodology in drug discovery, an α-boryl urea analog of nirmatrelvir was synthesized, exhibiting remarkable inhibitory activity (IC50 = 12 nM) against the SARS-CoV-2 main protease. This work not only provides a streamlined and practical synthetic route to diverse α-boryl ureas, but also underscores their potential as valuable scaffolds in the development of new therapeutics.

133 **DNAzyme-Based Tools to Probe Metal Chemistry in Neurodegeneration and Cancer**

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Metal ions and metabolites regulate gene expression and cellular function; however, methods that resolve their chemically distinct states and link them directly to biological regulation remain limited. Here, we develop DNA-based tools that resolve metal chemical states in living systems and translate these chemical measurements into quantitative and regulatory biological readouts for understanding neurodegenerative disease and cancer. In recent work, we developed the first DNAzyme-based fluorescent sensors that selectively image Fe^{2+} and Fe^{3+} in living systems, overcoming a long-standing barrier in oxidation-state specificity for iron imaging. Using these tools, we achieved spatially resolved mapping of iron redox balance in disease contexts. In Alzheimer's disease mouse models, we detected elevated Fe^{3+}/Fe^{2+} ratios localized to amyloid plaque regions, revealing iron redox imbalance within pathological microenvironments. We further extended oxidation-state-resolved iron measurements to normal aging and additional neurodegenerative disease models where we observed a shift in the labile iron redox balance toward oxidized Fe^{3+} with aging. Complementary functional studies showed that targeting the iron-associated protein FTL1 in aged mice brains improved cognitive performance, supporting a link between iron redox dysregulation and functional decline during aging. In cancer ferroptosis models, we further observed iron redox remodeling during ferroptosis and correlated labile iron redox states to ferroptosis sensitivity. Together, these studies establish iron redox chemistry as a measurable, spatially heterogeneous chemical feature of disease-associated tissues and demonstrate that oxidation-state-resolved measurements provide biological information not accessible from bulk iron quantification alone. Beyond measurement, we expanded DNAzyme-based sensing platforms to new molecular targets and signal outputs to improve performance in living systems. These advances include a genetically encoded fluorogenic DNA aptamer for real-time ATP monitoring in live cells, a bioluminescent DNAzyme (bioLUNA) for excitation-free Zn^{2+} imaging in vivo, and a BRET-based DNAzyme sensor for portable Zn^{2+} detection. In parallel, we engineered metal-responsive DNAzymes that enable conditional regulation of metastasis-associated oncomiRNAs in mammalian cells. By enhancing intracellular stability and selectively targeting structured RNA precursors, these DNAzymes enabled metal-dependent regulation of shRNA and pre-miRNA-21, thereby coupling intracellular metal ion availability to gene regulatory outcomes and cancer-relevant cellular phenotypes.

134 **Programmable DNAzyme Probes Illuminate Metal Ions in Human Health and Diseases**

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Metal ions serve as critical chemical regulators in biology, and their dysregulation is increasingly implicated in diverse human diseases. However, beyond well-studied calcium signaling and a few special cases, monovalent and redox-active metal ions remain poorly understood in disease contexts. A major gap in knowledge is understanding how metal ion distributions and speciation are regulated in living systems and how these processes influence human health and disease. A key barrier has been the lack of tools to selectively and quantitatively image distinct metal ion species in live cells, especially when those species are chemically similar. We address this urgent need by developing innovative DNAzyme-based imaging platforms. DNAzymes, which are DNA-based catalysts requiring specific metal ion cofactors, were engineered as highly specific fluorescent probes to visualize metal ion concentrations and redox states in living systems. Through selective, ratiometric, live-cell sensing of metal ions with molecular precision, these platforms enabled us to uncover new insights into metal homeostasis across three disease models. In a bipolar disorder (BD) neuron model, a Li^+ -specific DNAzyme probe revealed that BD patient-derived neurons accumulate more Li^+ than healthy neurons, in a differentiation stage-dependent manner. This suggests underlying ion channel differences that could influence BD progression and response to Li^+ therapy. In an Alzheimer's disease (AD) model, simultaneous imaging of Cu^+ and Cu^{2+} demonstrated that disrupted copper homeostasis and redox imbalance coincide with amyloid toxicity. Affected neurons also showed increased vulnerability to cuproptosis, a copper-dependent cell death pathway, implicating a copper-driven mechanism in neurodegeneration. In a metastatic cancer model, a K^+ -specific DNAzyme probe enabled live imaging of K^+ dynamics in the tumor microenvironment. Strikingly, aggressive cancer cells lost intracellular K^+ as tumors progressed, and elevated extracellular K^+ reduced chemotherapy efficacy. Furthermore, restoring K^+ homeostasis by blocking a K^+ channel, resensitized cancer cells to treatment. These findings point to a new mechanism-based intervention strategy targeting K^+ homeostasis in cancer. Collectively, our studies establish DNAzyme-based probes as a generalizable platform for in vivo metal ion imaging and define metal homeostasis as a dynamic, disease- relevant regulatory axis in human biology. Beyond imaging, this framework opens opportunities for metal-controlled gene regulation and propels the emerging field of functional metallomics, where metal ion dynamics are systematically linked to genetic and molecular networks. These advances provide conceptual and technological foundations for understanding metal-dependent mechanisms in health and disease.

135 **Conformational Pattern and Aggregation of GLP-1 Analogs**

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Understanding how sequence modifications reshape conformational preferences and aggregation behavior is central to rational design of peptide therapeutics. Glucagon-like peptide-1 (GLP-1) analogs, including liraglutide and semaglutide, exhibit distinct aggregation propensities and pharmacokinetic profiles, yet the molecular determinants underlying these differences remain incompletely understood. Here, we investigate the conformational landscapes and aggregation pathways of GLP-1, liraglutide, and semaglutide by integrating native ion mobility mass spectrometry (nIM-MS) with molecular dynamics (MD) simulations. Our results reveal that sequence-dependent conformational biases in the monomer state propagate into oligomer assembly, leading to distinct size-dependent structural preferences across analogs. While all systems exhibit heterogeneous oligomerization pathways, their assemblies converge toward partially ordered, anisotropic architectures governed by the distribution of hydrophobic residues and backbone flexibility. Comparative analysis identifies key modifications, particularly lipidation and residue substitutions, as modulators of both conformational stability and aggregation propensity. To further connect structure with

thermodynamics, variable-temperature electrospray ionization mass spectrometry (VT-ESI-MS) is employed to quantify binding energetics between GLP-1 analogs and their carrier protein, human serum albumin (HSA). These measurements reveal distinct enthalpic and entropic contributions across analogs, reflecting differences in lipid- mediated interactions and conformational adaptability. Together, this combined experimental and computational framework establishes a mechanistic link between monomer conformational patterns, lipid-mediated stabilization, and oligomer growth. These findings provide a unified perspective on how chemical modifications tune both aggregation behavior and binding thermodynamics in GLP-1–based therapeutics.