Oral Presentation Abstracts

Research Fellows & Others			
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O3	Backstage Passes to the Brain: A Minimally Invasive Enzyme Replacement Therapy for Angelman Syndrome ***Barbara Bailus,*** *Delihla Correa, Rachel Stoub, Ty Johnson, Linna Han, Yara Al Mashriki, Moses Lee, Lisa Ellerby, Albert Keung*	47	9:45-10:45 am
O7	Dose escalation of a blood-brain barrier traversing TNF-α inhibitor in a tauopathy (P301S) mouse model ***Nataraj Jagadeesan,*** *G. Chuli Roules, Katelyn Truong, Devaraj V. Chandrashekar, Adenike Oyegbesan , Emi Iwasaki, Sanjana Kolluru, Rachita K. Sumbria*	51	9:45-10:45 am
O10	Function of Phosphodiesterase Isoforms in Human Airway Smooth Muscle Cell cAMP Signaling Compartments ***Jordyn Margolis****, Isabella Cattani-Cavalieri, Eric Gebski, Rennolds Ostrom*	54	9:45-10:45 am
O13	Comparison of Statin Use for ASCVD Prevention in People with HIV at a Federally Qualified Health Center ***Shaien Rivers****, Jerika Lam*	57	9:45-10:45 am
Ph.D. and M.S. Students			
O1	Modifying Tryptophan and Indole-Derived Compounds Using Engineered Indole Prenyltransferase Enzymes ***Ashley K. Alexander****, Diem N. Nguyen, Ahmed R. Aoun, Tae Ho Kim, Nagaraju Mupparapu, Sherif I. Elshahawi*	45	11 am -12 pm
O2	Proximity-Dependent Proteomics Identifies Unique Interactomes of Adenylyl Cyclase Isoforms 6 and 9 in Human Airway Smooth Muscle Cells ***Camelia Anicolaesei****, Yong Li, Jordyn Margolis, Isabella Cavallieri, Carmen W. Dessauer, Rennolds S Ostrom*	46	11 am -12 pm
O4	Predictive Gene Expression Signatures for Alzheimer's Disease Using Post-Mortem Brain Tissue ***Ashley Duche****, Oliver Tran, Andrius Baskys, Rachita K. Sumbria, Moom Roosan*	48	11 am -12 pm

O6	Spatiotemporal differential regulation of extrasynaptic GluN2B receptor subunits and PSA-NCAM in brain aging and Alzheimer's disease ***Oghenetega E. Imiruaye**, Isis G. Perez, Brian C. Carson, Christian Crouzet, Jerome Garcia, Derick Han, Subhrajit Bhattacharya*	50	11 am -12 pm
O11	Development of Pharmaceutical Inhibitors Targeting nNOS for Melanoma Treatment ***Anika Patel**, Shirley Tong, Moom R. Roosan, Basir Syed, Amardeep Awasthi, Richard B. Silverman, Jennifer Totonchy, Sun Yang*	55	11 am -12 pm
O12	Structural Insights into the Pharmacological Modulation of KCa3.1 Channels by SKA-111 and DHP-103 Revealed by Cryo-EM ***Alena Ramanishka**, Young Woo Nam, Seow Theng Ong, Joshua Nasburg, Xuan Rui Ng, Zhong Zhuang, Yang Xu, Heike Wulff, George Chandy, Miao Zhang*	56	11 am -12 pm
PharmD. Students			
O5	The Impact of the Drug Addiction Treatment Act (DATA) Waiver Removal on Buprenorphine Prescribing and Access in California: A Geospatial and Trend Analysis (2022–2023) ***Elena Wu**, Harvey Duong, Ryan Stofer, Sherry Yun Wang*	49	2:45-3:15 pm
O8	Tracking Stimulant Use with Concurrent Controlled Substances from Adolescence to Young Adulthood in California ***Sangyoon Kim**, Anika Patel, Richard Beuttler, Sun Yang*	52	2:45-3:15 pm
O9	Role of PGRMC2: Insights from a Cardiomyocyte-Targeted Knockout Mouse Model ***Vivian La**, Farideh Amirrad, Miram Albotaif, Sha Webster, Surya M. Nauli*	53	2:45-3:15 pm

Poster Presentation Abstracts

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28	Sustained hepato-specific LRP-1 silencing exacerbates Alzheimer's disease pathology in mice ***Devaraj V. Chandrashekar**, Urvashi R. Panchal, G. Chuli Roules, Nataraj Jagadeesan, Josephine Chu, Derick Han, Rachita K. Sumbria*	34	3:15-4:30 PM
13	Development and Synthesis of an MCC-Doxorubicin Conjugate as a Precursor for Peptide-Drug Conjugate Therapeutics ***Keon Niles Jafari**, Kamaljit Kaur*	19	3:15-4:30 PM
19	Predictors of longitudinal symptom trajectory in young adults with low back pain. ***Jules Leigh**, Jo Armour Smith*	25	3:15-4:30 PM
23	Anticoagulation Treatment Outcomes in the Long-Term Acute Care Population ***Thuy Vi Nguyen**, Viet-Huong Nguyen*	29	3:15-4:30 PM
30	Evaluating the Impact of a Utilization Management Pharmacist's Interventions in a Medical Group ***S. Salazar**, J. Lewis*	36	3:15-4:30 PM
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2	Exploring microbial natural products from unique niches for novel antibiotics targeting Gram-negative bacteria ***J. Amaya Jr, A**. Thammavongsa, Y-HC Lin, S. Ly, R. Hsieh, SI. Elshahawi*	8	12:45-2:15 PM
3	Trends in FDA approvals of cardiovascular drugs from 1980 to 2024 ***A. Bakare**, A. Alexander, M.L. Fleming, E. Seoane-Vazquez*	9	12:45-2:15 PM

4	A novel 16-mer analog of neuroprotective peptide AC253 ***Riad Bellili**, David Salehi, Kamaljit Kaur*	10	12:45-2:15 PM
7	Brain delivery of erythropoietin results in a significant reduction of brain Aβ and improvement in spatial memory in the AppSAA knock-in mouse model ***Rudy Chang**, Devaraj V. Chandrashekar, Nataraj Jagadeesan, G. Chuli Roules, Emi Iwasaki, Rachita K. Sumbria*	13	12:45-2:15 PM
9	Exploring hepatic amyloid precursor protein (APP) as a source of peripheral amyloid-beta (aB): Implications in alcohol-dependent Alzheimer's disease (AD) ***Josephine Chu**, Ross A. Steinberg, Devaraj V. Chandrashekar, Brian Carson, Rachita K. Sumbria, Derick Han*	15	12:45-2:15 PM
10	Cyclic antimicrobial peptides containing arginine mimics ***D. Davani-Davari**, N. Salem El-Sayed, E. Mohammed, R.K. Tiwari, K. Parang*	16	12:45-2:15 PM
12	Risks of bisphenol alternatives on human embryonic stem cell osteoblast differentiation ***Nneamaka Iwobi**, Nicole R.L. Sparks*	18	12:45-2:15 PM
15	Proteomic profiling of Neem (A*zadirachta indic*a) leaves ***Abigail Kahsay**, Basir Syed, Aftab Ahmed*	21	12:45-2:15 PM
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18	Specificity of antimicrobial peptide interactions with cell membrane ***Srishhti K Jha***	24	12:45-2:15 PM
21	Functional analysis of a thyroglobulin variant in its C-terminal cholinesterase-like (ChEL) domain: Implications for congenital hypothyroidism ***Berenice Morales-Rodriguez**, Jessie Tsai, Jennifer Le, Cintia E. Citterio*	27	12:45-2:15 PM
22	Mechanistic insights of Trp-modified daptomycin antibiotic ***D.N. Nguyen**, A. Oum, D.V. Chandrashekar, R.K. Sumbria, I. Maslennikov, S.I. Elshahawi*	28	12:45-2:15 PM

26	The role of neonatal Fc receptor in transferrin receptor- antibody fusion protein pharmacokinetics ***Adenike Oyegbesan**, Nataraj Jagadeesan, Devaraj V. Chandrashekar, Rachita K. Sumbria*	32	12:45-2:15 PM
27	Effectiveness of intravesical BCG in the treatment of non-muscle invasive bladder cancer: An umbrella review ***Gerald Ozota**, Ogbonna Emmanuella, Sabastine Ruth, Eze Shadrach, Ben-Umeh Kenechukwu, Lawrence Brown*	33	12:45-2:15 PM
6	Chronic heavy alcohol intake and liver-specific LRP-1 reduction increase amyloidosis in Alzheimer's disease mice *Devaraj V. Chandrashekar, G. Chuli Roules, Ross A. Steinberg, **Urvashi R. Panchal**, Nataraj Jagadeesan, Adenike Oyegbesan, Trinh, Roselyn, Joshua Yang, Sharda R. Bhagwat, Hiya Rakholia, Rutvi D. Mevawala, Derick Han, Rachita K. Sumbria*	12	12:45-2:15 PM
29	Impact of Western diet-induced liver changes on Alzheimer's disease ***G. Chuli Roules**, Devaraj V. Chandrashekar, Nataraj Jagadeesan, Josephine Chu, Derick Han, Rachita K. Sumbria*	35	12:45-2:15 PM
34	Breast cancer drugs approved by the US Food and Drug Administration, 1980-2024 ***Daniel Umoru**, Wonsuk Choi, Enrique Seoane-Vazquez, Lawrence Brown*	40	12:45-2:15 PM
35	Characterizing immunoproteasome mediated antigen presentation using bioorthogonal labeling ***Shawn Vinogradsky**, Cody Loy, Darci J. Trader, Darci Trader*	41	12:45-2:15 PM
38	A peptide-drug conjugate targeting triple-negative breast cancer enhances drug uptake in mice tumors ***Jane (Shih-Jing) Yao**, Kamaljit Kaur*	44	12:45-2:15 PM
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8	The Role of Artificial Intelligence in Enhancing Patient Safety: A Scoping Review ***Jasmine Cho**, Reza Taheri*	14	3:15-4:30 PM
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14	Global Systemic Review of Pharmacist's Roles in Antimicrobial Stewardship Program Guidelines: A Protocol ***H. Jeong**, M. Phung, B. Leung, B. Langford, A. Arora, C. Lee, I. Portillo, A. Kang*	20	3:15-4:30 PM
16	Targeted Cancer Therapies: Advances in PDCs, ADCs, and Radioligand Approaches ***Shelby Kim**, Stacy Dong, Kamaljit Kaur*	22	3:15-4:30 PM
20	Soil Bacteria Isolated from Unexplored Ecological Niches as Source for Bioactive Natural Products ***Stephanie Ly**, Alan Thammavongsa, Yu-Hsin Cindy Lin, Aws Al-Hashimi, Rayann Hsieh, Sherif Elshahawi*	26	3:15-4:30 PM
24	Enzyme Immobilization for Large-Scale Biocatalytic Synthesis of Novel Antibiotic Analogs with Enhanced Antimicrobial Activity ***Alice Oum**, Diem N. Nguyen, Sherif I Elshahawi*	30	3:15-4:30 PM
25	The Impact of Shadowing Experiences on Early PharmD Students' Understanding of Clinical Pharmacist Roles ***Alice Oum**, Priscilla Sajonas, Gary Fong*	31	3:15-4:30 PM
31	Genetic Insights into Alcohol-Induced Alzheimer's Pathology using Gene Expression Analysis ***Tila Nguyen**, Rayna Thomas, Ashley Duche, Devaraj V. Chandrashekar, Rachita K. Sumbria, Moom Roosan*	37	3:15-4:30 PM
32	Role of fibroblast and macrophage-derived cytokines and chemokines in the ocular GVHD associated conjunctival fibrosis ***Ethan Tran**, Karthikeyan Ramasamy, Ajay Sharma*	38	3:15-4:30 PM
33	Differential Expression of Brain Transferrin Receptors in a Tauopathy (PS19) Mouse Model ***Katelyn Truong**, Nataraj Jagadeesan, Rachita K. Sumbria*	39	3:15-4:30 PM
36	Endogenous Triiodothyronine in Cardiometabolic Health ***Catherine K. Vu**, Rachel T. Nguyen, Sha Webster, Gabriel T. Malik, Christian Kremser, Bernhard Radlinger, Susanne Kaser, Cintia E. Citterio*	42	3:15-4:30 PM
37	Development of a Plastic Waste Calculator to Help Clinicians Make More Sustainable Antimicrobial Choices ***Tien Dinh**, Misty Vu, Gary Fong, Pamela Lee*	43	3:15-4:30 PM

Poster No.	Abstracts
1	**Engineering lipid-polymer nanoparticles for siRNA delivery to breast cancer cells** ***Abdulelah Alhazza****, Hamidreza Montazeri Aliabadi, Hasan Uludag* RNA interference (RNAi) is a powerful tool that can specifically target the expression of virtually any protein without the expensive and time-consuming drug development studies. Despite the initial excitement and extensive efforts, the potential impact of RNAi approaches is yet to be materialized fully in clinical settings. This is mainly due to the challenges in delivering RNA molecules. Lipid nanoparticles (LNPs) have been the leading delivery system for nucleic acids, an achievement established by introducing the first FDA approved small interfering RNA (siRNA) drug and COVID-19 vaccine to clinics. However, targeted delivery to a solid tumor still eludes the developed LNPs. On the other hand, polymers are among the oldest delivery systems for nucleic acids, and polyethyleneimine (PEI) was once considered the gold standard in nucleic acid delivery. In this study, we introduce a novel lipid-polymer nanoparticle (LPNP) platform, meticulously engineered for targeted delivery of siRNA to cells implicated in breast cancer. We hypothesized that specially designed low molecular weight PEIs can partially or completely replace the ionizable lipids for a more accommodating structure for additional moieties, which could lead to a safer and more efficient nucleic acid delivery. We first optimized the LNP formulations as a point of reference for cellular uptake, cytotoxicity, and protein silencing efficiency, employing sophisticated designs facilitated by the Design-Expert software. Leveraging the optimal LNP formulation, we integrated specifically designed cationic polymers as partial or complete replacements for the ionizable lipid. This methodological approach, incorporating optimal combined designs and response surface methodologies, refined the LPNPs to an optimal efficiency. Our results indicate that these refined LPNPs enhance the delivery of siRNA, leading to efficient gene silencing in targeted cancer cells. The improved delivery efficiency not only underscores the potential for specific therapeutic applications but also suggests a broader utility for this platform in various cancer treatments.

2	**Exploring microbial natural products from unique niches for novel antibiotics targeting Gram-negative bacteria** ***J. Amaya Jr**, A. Thammavongsa, Y-HC Lin, S. Ly, R. Hsieh, SI. Elshahawi* Due to their distinctive structure, Gram-negative bacteria tend to be more resistant to antibiotics and cause significant morbidity and mortality worldwide. Multidrug-resistant Gram-negative bacteria poses a critical threat to global health, necessitating the discovery of new antibiotics with novel mechanisms of action. The World Health Organization declared in 2015 antimicrobial resistance a global emergency and in 2017 published a list of resistant priority pathogens. This list was updated in 2024 to reflect the evolving landscape of resistance and to guide research and development efforts towards these needs. Soil microbes from unusual environments represent an untapped reservoir of biodiversity and chemical novelty. These environments exert unique selective pressures, driving the evolution of microbes capable of producing specialized natural products (NPs) with potent bioactivity. In this study, we aimed to discover novel NPs targeting Gram-negative pathogens by screening soil microbes cultivated from these under-explored niches with minimal human impact, where microbial communities remain unaltered and highly specialized. Soil samples collected from unexplored areas were used to create a library of 962 pure bacterial strains. Previous work in our lab performed small-scale fermentation to obtain the crude organic extracts for each. In this work, we screen the crude extracts for activity against six Gram-negative pathogens including *Salmonella enterica*, *Serratia marcescens*, *Escherichia coli*, *Acinetobacter baumannii*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*. Moreover, the liquid chromatography-mass spectrometry (LC-MS) profiles for each extract was obtained. The combined data were used to prioritize a list of strains. The growth conditions for these “prioritized” strains were further optimized testing different microbiological media and different time points to obtain the best conditions for production of compounds with anti-Gram-negative bacterial inhibition and to ensure reproducibility. Through bioassay-guided fractionation, we will isolate and purify the NP responsible for the antibacterial activity using column chromatography, preparative thin layer chromatography and HPLC. We will elucidate the chemical structure of this compound using high-resolution mass spectrometry (HR-MS) and tandem MS in addition to 1- and 2D nuclear magnetic resonance (NMR) spectroscopy. This study highlights the potential of underexplored soil microbes as a source for novel NPs targeting Gram-negative bacteria. By leveraging the unique chemical diversity of these microbes, we aim to advance the development of new antibiotics to combat the growing threat of antimicrobial resistance.

3

Trends in FDA approvals of cardiovascular drugs from 1980 to 2024

***A. Bakare**, A. Alexander, M.L. Fleming, E. Seoane-Vazquez*

Objectives: Approximately 20% of all deaths in the United States in 2022 were attributed to heart disease. Although cardiovascular disease remains a significant health burden, innovation in the field of cardiovascular drug development and approval has markedly decreased in recent decades. We assessed the trends in FDA approvals for cardiovascular medicines over a 45-year period from 1980 to 2024.

Methods: We collected information for new molecular entities (NME) and new therapeutic biologics cardiovascular drugs approved by the FDA between 1980 and 2024 via publicly available data from the FDA database, Orange Book, and Purple Book. Data were analyzed using descriptive analysis.

Results: A total of 123 drugs were approved during 1980-2024,102 (82.9%) remain marketed, and 21 (17.1%) were discontinued as of December 31, 2024. NMEs represented 119 (96.7%) and BLA had 4 (3.3%) cardiovascular drug approvals. There were 34 (27.6%) cardiovascular drugs classified as first-in-class, 40 (32.1%) underwent fast-track review to expedite availability, 3 (2.4%) breakthrough therapy designation. There were 17 (13.8 %) drugs that received orphan drug designation at first approval. The highest number of approvals occurred between 1980-1989. Cardiovascular drug approvals declined from an average of 4.0±3.3 from 1980-1989 to 1.3±0.7 from 2020-2024. Cardiovascular drugs represented 6.9% of the total new drug approvals in the study period.

Conclusions: Most cardiovascular drugs approved by the FDA from 1980-2024 did not represent an improvement over the therapies already available in the market, with only three new drugs designated by the FDA with breakthrough therapy designation. The highest number of approvals occurred between 1980 and 1989; the analysis shows a decline in cardiovascular drug approvals over the study period. Innovation in cardiovascular drug development remains critical to addressing unmet medical needs in this therapeutic area.

4	**A novel 16-mer analog of neuroprotective peptide AC253** ***Riad Bellili**, David Salehi, Kamaljit Kaur* Amylin receptor antagonist AC253 is a 24-amino acid peptide that provides neuroprotection against amyloid beta (Aβ)-induced cell death and toxicity. Additionally, AC253 has been shown to improve spatial memory in mouse models of Alzheimer's disease (AD). Based on previous structure-activity relationship studies, we have designed a novel 16-mer analog of AC253. The goal of this study is to evaluate proteolytic stability of the 16-mer peptide analog in both human and mouse serum. This presentation will report results related to the solid-phase synthesis, characterization by MALDI-TOF mass spectrometry and reversed-phase HPLC, half-life of the 16-mer in serum, truncation sites revealing fragments, and strategies for stabilizing the 16-mer.

5

Hepatocyte-specific LRP1 silencing exacerbates brain amyloidosis without compensatory LDL receptor family involvement

***Brian C. Carson**, Josephine Chu, Dakoda M. Talamantes, Devaraj V. Chandrashekar, Jerome Garcia, Rachita K. Sumbria, Derick Han*

LDL)-receptor related protein 1 (LRP1) is a major hepatic receptor involved in lipoprotein metabolism, protease degradation, transmembrane receptor modulation, and clearance of excess protein, such as Aβ. Decreased LRP1 expression due to liver injury can impair receptor-mediated clearance, increasing peripheral Aβ. We investigated the effects of hepato-specific silencing of LRP1 on brain Aβ deposition. Other LDL-family members (LRP5, LRP6, LDLR) that may participate in Aβ clearance were monitored in the liver to ensure non-compensatory effects of LRP1 silencing. 4-month-old male double transgenic (APP/PS1) AD mice were injected with adeno-associated virus 8 (AAV8) containing microRNA targeting LRP1 (LRP1-silenced) or LacZ (control)(n=6-7 per group). Organs were harvested 12- and 28-weeks post injection, homogenized and assayed using western blotting. Western blots of liver homogenates were probed for LDL-receptor related proteins (LDLR, LRP1, LRP5, LRP6), receptors involved in Aβ clearance (RAGE, MDR1), and AD biomarkers (APOE) with beta-actin and GDH as loading controls. Brain and liver Aβ were quantified using sandwich enzyme-linked immunosorbent assays (ELISA). Hepatic LRP1 (hLRP1) was silenced >80% in both 12- and 28-week mouse samples ($p \leq 0.05$) compared to AAV8 LacZ control. hLRP1 silencing significantly increased TBS-soluble mouse (mAβ42) and human (hAβ42) amyloid beta levels in the brain and hAβ42 in the periphery ($p \leq 0.05$). No significant change in hepatic MDR1 or APOE expression was observed. Hepatic APP showed a non-significant increasing trend in expression with LRP1 silencing. Hepatic LDL-receptor family proteins did not show significant changes at 12- or 28-weeks. hLRP1-mediated clearance of peripheral Aβ plays an important role in mitigating brain amyloidosis. hLRP1 downregulation in AD mice correlates with brain amyloidosis that is neither the result of LDL-family expression compensation nor changes in receptors involved in Aβ clearance. Hepatic LRP1 specifically may hold promise as a therapeutic target, especially in obesity and alcoholism, known modifiable risk factors for AD.

6

Chronic heavy alcohol intake and liver-specific LRP-1 reduction increase amyloidosis in Alzheimer's disease mice

Devaraj V. Chandrashekar, G. Chuli Roules, Ross A. Steinberg, ***Urvashi R. Panchal****, Nataraj Jagadeesan, Adenike Oyegbesan, Trinh, Roselyn, Joshua Yang, Sharda R. Bhagwat, Hiya Rakholia, Rutvi D. Mevawala, Derick Han, Rachita K. Sumbria*

Background: Chronic heavy alcohol drinking may be a modifiable risk factor for Alzheimer's disease (AD), but studies in rodent AD models more closely mimic chronic moderate alcohol drinking in humans and largely focus on the brain. The role of the liver, which is significantly impacted by chronic heavy alcohol intake, in driving brain changes in alcohol-dependent AD remains unexplored. Our study using intragastric-ethanol feeding, which mimics chronic heavy alcohol intake in humans, in C57BL/6J mice showed significant AD-relevant changes in the brain and liver. Therefore, we aimed to investigate how hepatic changes using this model of chronic heavy drinking drive AD pathology in AD mice, which has never been attempted.

Methods: Eight-month-old male APP/PS1 mice were fed with ethanol or control diet intragastrically for 5 weeks (n=7-11/group). Brain and liver Aβ were assessed using immunoassays. The contribution of three important mechanisms underlying brain amyloidosis was investigated: hepatic LRP-1 (major peripheral regulator of Aβ), blood-brain barrier (BBB) function (vascular regulator of Aβ), and microglia (major brain regulator of Aβ) using immunoassays. To elucidate the role of hepatic LRP-1 in brain amyloidosis, hepatic LRP-1 was silenced by injecting LRP-1 microRNA delivered by the adeno-associated virus 8 (AAV8) and the hepato-specific thyroxine-binding globulin promoter to 4-month-old male APP/PS1 mice (n=6). Control APP/PS1 mice received control AAV8 (n=6). Spatial memory was assessed 12 weeks after LRP-1 silencing using Y-maze, and brains and livers were harvested to detect Aβ.

Results: Chronic heavy alcohol feeding significantly increased aggregated Aβ ($p<0.05$) by ELISA and 6E10-positive Aβ load ($p<0.05$) by immunostaining in APP/PS1 mice brains. Alcohol feeding significantly reduced plaque-associated microglia in APP/PS1 mice. Further, alcohol-fed APP/PS1 had liver steatosis and significantly downregulated hepatic LRP-1 ($p<0.001$), and brain and hepatic Aβ were positively correlated ($p<0.05$). Hepato-specific LRP-1 silencing significantly increased brain Aβ load ($p<0.05$) in APP/PS1 mice and reduced entries into the novel arm of the Y-maze ($p<0.05$).

Conclusion: Chronic heavy alcohol intake reduced hepatic LRP-1 expression, and hepato-specific LRP-1 silencing increased brain Aβ and spatial memory deficits in APP/PS1 mice. Our results place hepatic LRP-1 as a potential key driver of brain amyloidosis in alcohol-dependent AD.

7

Brain delivery of erythropoietin results in a significant reduction of brain Aβ and improvement in spatial memory in the AppSAA knock-in mouse model

Rudy Chang, *Devaraj V. Chandrashekar, Nataraj Jagadeesan, G. Chuli Roules, Emi Iwasaki, Rachita K. Sumbria*

Background: While emerging Alzheimer's disease (AD) treatments show modest benefits, therapies targeting AD pathology with neuroprotective effects are desired. Erythropoietin (EPO) is neuroprotective but limited by poor brain penetration and hematopoietic side effects. To address this, EPO was conjugated with a transferrin receptor monoclonal antibody (cTfRMAb) to enable blood-brain barrier transport. This study evaluated the safety and pharmacokinetics of modified EPO in healthy mice, then tested its efficacy against Aβ pathology in App-SAA knock-in (KI) mice, a model of AD without human APP overexpression.

Methods: For the PK and safety study, a multidose design was employed with 10-week-old C57 male mice (n = 4–5/dose) receiving doses ranging from 1 to 20 mg/kg SQ for 4 weeks. The study aimed to evaluate dose-dependent brain and plasma concentrations, as well as the metabolic and hematologic safety of the modified EPO. The dose that demonstrated the highest safety, adequate brain exposure, and sustained plasma levels was subsequently administered subcutaneously to 5.5-month-old male APP-SAA KI mice (n = 6) for 14 weeks. Control APP-SAA KI mice (n = 5) received vehicle only. The effect of modified EPO on Aβ load (via immunoassays) and spatial memory (via Y-maze test) was assessed.

Results: The 1 mg/kg dose resulted in no adverse effects, robust brain exposure, and maintained sustained plasma exposure, supporting its suitability for longitudinal dosing. APP-SAA KI mice treated with the modified EPO showed a significant reduction (70–80%, $p < 0.001$) in 6E10-positive Aβ area and number in the brain. Aggregated Aβ measured by ELISA was also significantly lower ($p < 0.05$) with modified EPO treatment. Additionally, modified EPO increased the discrimination index for the novel arm ($p < 0.05$), suggesting improved spatial memory recall of the reinforced arm of the maze.

Conclusions: These findings provide essential data for dose optimization for longitudinal studies using TfRMAb-based therapeutics, and specifically modified-EPO used herein, and illustrate the therapeutic potential of the brain-penetrating EPO in a novel AD mouse model devoid of APP overexpression.

8

The role of artificial intelligence in enhancing patient safety: A scoping review

Jasmine Cho, *Reza Taheri*

Introduction: Healthcare industry is increasingly integrating artificial intelligence (AI) into systems and platforms. Machine learning algorithms, large language models, predictive analytics, and clinical decision support systems (CDSS) are examples of AI integration. Impact of these technologies on enhancing patient safety remains unclear.

Objective: The objective of this scoping review is to identify evidence linking AI with enhanced patient safety across various healthcare settings.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology for performing a scoping review was utilized to search PubMed, CINAHL, Cochrane, and IPA databases for relevant literature. Studies were identified using the search terms ("artificial intelligence" OR "machine learning") AND ("patient safety"). English language articles were screened from earliest available until February 21, 2025. Additionally, AI-powered search platforms, Google Gemini 2.0 Flash and 2.0 Flash Thinking Experimental and Perplexity Auto, Pro, R1, Deep, and o3-mini were utilized to screen for relevant literature. The following prompts were used for search in the AI platforms "What is the evidence linking artificial intelligence with enhanced patient safety? Provide evidence from primary, secondary, and tertiary literature. Clearly identify which sources are primary vs secondary vs tertiary literature. Cite all references.".

Results: A total of 1,057 studies were initially identified with the search terms utilizing traditional search engines. After review of title/abstract, 481 articles remained eligible for full text review. Currently full text articles are being extracted for review. The AI search yielded 27 studies after screening for duplicates. One duplicate article was identified across all 7 search engines followed by 5 engines identifying another article. Further analysis of the AI search results are in progress.

Conclusions: Search of traditional databases and AI tools yielded a number of articles meeting inclusion criteria. Further analysis is in progress to evaluate evidence linking AI with enhanced patient safety.

9

Exploring hepatic amyloid precursor protein (APP) as a source of peripheral amyloid-beta (aB): Implications in alcohol-dependent Alzheimer's Disease (AD)

Josephine Chu, *Ross A. Steinberg, Devaraj V. Chandrashekar, Brian Carson, Rachita K. Sumbria, Derick Han*

Background: Alcohol-induced liver injury occurs in the pericentral region of the liver and can induce mitochondrial remodeling and exacerbate Alzheimer's Disease (AD) progression. Mitochondrial subpopulations such as the general mitochondria (GM), peridroplet mitochondria (PDM) and endoplasmic reticulum-bound mitochondria (ERM) are subpopulations that maintain cellular homeostasis and damage in these regions can contribute to AD pathogenesis. Hepatic amyloid precursor protein (APP) is a source of peripheral amyloid beta (aB) and can confer risk in AD pathology. Understanding the localization and expression of hepatic APP in mitochondrial subpopulations are therefore critical to understanding aB metabolism and may play a role in identifying a potential mechanism for metabolic dysfunction. Here, site-specific expression of hepatic APP and aB processing proteins are measured in the subpopulations of the mitochondria of ethanol-fed AD mice to identify the regions where aB metabolism occurs.

Method: Double transgenic (APP/PS1) AD mice were intra-gastric fed with ethanol or control diet for 5 weeks (n =7-11/group). Liver tissue was harvested for digital spatial profiling (DSP) analysis to measure pathogenic AD biomarkers (APP, PSEN1, BACE1) in the periportal and perivenous regions. Mitochondrial fractions were isolated using differential centrifugation and amyloid beta was pulled down using co-immunoprecipitation.

Result: Hepatic APP expression increased 2-fold and PSEN1 increased over 5-fold in the mitochondria compared to the cytosol of both ethanol-fed and non-ethanol fed AD mice ($p \leq 0.05$). APP expression increased in the GM and ERM but not in the PDM of ethanol-fed mice compared to control ($p \leq 0.05$). APP transcript increased in the pericentral region of ethanol-fed mice ($p \leq 0.05$) and both APP and aB showed an increased trend at the protein level ($p=0.06$ and $p=0.07$, respectively).

Conclusion: Increased expression of APP in the GM and ERM suggests that hepatic mitochondria may be a source of peripheral aB. AD-associated mitochondrial genes and AD pathological hallmarks are specifically expressed in the perivenous region, which is the site of alcohol-induced liver injury and suggests a link between alcohol induced liver injury and AD. Localization of aB in hepatic mitochondria suggests that aB processing in the liver may be a source of aB in the periphery and brain. Future studies modulating hepatic APP in vivo will provide future insights on the contribution of hepatic aB on AD pathogenesis.

10	**Cyclic antimicrobial peptides containing arginine mimics** ***D. Davani-Davari,*** *N. Salem El-Sayed, E. Mohammed, R.K. Tiwari, K. Parang* Cyclic antimicrobial peptides (CAMPs) offer a promising alternative to conventional antimicrobial peptides (AMPs), which face challenges such as serum instability, hemolytic effects, and toxicity at high intravenous doses. The cytotoxicity of AMPs is largely attributed to arginine (R), a positively charged residue. This study focuses on engineering CAMPs with arginine-mimicking residues to enhance antibacterial efficacy while reducing toxicity by modifying the pKa of the positively charged residues. Three classes of CAMPs were synthesized: piperidine-based cyclic peptides (PBCPs), 4-guanidinophenylalanine-based cyclic peptides (GBCPs), and Dab-based cyclic peptides (DBCPs), where Dab is L-(2,4-aminobutyric acid). The goal was to determine whether replacing R residues with less basic positively charged amino acids improves bacterial selectivity and reduces cytotoxic effects. Among PBCPs, [R2(Pip)3W4] and [R4PipW4] demonstrated potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa, with MIC values of 8 μg/mL and 32 μg/mL, respectively. They showed no significant cytotoxicity (CC50 > 300 μg/mL) in MRC-5, HEK293, HepG2, and H9C2 cells, showing improved safety compared to IFX 301. In the GBCP series, [(Fg)5W4], [R(Fg)4W4], [R2(Fg)3W4], and [R3(Fg)2W4] were synthesized, incorporating 4-guanidinophenylalanine (Fg). These compounds exhibited lower cytotoxicity than [R5W4] in HEK-293 cells, maintaining 93-100% cell viability at concentrations below 50 μg/mL. However, [R5W4] demonstrated stronger antibacterial activity, with MIC values of 4–16 μg/mL against various bacteria, whereas [Fg)5W4] had higher MIC values (32–128 μg/mL). Among the DBCPs containing Dab, [R2(Dab)3W4] demonstrated enhanced antimicrobial activity compared to [R5W4]. Specifically, it exhibited twofold higher potency against MRSA LAC (MIC = 4 μg/mL) and fourfold higher activity against P. aeruginosa (ATCC 27853) (MIC = 8 μg/mL), whereas [R5W4] had an MIC of 32 μg/mL. These results indicated the potential of CAMPS with arginine mimics as alternative antimicrobial agents with better safety profile.

11	**Harnessing artificial intelligence to optimize antimicrobial stewardship programs: A scoping review** ***Philip Tran**, Tien Dinh, Ivan Portillo, Emi Minejima, Amy Kang* Antimicrobial stewardship programs (ASP) commonly use prospective audit with feedback (PAF), but this can be labor intensive. Improving efficiency in PAF activities is crucial. While there have been several publications that investigated the use of artificial intelligence (AI) to identify interventions that may lead to actionable plans, there has yet to be a comprehensive review of the literature on this topic. The search was conducted on July 10, 2024 across Ovid Medline, Embase, IPA, Web of Science, and CINAHL using keywords such as "antimicrobial stewardship," "antibiotic stewardship," "machine learning," and "artificial intelligence,". The search covered all articles from the start of each database until July 2024. Two reviewers independently evaluated articles for inclusion using Rayyan software, with a third reviewer to resolve conflicts. The data extraction was performed through REDCap after a pilot test of 3 articles following a predeveloped data extraction form. Extracted data underwent a verification process by a second team member, and discrepancies were resolved by a third team member. The quality of the articles was assessed using the Newcastle-Ottawa Scale (NOS) to help gauge quality and bias. Our search yielded over 105 articles. Out of those 105 articles, 5 were included at the end of extraction. This scoping review aims to provide a comprehensive overview of the current research on the utilization of AI and machine learning technologies in ASPs, and how these technologies impact the workload and intervention strategies of ASP pharmacists. By synthesizing available evidence, this review will identify gaps in the literature and assess the potential for AI-driven models to enhance the efficiency of ASPs and reduce the workload of infectious disease pharmacists. The findings of this review are expected to inform future research directions and the feasibility of integrating AI into clinical workflows to optimize antimicrobial stewardship efforts

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Risks of bisphenol alternatives on human embryonic stem cell osteoblast differentiation

Nneamaka Iwobi, *Nicole R.L. Sparks*

Bisphenols, particularly bisphenol A (BPA), are a well-known endocrine disrupter widely used in consumer products. They are pervasive in the environment and contaminate marine waters, rivers, and even the air. The adverse health effects of BPA exposure have been well studied, leading to restrictions on BPA usage. In substitution, increased usage of bisphenol F (BPF) and bisphenol S (BPS) has increased. Studies have shown BPA to inhibit osteoblast differentiation and promote osteoblast apoptosis, which can result in long-term effects on bone health. However, embryonic exposure of BPF and BPS on bone differentiation and maturation is unclear. Here we explore the developmental toxic effects of BPA, BPF, and BPS on osteoblast development. Human embryonic stem cells (hESCs) of the H9 line were osteogenically differentiated using 1,25(OH)2 vitamin D3 (VD3), β-glycerophosphate (βGP), and ascorbic acid (AA). Human ESCs were exposed to increasing 0.0001-100 μM doses of BPs during the osteogenic differentiation process. BPA and BPF dose-dependently inhibited hESC osteoblast cell viability and osteoblast, measured by MTT and alkaline phosphatase (ALP) assays. Interestingly, BPS did not cause cell death at 100 μM but did decrease osteoblast differentiation. We present that BPA and BPF exposure affected osteoblast development through cytotoxicity. More alarming, BPS did not cause cytotoxicity but inhibited the osteoblast differentiation and mineralization process. These findings promote the need for more studies focusing on the mechanistic effects of BP exposure and to further clarify the usage of perceived safer BP alternatives.

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Development and synthesis of an MCC-doxorubicin conjugate as a precursor for peptide-drug conjugate therapeutics

Keon Niles Jafari*, Kamaljit Kaur*

In the last decade, Peptide-Drug conjugates have arisen as promising alternatives to traditional methodologies, such as Chemotherapies, in treating various types of cancer. The general structure of a PDC comprises three main elements: A drug, a linker, and a peptide. The cytotoxic drug serves as a targeting agent for eliminating or inhibiting cell proliferation, providing therapeutic relief in hard-to-reach cancer locations. The linker connects the cytotoxic drug to the peptide selected; its stability is vital in preventing premature drug release in the bloodstream and must ensure drug delivery under specific release conditions (i.e., pH, enzymatic cleavage, etc.). The peptide constructed directs the conjugate of the target of interest with increased specificity by binding to overexpressed receptors or overexpressed biomarkers viewed on disease cancer cells. Certain peptides have been noted in their ability to penetrate cells deeper than larger molecules, such as antibodies, reducing peripheral toxicity to surrounding healthy cells and tissues.2 The peptide of interest is a highly specific proteolytically stable breast cancer cell targeting peptide (WxEAAYQrFL) conjugated to a drug, Doxorubicin (DOX), to synthesize peptide-DOX thioether.1 Hence, we performed the initial steps of constructing a PDC, involving the synthesis of combining a drug, DOX, with its linker, Microcrystalline Cellulose (MCC), where later can be incorporated with a unique peptide targeting a specific tumor location to view its effects.

14

Global systemic review of pharmacist's roles in antimicrobial stewardship program guidelines: A protocol

***H. Jeong**, M. Phung, B. Leung, B. Langford, A. Arora, C. Lee, I. Portillo, A. Kang*

Introduction: The escalating global threat of antimicrobial resistance (AMR) demands a coordinated interdisciplinary response. Antimicrobial stewardship programs (ASPs) are a key initiative to optimize antimicrobial use and mitigate AMR. However, the specific roles and responsibilities of pharmacists within ASPs exhibit considerable variability between and within countries. Addressing these differences can enhance the impact of pharmacists in ASPs and strengthen efforts to combat AMR worldwide.

Study Objective: This systematic review aims to evaluate the commonalities and variations in national and international guidelines for antimicrobial stewardship programs (ASPs) regarding the role of the pharmacist.

Methods: A comprehensive search was conducted using both indexed and grey literature sources. Additionally, searches were performed on international public health organizations and associations identified by ChatGPT 3.5. This search focused on national, multinational, or international guidelines related to antimicrobial stewardship without any restrictions on language or publication date. Guidelines focusing on non-human populations, antimicrobial treatment of specific infectious diseases, and documents not considered guidelines were excluded.

Covidence was used by two investigators to screen independently for eligibility with discrepancies resolved by discussion. Data extraction will be conducted through a pre-developed form with predefined outcomes of interest (including key ASP activities, staffing requirements, and recommendations regarding the role of pharmacists, and other clinicians, for each ASP activity). A second investigator will verify the extracted data, and a third will resolve any discrepancies. The quality of each guideline will be assessed using the AGREE II instrument by two independent investigators.

Planned Data Analysis: The extracted data will be descriptively summarized and thematically organized based on key concepts. A summary table will compile the findings, illustrating key similarities and differences across guidelines to identify overarching themes and gaps related to the role of the pharmacist in ASPs.

15

Proteomic profiling of Neem (*Azadirachta indica*) leaves

Abigail Kahsay, *Basir Syed, Aftab Ahmed*

With the increasing use of plant-based medicine, Neem tree stands out as the mystical medicinal tree with countless pharmaceutical benefits. The neem tree is a tall and drought-resistant plant that has been expanding from Asia to Africa for centuries. Neem (*Azadirachta indica*) is a member of the plant family *Meliaceae*. Neem plant is a wholesome blessing, and all its components, including leaves, seeds, and bark, are beneficial in many aspects of pharmaceutical science. Even though there is limited research on Neem, peptides found in the leaves have shown significant contributions in bioactivity-assay, including anti-cancer, antibacterial, and anti-microbial properties, making it an excellent candidate for Proteomic studies. Neem contains several compounds primarily responsible for its bioactive properties, like *Limonoids*, *Azadirachtin*, *Nimbin*, and *Nimbidin*, all belonging to the small molecules. The Swiss- Prot database searches revealed only three proteins from Neem: Tircalladinol synthase, Melianol synthase, and Dihydrniloticin. Our study focuses on global proteome analysis, employing analytical techniques for extracting, purifying, and characterizing proteins from Neem leaves. The defatted neem leaves were in n-hexane, followed by the extraction in 20mM Tris/HCl, pH8 buffer, and precipitated using 80% ammonium sulfate. The crude extract was dialyzed and lyophilized in water using a 3.5 MWCO dialysis tubing. Partial purification was achieved using gel filtration chromatography (SEC) on the Hiload Superdex -200 column. SDS-PAGE electrophoresis using a 10% Tris/Glycine gel confirms protein bands of MW of the proteins from 10 to 70 kDa. The Proteomic profiles were established by peptide mass fingerprinting using LC/MS/MS. Bioinformatic analysis via PeakStudio-X and Uniprot KB TrEMBL, Viridiplantae database revealed four protein groups and 25 proteins at FDR of ≤ 1 and with 2 minimum unique peptide matches.

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Targeted cancer therapies: Advances in PDCs, ADCs, and radioligand approaches

Shelby Kim, *Stacy Dong, Kamaljit Kaur*

Cancer therapy focuses on delivering therapeutic agents to cancerous cells in order to neutralize them, induce apoptosis, and eradicate the disease. However, limitations in traditional drug delivery methods have driven the need for more precise, targeted approaches. By identifying overexpressed receptors in cancer cells, researchers have developed peptide-drug conjugates (PDCs) and antibody-drug conjugates (ADCs) to selectively bind to these receptors and deliver therapeutic agents directly to tumors while minimizing exposure to healthy tissues. Receptors such as HER2, somatostatin, and Nectin-4 serve as key targets for these therapies. Antibodies and peptides are designed to bind to these receptors and are internalized by cancer cells where the drug is released in a controlled manner. This review aims to summarize receptor targets for PDCs and ADCs by outlining their potential uses in imaging and targeted drug delivery, as well as highlighting the role of current PDC and ADC therapies in cancer treatment. Several ADCs received FDA approval for cancer therapy. Additionally, radioligand therapy (RLT) which selectively targets cancer cells via overexpressed receptors has also been approved for cancer treatment. Despite their potential in cancer therapy, RLTs, PDCs, and ADCs face challenges including insufficient efficacy, off-target toxicity, and manufacturing difficulties. Arising resistance mechanisms within cancer cells is one of the reasons for reduced ADC efficacy. Ongoing clinical trials aim to enhance receptor specificity, improve diagnostic accuracy, and refine targeted drug delivery to maximize therapeutic outcomes while minimizing adverse effects.

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Enhancing proteasomal activity: Effects of small molecule stimulators on cellular growth and stress adaptation

Kate Kragness, *Darci Trader*

Proteasome activity plays a crucial role in maintaining cellular homeostasis, and the enhancement of its activity has been associated with increased resistance to cellular stress. While genetic manipulation has traditionally been used to upregulate proteasome function, small molecule proteasome stimulators offer a promising alternative. In this study, we investigated the effects of the small molecule proteasome stimulators Miconazole (MO) and TCH-165 on proteasome activity, cellular growth, metabolism, and endoplasmic reticulum (ER) stress response. Our findings show that both compounds effectively enhance proteasome activity in HEK-293T, MRC-5 fibroblasts, and U87 glioblastoma cells without inducing cancer-like properties such as uncontrolled proliferation or metabolic reprogramming. Additionally, we explored their role in modulating XBP1 signaling during ER stress and found that pre-incubation with a 20S proteasome stimulator prior to ER stress induction significantly reduces XBP1 signaling. These results highlight the potential of small molecule proteasome stimulators as safe therapeutic candidates for proteostasis-related diseases, such as neurodegeneration, without increasing tumorigenic risk. Further research is needed to assess their long-term effects across diverse cellular models and refine their molecular structures for enhanced therapeutic efficacy.

18

Specificity of antimicrobial peptide interactions with cell membrane

Srishhti K Jha

Antimicrobial resistance (AMR) poses a crucial public health threat, responsible for approximately 35,000 deaths annually in the United States and directly linked to 1.27 million fatalities globally in 2019. The growing incidence of AMR, primarily fueled by the misuse and overuse of antimicrobials in human, animal, and agricultural sectors, necessitates the urgent need for alternative therapeutic strategies. This project investigates antimicrobial peptides (AMPs) as viable alternatives to conventional antibiotics. Dr. Parang's group synthesized a number of short amphiphilic cyclic peptides that exhibited antimicrobial activity, with minimum inhibitory concentrations (MIC) against various pathogenic microorganisms ranging from 1.5 to 3.1 µg/ml. Minor variations in peptides' sequences significantly affected their toxicity, with 50% hemolysis observed at concentrations between 70 and 230 µg/ml. We employed a series of biophysical techniques, including nuclear magnetic resonance (NMR), fluorescence quenching, and surface plasmon resonance (SPR) to assess the interactions of these peptides with different models of cell membrane. We utilized liposomes (Large unilamellar vehicles, LUV) to mimic a bacterial (DOPC:DOPG at a 70:30 molar ratio) or mammalian (DOPC: Cholesterol at a 90:10 molar ratio) membranes. Our 1H- and 31P-NMR studies of peptide mixtures with bacterial membrane-mimic liposomes revealed a transition from broad anisotropic signals characteristic of stable LUVs to relatively narrow isotropic signals of smaller, disrupted lipid particles with the increase of peptide concentration, thus confirming the membrane-active mechanism of these AMPs. In contrast, no effect or minimal increase in signal linewidths was detected for the mammalian membrane-mimic liposomes. In conclusion, our findings enhance the understanding of the structural basis for the specificity of these peptides toward bacterial versus mammalian membranes, highlighting their potential for development as therapeutic agents against drug-resistant pathogens.

19

Predictors of longitudinal symptom trajectory in young adults with low back pain.

***Jules Leigh**, Jo Armour Smith*

The severity and frequency of painful episodes change over time in individuals with chronic low back pain (LBP). Recalling previous episodes' severity/frequency is often considered inaccurate. This study's purpose was to determine if recall of LBP history or psychological characteristics are predictors of future symptom trajectories in young adults with LBP.
The 57 young adult participants had a year or more history of LBP and were not currently in pain. Baseline LBP history was characterized by recall of pain severity and frequency during symptomatic episodes. Participants completed measures of anxiety, depression, and fear avoidance beliefs. Pain trajectories were tracked via survey every 2 months for 18 months, where participants identified average and worst pain. Participants were grouped based on pain trajectories over the follow-up period using latent class analysis (LCA). Logistic regression was used to identify if LBP history or psychological traits were predictors of average and worst pain trajectories.

The survey completion rate was 95%. LCA found two sub-groups for both average and worst pain trajectories, where individuals in the adverse trajectory group had more severe and frequent episodes than the less adverse group ($p < 0.01$ for both comparisons). Predictors of more adverse average pain were typical pain ($p = 0.01$), symptom frequency ($p = 0.02$) at baseline, and depression score ($p = 0.04$) (percentage accuracy in classification (PAC) 84.9%, omnibus $p = 0.0004$). Predictors of more adverse worst pain were typical pain ($p = 0.05$) and depression at baseline ($p = 0.02$) (PAC 69.8%, $p = 0.02$).

Even during no pain, self-reporting pain history is predictive of future LBP episodes. Determining factors that predict symptom fluctuation across lifespans is essential to enhance LBP management. As depression is linked with more adverse history of LBP longitudinally, clinicians should assess psychological traits in young adults with chronic pain.

20	**Soil bacteria isolated from unexplored ecological niches as source for bioactive natural products** ***Stephanie Ly**, Alan Thammavongsa, Yu-Hsin Cindy Lin, Aws Al-Hashimi, Rayann Hsieh, Sherif Elshahawi* Natural products (NPs) represent a cornerstone of pharmaceutical discovery, with an estimated 50% of approved drugs tracing their origins to natural sources. Among these, microbial natural products hold exceptional importance due to their remarkable structural diversity, novel scaffolds, and biological activity. Microbial NPs often possess unique chemical scaffolds and functional groups rarely found in synthetic libraries, making them invaluable starting points for drug development. Additionally, they exhibit high target specificity and potency, having evolved under selective pressure to interact with specific biological targets. Examples of microbial NPs include antibiotics (penicillin, daptomycin, streptomycin, tetracycline), immunosuppressants (cyclosporine, rapamycin), antitumor agents (doxorubicin, bleomycin), and antiparasitics (avermectins). Our research explores the potential of soil microbiomes from previously unexplored ecological niches as sources of novel bioactive NPs. We collected soil samples from different distinct unexplored regions characterized by diverse environmental conditions. Using selective isolation techniques and specialized growth media, we successfully cultivated ~1,000 bacterial isolates predominantly belonging to Actinomycetes. This class of bacteria is known to be a rich source for natural products with new chemical space and biological activities. Each bacterial isolate underwent small-scale fermentation under optimized conditions, followed by organic solvent extraction to obtain crude extracts. All extracts were subjected to comprehensive LC-MS analysis to generate a chemical fingerprint database and identify potential novel molecular scaffolds. The extracts were screened against a panel of pathogens, including drug-sensitive and drug-resistant Gram-positive (Staphylococcus aureus, Bacillus subtilis) and Gram-negative (Escherichia coli, Salmonella enterica) bacteria and fungi (Candida albicans and Saccharomyces cerevisiae). The extracts were also screened against CCRF-CEM, human lymphoblast peripheral blood cells. Our preliminary data results indicate most extracts to be rich in organic NPs with several to be biologically active. This work highlights the significance of exploring chemical diversity from microbes cultivated from unexplored environments as a viable strategy for discovering novel bioactive compounds.

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Functional analysis of a thyroglobulin variant in its C-terminal cholinesterase-like (ChEL) domain: Implications for congenital hypothyroidism

Berenice Morales-Rodriguez*, Jessie Tsai, Jennifer Le, Cintia E. Citterio*

Over 230 different thyroglobulin (Tg) gene variants have been proposed to be linked to congenital hypothyroidism in humans. These mutations are scattered across various regions of thyroglobulin, including the upstream regions and the C-terminal Cholinesterase-Like (ChEL) domain, which shares high similarity with the enzyme acetylcholinesterase (AChE). Although it seems likely that different mutations may create distinct functional/structural defects in Tg, this remains to be elucidated. We aim to analyze the functional effects of a Tg variant that falls within the Tg ChEL domain to help explain the spectrum of phenotypes observed in congenital hypothyroidism. Here, we combined structural analyses with functional characterization of recombinant Tg-ChEL domain expressed in cell culture. We identified the hTg-A2234D mutation that falls within the ChEL domain and has been reported in patients with congenital hypothyroidism. Bioinformatics analyses showed that A2234 is highly conserved between species, and prediction tools indicate that the mutation is 74% likely to be damaging, with structural proximity to a highly conserved disulfide bond in the ChEL domain. We employed site directed mutagenesis to create the recombinant secretory Flag-ChEL-A2234D and determined the impact of this mutation by studying the cultured cells that do not endogenously express Tg. We found that the mutation A2234D causes intracellular retention of Flag-ChELA2234D, preventing its normal secretion, which is needed for normal thyroid hormonogenesis, confirming the pathogenic nature of this mutation. Additionally, Tg-A2234 is located at the equivalent aminoacidic position (A69) in AChE, and AChE-A69V has been reported as a pathogenic mutation. In the future, we will utilize AChE as an enzymatic colorimetric reporter of the effects of mutations in the Tg-ChEL domain to yield quantitative information on mutant AChE activity, which may predict the severity of Tg-ChEL mutations associated with congenital hypothyroidism.

22

Mechanistic insights of Trp-modified daptomycin antibiotic

***D.N. Nguyen**, A. Oum, D.V. Chandrashekar, R.K. Sumbria, I. Maslennikov, S.I. Elshahawi*

Background: The widespread use of antibiotics, while highly effective, has led to the rise of antibiotic-resistant bacterial pathogens. Some antibiotics are reserved as a last resort when standard treatments fail. Daptomycin (Dap) is one such last-line antibiotic. It is a calcium-dependent lipopeptide used to treat Gram-positive bacterial infections. However, resistance to Dap has been increasing. To combat this issue, our lab developed a site-specific chemoenzymatic approach that selectively modifies the tryptophan residue in Dap. Using this strategy, we synthesized a Dap analog, Dap2, which exhibits calcium-independent activity and effectively inhibits Dap-resistant bacterial strains.

Methods: Biophysical experiments (NMR, CD, fluorescence) were done to observe the structural changes of Dap2 as a result of the compound's interaction with calcium and liposomes and compare it to that of Dap. In addition, microscopy studies were conducted to assess how quickly Dap2 works and how much more effective it is in killing the susceptible and resistant strains when compared to the calcium complex. Toxicity studies of Dap2 were also performed and its success in clearing infectious Dap-resistant bacteria locally and systemically was further tested in mouse models.

Results: The NMR peaks broadened for Dap, and the LWHH values of Dap2 were large even without calcium. In CD, Dap2 and liposomes had a negative ellipticity curve even without calcium. For fluorescence, Dap2 by itself was able to produce an effect nearly similar to that of Dap with 60–80 mM calcium. Confocal experiments indicated that Dap2 alone and with calcium entered the bacteria as early as 5 min and killed more cells than Dap or Dap with calcium. Finally, the animals survived more than 5 days after given Dap2 and it helped the mice lower the CFUs of resistant bacteria from their bodies.

Conclusion: These findings confirm that Dap2 exhibits superior activity compared to Dap even in the absence of calcium.

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Anticoagulation treatment outcomes in the long-term acute care population

Thuy Vi Nguyen, *Viet-Huong Nguyen*

Background: Long-term acute care hospitals (LTACHs) provide ongoing care for patients requiring extended treatment beyond a general acute care hospital stay, often serving as a bridge to skilled nursing or subacute care facilities. Patients in LTACHs represent a unique high-risk population that are often medically complex with multiple comorbidities. Many LTACH patients also require high-risk anticoagulation therapy for various conditions such as deep vein thrombosis (DVT) treatment or atrial fibrillation. This study aims to evaluate anticoagulation use and outcomes in the LTACH population in order to identify areas for improved in-hospital monitoring and safety.

Methodology: A retrospective review of patients admitted from October 1, 2023, to October 31, 2024, at Kindred Hospitals La Mirada, San Gabriel, and Santa Ana will be conducted. All patients receiving either direct oral anticoagulants (DOACs) or warfarin during this period will be identified; one-hundred patients will be randomly selected for analysis using an online number randomizer. Data collected will include patient characteristics, anticoagulation indication and dosage, Charlson Comorbidity Index score, ventilator status, bleeding and thrombotic events, length of stay, duration of therapy, and overall clinical outcomes. The primary outcome is proportion of patients with bleeding or thrombotic events. Descriptive statistics will be used to describe outcomes.

Results and conclusions: This is a research in progress submission. Results and conclusions will be reported upon completion of study.

24	**Enzyme immobilization for large-scale biocatalytic synthesis of novel antibiotic analogs with enhanced antimicrobial activity** ***Alice Oum**, Diem N. Nguyen, Sherif I Elshahawi* Daptomycin (Cubicin®) is an FDA-approved antibiotic that has shown efficacy against various Gram-positive bacterial infections. Daptomycin is a calcium (Ca2+)-dependent lipopeptide and is used to inhibit drug-resistant bacteria including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE). However, its complex chemical structure presents substantial challenges for regiospecific modification through traditional synthetic chemistry methods, limiting efforts to expand its functionality and antimicrobial spectrum. Due to these limitations, our laboratory recently developed a chemoenzymatic method that enables the synthesis of daptomycin derivatives. These derivatives show an expanded antimicrobial spectrum that are several-fold more active than the parent drug. The new modified derivatives do not rely on Ca2+ for activity, and were active against Dap-resistant S. aureus and Dap-resistant Enterococcus strains, suggesting that the chemoenzymatic-synthesized daptomycin derivatives have a novel mechanism of action that could potentially address emerging resistance in pathogenic bacteria. To scale up production for in-depth mechanistic studies, we established a more efficient and cost-effective approach utilizing enzyme immobilization. Immobilizing the enzyme on a solid support preserves its catalytic activity, permitting enzyme recycling without requiring additional purification steps. This advancement enables continuous biocatalytic synthesis, significantly reducing both the time and cost associated with conventional enzymatic processes. After purification, the structures of these daptomycin analogs were confirmed through NMR spectroscopy and HR-MS. Our enzyme immobilization approach led to an increase of synthesis of analogs 10–14-fold compared to traditional biocatalysis reactions. Our method provides a streamlined and sustainable strategy for producing several hundred milligram-scale quantities of daptomycin analogs, which is crucial for uncovering their mechanisms of action and for evaluating their efficacy against resistant bacterial strains in animal models. By addressing the current limitations in daptomycin derivative synthesis, our work opens new avenues for the rapid production of structurally diverse analogs that could lead to next-generation antibiotics used to combat Gram-positive infections.

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The impact of shadowing experiences on early PharmD students' understanding of clinical pharmacist roles

Alice Oum, *Priscilla Sajonas, Gary Fong*

PURPOSE: Shadowing experiences provide PharmD students with the opportunity to explore diverse practice settings. The purpose of this study was to assess the impact of shadowing experiences on PharmD students' understanding of the role of clinical pharmacists in acute and ambulatory care settings.

METHODS: An electronic survey was sent to 12 students who participated in shadowing opportunities offered by the ACCP student chapter at Chapman University School of Pharmacy. Participants were asked to complete a 14 item pre- and post-survey consisting of Likert-scale, categorical, and free response questions to assess their experience. Likert-scale and categorical data were compared using paired t-test and Fisher's exact test, respectively. Qualitative comments were summarized by theme.

RESULTS: The survey response rate was 91.66% (11/12). After the shadowing experience, students were more likely to have watched a pharmacist work in an interdisciplinary team and practice evidence-based medicine ($p = 0.0861$ and $p = 0.0635$, respectively). Students were more likely to agree that pharmacists are capable of reviewing and adjusting medications based on a patient's lab results or clinical condition, with median scores of agreement increasing from 8 to 10 ($p = 0.003$). Students appreciated observing the application of clinical knowledge learned in the classroom to patients, including how pharmacists modified treatment plans and influenced antibiotic choices through interprofessional collaboration. Overall, respondents felt the experience was valuable and added to their understanding of clinical pharmacists.

CONCLUSION: Data from pre- and post-surveys suggest that shadowing experiences increased PharmD students' familiarity with clinical pharmacy and exposure to pharmacists in acute and ambulatory care settings, highlighting the value of experiential learning. Survey data will be utilized to justify expansion of shadowing opportunities and consideration of integrating into the curriculum.

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The role of neonatal Fc receptor in transferrin receptor- antibody fusion -protein pharmacokinetics

***Adenike Oyegbesan**, Nataraj Jagadeesan, Devaraj V. Chandrashekar, Rachita K. Sumbria*

The blood-brain barrier (BBB) restricts the delivery of biologics to the brain, necessitating strategies like targeting the BBB transferrin receptor (TfR) using TfR-targeting antibodies (TfRMAbs) for effective brain drug delivery. Building on prior single dose (acute) pharmacokinetic data that showed a significant, albeit varying, role of the neonatal Fc receptor (FcRn) in sustaining systemic exposure of TfRMAb fusion proteins, this study explores how FcRn influences the systemic exposure and biodistribution of TfRMAb fusion proteins following chronic dosing in wild-type (WT) and FcRn knockout (KO) mice. Mice were dosed subcutaneously with TfRMAb and two model TfRMAb fusion proteins, TfRMAb-EPO and TfRMAb-TNFR, at 3 mg/kg, three times a week for four weeks. We evaluated plasma pharmacokinetics, tissue distribution, and systemic side-effects using ELISA, electrochemiluminescence, and hematologic profiling. Compared to acute dosing, chronic dosing lowered plasma levels of all fusion proteins in both WT and FcRn KO mice. The impact of chronic dosing and FcRn on tissue distribution differed for the different TfRMAb fusion proteins. For example, TfRMAb-EPO tissue biodistribution following chronic dosing showed less retention in the spleen, brain, kidneys, and liver compared to acute dosing for WT and FcRn KO mice. However, chronic TfRMAb treatment significantly lowered kidney, liver, and spleen levels, while FcRn KO mice saw reduced exposure only in the spleen. Overall, these findings emphasize the importance of FcRn in sustaining both systemic and tissue levels of TfRMAb fusion proteins largely after a single dose, with reduced impact following chronic dosing. This suggests that there may be alternative pathways that regulate the plasma exposure and tissue distribution of TfRMAb fusion proteins following chronic dosing. Further, the contribution of FcRn-mediated IgG protection varies depending on the TfRMAb fusion partner and needs to be carefully considered on a case-by-case basis as the field progresses towards the development of TfRMAb Fab-fusion proteins.

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Effectiveness of intravesical BCG in the treatment of non-muscle invasive bladder cancer: An umbrella review

Ozota Gerald, *Ogbonna Emmanuella, Sabastine Ruth, Eze Shadrach, Ben-Umeh Kenechukwu, Lawrence Brown*

Introduction: Bladder cancer is currently the ninth most diagnosed cancer worldwide, with approximately 220,000 deaths. NMIBC accounts for over 75% of diagnosed bladder cancer cases and is characterized by a high recurrence (55-75%) and high progression rates (5-45%). This umbrella review synthesizes data from systematic reviews to evaluate the effectiveness of intravesical BCG in reducing recurrence, delaying progression, and improving survival outcomes in NMIBC patients.

Method: We conducted a 10-year (July 2014 to September 2024) review of systematic reviews adhering to PRISMA guidelines. The search was performed in MEDLINE, Embase, CINAHL, and Cochrane Library using search terms defined by the population, interventions, comparisons, outcomes, and study design (PICOS) approach. Data extraction included study characteristics, intervention details, and outcomes, including recurrence, progression, overall survival, and adverse drug reactions. To assess the risk of bias (RoB), two reviewers independently reviewed all included studies using the AMSTAR-2 checklist and rated the quality of evidence using the GRADE system.

Result: We included 22 studies with 137283 participants in this review. The study highlighted the effectiveness of BCG in multiple outcomes, including recurrence-free, progression-free, disease-free, overall survival, and ADE and recurrence rates in NMIBC patients undergoing intravesical therapies. The review's findings are corroborated by recent studies, which emphasize the continued effectiveness of BCG while highlighting promising alternative therapies. However, heterogeneity in study methodologies, ROB, and GRADE score was a limitation of the evidence.

Conclusion: While BCG remains the gold standard for NMIBC treatment, its efficacy must be balanced against the risks of adverse effects and therapy limitations. Low-dose BCG remains a potential option for patients experiencing toxicity or during supply shortages, though full-dose regimens still offer superior efficacy. Alternative intravesical therapies, such as gemcitabine/docetaxel and device-assisted delivery systems, show comparable recurrence rates and may be viable alternatives for BCG-unresponsive NMIBC. Strategies to optimize compliance and minimize adverse effects are crucial for maximizing treatment success.

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Sustained hepato-specific LRP-1 silencing exacerbates Alzheimer's disease pathology in mice

Devaraj V. Chandrashekar, *Urvashi R. Panchal, G. Chuli Roules, Nataraj Jagadeesan, Josephine Chu, Derick Han, Rachita K. Sumbria*

Background: Hepatic low-density lipoprotein receptor-related protein 1 (LRP1) plays a vital role in the removal of amyloid beta (Aβ) from the periphery and may thus significantly impact Aβ brain pathology of Alzheimer's disease (AD). Our previous work showed a significant increase in brain Aβ load with 12 weeks of hepatic-specific LRP1 silencing in AD transgenic mice. However, the impact of prolonged hepatic LRP-1 downregulation on AD pathology remains unclear and was our aim in this study.

Methods: To evaluate the role of long-term hepatic LRP1 in brain amyloidosis, 4-month-old male APP/PS1 AD transgenic mice (n=7) were subjected to hepato-specific LRP1 silencing by intravenous injections of LRP1 microRNA (mi-RNA) delivered by the adeno-associated virus 8 (AAV8) in conjunction with hepato-specific promoter, thyroxine-binding globulin (TBG). The control APP/PS1 mice were injected with control AAV8 (n=6). Seven months after hepatic-LRP1 silencing, spatial reference memory (Y-maze test) and exploratory behavior (open-field test) were assessed, followed by harvesting of plasma, brain, and liver samples to detect LRP1 and Aβ levels. Brains and plasma were also assessed for neuroinflammation (microglia, TREM2, and GFAP) and lipoproteins (ApoE and ApoB), respectively, using immunoassays.

Results: Organ-LRP1 western blot data confirmed liver-specific LRP1 silencing in APP/PS1 mice. Hepato-specific LRP1 silencing significantly increased insoluble Aβ1-42 ($p<0.05$) by ELISA and 6E10-positive Aβ load ($p<0.001$) and Thioflavin-S-positive mature Aβ load ($p<0.01$) by histology in APP/PS1 mice brains. Plasma Aβ1-42 levels were significantly increased ($p<0.05$) with hepatic LRP1 silencing in APP/PS1 mice. Insoluble brain and plasma Aβ1-42 levels were positively correlated ($p<0.05$). Further, prolonged hepatic LRP1 silencing altered neuroinflammatory response with increased astrogliosis ($p<0.01$) and TREM2-positive area ($p<0.05$), but a significant decrease in microgliosis in APP/PS1 mice brains. Furthermore, hepato-specific LRP1 silencing showed a significant reduction in the spatial reference memory during the Y-maze test ($p<0.05$). Liver LRP1 silencing significantly impacted plasma lipoprotein and cholesterol homeostasis, with a significant decrease in plasma cholesterol ($p<0.05$) and a significant increase in the plasma LRP1 ($p<0.01$) and ApoB48 ($p<0.05$) levels, but no change in the plasma ApoE levels.

Conclusion: Overall, this study shows significant effects of prolonged hepato-specific LRP-1 silencing on markers of AD pathology, including Aβ and neuroinflammation, and cognition. The impact of hepatic LRP1 silencing on AD pathology is robust yet complex and likely involves a significant interplay between plasma lipid homeostasis and brain pathology, which needs to be further investigated.

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Impact of Western diet-induced liver changes on Alzheimer's disease

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Alzheimer's disease (AD) and obesity are two public health challenges with growing evidence linking them. Obesity, driven by Western diets (WD) high in fat and sugar, is a known risk factor for AD, with up to 90% of obese individuals developing non-alcoholic fatty liver disease (NAFLD). Liver steatosis, a hallmark of NAFLD, has been shown to upregulate hepatic amyloid precursor protein (APP) and downregulate lipoprotein receptor-related protein 1 (LRP-1), a key receptor for peripheral amyloid-beta (Aβ) clearance. These changes may dysregulate peripheral Aβ homeostasis, increase brain Aβ levels, and exacerbate AD pathology. While the liver's role in peripheral Aβ regulation is well studied, the mechanisms by which obesity-induced hepatic changes contribute to brain amyloidosis remain unclear. Our study aims to describe the impact of liver steatosis on peripheral and cerebral Aβ by investigating the relationship between obesity-induced hepatic Aβ dysregulation and AD pathology. For this, female APP SAA knock-in (KI) mice that carry the human Swedish, Arctic, and Austrian mutations of the APP gene, and wild-type (WT) mice were fed a WD for 4 months. APP mice without SAA mutations were used as additional controls. Mice were monitored 3 days a week for weight gain and feed intake for 4 months, after which the mice were sacrificed, and organs were collected. Behavior and cognitive testing were also done before and after WD feeding. Currently, the brain and liver samples are being assessed for APP and its cleavage products, and key Aβ regulators (LRP1, BACE1, IDE, and neprilysin). Additionally, we are assessing AD-related brain pathology, including gliosis, neuronal loss, and cognitive function, in WD-fed APP SAA KI, APP, and WT mice. Our findings aim to fill critical gaps in understanding how systemic metabolic changes contribute to AD.

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Evaluating the impact of a utilization management pharmacist's interventions in a medical group

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Prescription medications in the United States can be covered under the prescription benefit or the medical benefit. Health insurance companies and medical groups negotiate contracts of Division of Financial Responsibility (DOFR), which specify which party is responsible for which benefits or if there is shared risk between the two entities. A majority of DOFRs between Providence Medical Foundation and different health plans designate Providence at full risk for medications covered under the medical benefit. This ultimately means that the medical group is responsible for 1) assessing the medical necessity of referrals made from providers for these medications, 2) selecting the appropriate site of service for the administration of these medications, 3) obtaining the supply of medications, and 4) all the costs associated with the administration of the medication. A utilization management (UM) team can identify which medications are driving high costs to target their interventions. One type of intervention is influencing prescriber behavior to use more cost-effective therapy alternatives that are just as clinically effective. Another method is recommending these medications to be administered at more cost-effective sites of service, such as 340B hospital infusion centers when appropriate. Additionally, UM teams can recommend where the medication should be purchased from, such as directly from the wholesale distributor with contracted pricing or through specialty pharmacies with negotiated rates. This is a quality improvement project conducted at Providence Medical Group in California. Data will be collected from January 2024 to January 2025 on referrals made for Prolia and intra-articular hyaluronic acid products covered under the medical benefit. Dates and types of UM pharmacist interventions will be tracked. 1) Number of referrals for each drug, 2) sites of service, and 3) medical group spending will be compared between the time periods before and after UM team interventions.

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Genetic insights into alcohol-induced Alzheimer's pathology using gene expression analysis

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Background: Alzheimer's disease (AD) is a neurodegenerative disease characterized by amyloid-beta and tau accumulations in the brain. Emerging evidence suggests chronic alcohol exposure may contribute to AD pathology. This study investigates molecular mechanisms underlying this relationship by performing differential gene expression (DGE) analysis in the APP/PS1 double-transgenic mice to identify potential links between chronic alcohol exposure and AD progression.

Objective: This study explores the impact of chronic alcohol exposure on the pathological mechanisms of AD by analyzing the gene expression in specific regions of interest in brain and liver tissues.

Methods: NanoString GeoMx Digital Spatial Profiler was used to perform spatial transcriptomics in the plaque-bearing hippocampus of the brain, along with the periportal and perivenous areas of the liver from 8-month-old APP/PS1 mice that had been fed with alcohol or control diet for 5 weeks. Significant DEGs in alcohol versus control fed mice were identified using a log2-fold change ≥1.25 and p-adjusted <0.01. Overrepresented functional annotations and pathways were revealed using g:Profiler to identify dysregulated processes using default parameters. Overlap of DEGs and enriched pathways were assessed to determine shared and tissue-specific molecular disruptions.

Results: Tmem267 and S100a8 were consistently differentially expressed across all three analyzed regions suggesting a role in neuroinflammation and neurodegeneration linked to chronic alcohol exposure and AD pathology. In contrast, 74 genes were shared between periportal and venous regions, while 5 genes were shared between the plaque hippocampus and venous regions. Of note, liver disease was identified as a dysregulated process from the hippocampal DGEs, suggesting a liver-brain crosstalk in the alcohol-fed AD mice. Additionally, dysregulation in protein binding, cytoplasm, cytosol, cellular structure, mitochondrial envelope, and intracellular structure was revealed across all tissues. This suggests widespread cellular disruptions contributing to oxidative stress, impaired protein interactions, and mitochondrial dysfunction, potentially linking chronic alcohol exposure to AD.

Conclusions: As inflammation plays a critical role in AD, the identified genes and pathways may serve as potential biomarkers or therapeutic targets. Additionally, our DGE analysis suggests the involvement of liver-brain crosstalk in alcohol-dependent AD, and further research is needed to evaluate their significance in AD development and progression.

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Role of fibroblast and macrophage-derived cytokines and chemokines in the ocular GVHD associated conjunctival fibrosis

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Purpose: Graft versus host disease remains a major complication of hematopoietic stem cell transplant. Due to HLA-matching and milder conditioning regimens, incidence of acute GVHD has decreased, but chronic GVHD (cGVHD) remains high. The cGVHD leads to severe dry eye and fibrotic changes in the conjunctiva and lacrimal gland. The pathogenesis of ocular GVHD (oGVHD)-associated fibrosis remains poorly understood. In this study, we investigated the role of chemokines and cytokines derived from conjunctival fibroblasts and macrophages that can initiate and perpetuate oGVHD-associated fibrosis.

Methods: A mouse model of chronic GVHD with major MHC-match allogeneic bone marrow transplant (allo-BMT) with B10.D2 mice as donors and BALB/c mice as recipients was used. The syngeneic BMT group served as a control. The conjunctiva was harvested at 3 & 6 weeks after BMT. Conjunctival fibroblasts and macrophages were isolated using anti CD90 and CD11b magnetic beads. Protein expression of chemokines was quantified using the proteome array. Cytokines were also quantified in conjunctival macrophages using antibody-conjugated beads and flow cytometry. Immunostaining was performed for CSF and goblet cells.

Results: The mouse model showed typical signs and symptoms of oGVHD, including reduced tear secretion, corneal keratopathy, and lid edema. The presence of fibrosis was confirmed by smooth muscle actin staining in the conjunctiva. There was an increase in several chemokines including CCL2, CCL5, CXCL1, CXCL2, CXCL11 in the conjunctival fibroblasts obtained from mice with GVHD. There was also notable increase of CSF-1 and a decrease in goblet cells in the conjunctival fibroblasts of oGVHD mice. A significant increase in macrophage cytokine levels such as IL-18 and G-CSF was observed.

Conclusions: Our study demonstrates that after allo-BMT, conjunctival fibroblasts have increased levels of chemokines and CSF-1 that may promote macrophage recruitment. The recruited macrophages, in turn, secrete cytokines that can perpetuate conjunctival inflammation and fibrosis in oGVHD.

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Differential expression of brain transferrin receptors in a tauopathy (PS19) mouse model

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The transferrin receptor (TfR) is a membrane-associated protein that is involved in receptor-mediated uptake of the transferrin-iron complex and is essential for maintaining iron homeostasis, which is disrupted in Alzheimer's Disease (AD). In the brain, TfR is present on cell membranes of various cells, including neurons, astrocytes, and endothelial cells. Given its enrichment at the blood-brain barrier (BBB), TfR is widely used as a target to deliver biologics into the brain. Therefore, TfR expression at the BBB can significantly impact drug delivery efficiency. Previous research has investigated TfR expression in the brains of female AD mouse models; however, its expression in tauopathy models, specifically PS19, has not been investigated. PS19 mice are transgenic mice expressing the human tau protein with the P301S mutation exhibiting neurodegenerative characteristics observed in tauopathies. Data on the expression of TfR in WT and PS19 mice show that the percent-positive TfR area was significantly higher in PS19 mice compared to WT mice ($p < 0.006$). There was no difference between the number of vessels stained for CD31 between the WT and PS19 mice ($p > 0.05$), indicating that the differences in TfR expression are not due to higher vessel counts. This study demonstrates that TfR expression is higher in PS19 mice compared to WT mice. This difference in expression is significant for drug delivery, as it can enhance the precision and effectiveness of drug delivery by maximizing the interaction between the drug and TfR. Future work aims to investigate the sex difference between TfR expression, which is both warranted and ongoing.

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Breast cancer drugs approved by the US Food and Drug Administration, 1980-2024

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Breast cancer is the most common cancer among women and the leading cause of cancer death among women. The pharmacological options for breast cancer include chemotherapy, hormone therapy, targeted therapy, and immunotherapy, which are used for the prevention or treatment of breast cancer. Examining drug-specific information, such as biological targets and intervention methods, to provide insights into innovation and regulatory efficiencies in breast cancer therapeutics. This study assessed the characteristics and trends in the FDA approval of drug for breast cancer from 1980 to 2024. We collected regulatory information from the drugs@FDA, FDA Label Search, and DailyMeds databases. We assessed trends in the number of approvals, FDA review time, and regulatory procedures and designations analyses using Microsoft Excel and Python 3.13.1.

The FDA approved 68 drugs for breast cancer in 1980-2024, including 49 new molecular entities and 19 new biologics. The FDA approved 46 (67.6%) drugs using priority review designation, 14 (20.6%) used accelerated approval pathways, and 9 (13.2%) drugs were granted orphan designation. The indications were approved by the FDA for Stages 1 (12,11.8%), 2 (18, 17.6%), 3 (23, 22.5%), and 4 (49, 48.0%). The FDA review time decline over time from an average ± standard deviation of 13.01 ± 13.43 months from 1980 to PDUFA 1 in 1992 to 9.51 ± 5.85 months in 1992-2024. The FDA review time varied by cancer stage from 9.0 ± 2.9 for Stage 1 to 9.5 ± 6.1 for Stage 4.

The FDA approved more than 30 drugs per year for breast cancer treatment and prevention. Most drugs approved after 2000 were indicated for late-stage breast cancer. Most drugs were approved using priority review and only a few were granted orphan drug designation. The FDA review time for breast cancer drugs declined over time.

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Characterizing immunoproteasome mediated antigen presentation using bioorthogonal labeling

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The Immunoproteasome (iCP) is an inducible proteasome isoform that is constitutively expressed in antigen presenting cells. Similar to the standard proteasome, the iCP is responsible for the degradation of intracellular proteins, however its distinct substrate specificity allows it to produce more major histocompatibility-I complex compatible antigens. This function is incredibly important for antigen presentation and immune surveillance. Our lab's work has demonstrated the development of a probe that can selectively release antigenic peptides via the iCP using the SIINFEKL model antigen system. However, in order to expand beyond this model system and explore a more biologically and pharmacologically relevant context we developed a new technique for identifying antigens on the cell surface. Utilizing triazole forming click chemistry we are able to identify propargylglycine labeled antigenic probes on the cell surface, bypassing the need for a specific antibody. This technique will be useful for elucidating the mechanisms of antigen presentation and immune response and correlate these with iCP activity.

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Endogenous triiodothyronine in cardiometabolic health

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Hypothyroidism effects 10% of the population, increasing the risk of cardiovascular disease. Differentiating the roles of the two thyroid hormones, triiodothyronine (T3) and thyroxine (T4), is important to improving the treatment of this disease. Thyroglobulin (Tg) is the sole precursor for thyroid hormone synthesis in vertebrates. Tg upstream region is responsible for the synthesis of T4, while the C-terminal Cholinesterase-Like (ChEL) domain is linked to the de novo synthesis of T3, with the remainder body's T3 resulting from T4 deiodination in several tissues. Thyroid hormones stimulate cardiac output by enhancing beta-adrenergic receptor sensitivity, leading to higher systolic blood pressure (SBP) and also regulate body composition. But can T3 produced de novo in the thyroid gland alone support cardiometabolic functions? Our lab has a mouse model, named ChEL-KI, designed to produce normal serum levels of T3 but negligible T4, limiting local T3 production. We utilized ChEL-KI mice along with conventionally hypothyroid cog/cog mice (with both low serum T4 and T3) and euthyroid (wild type) controls to determine the consequences of a T3-only hormonal environment in body composition (through MRI imaging) and blood pressure (through non-invasive monitoring). Analyses of our MRI scans of ChEL-KI mice showed no significant differences in fat mass and lean body mass percentages compared to wild type mice. Cog/cog mice showed more pronounced differences in body composition although these did not achieve statistical significance. Comparing blood pressure, ChEL-KI exhibited a near-normal SBP that was not significantly different from that of wild type mice. Conversely, cog/cog mice showed significantly lower SBP compared to ChEL-KI and wild type mice. These studies demonstrate how normal levels of T3 in the setting of negligible T4 can sustain certain phenotypes commonly affected in hypothyroidism. Future development of targeted therapies could improve the quality of life for patients struggling with traditional T4 hormonal replacement.

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Development of a plastic waste calculator to help clinicians make more sustainable antimicrobial choices

***Tien Dinh**, Misty Vu, Gary Fong, Pamela Lee*

Climate change and pollution pose significant threats to infectious diseases (ID) practice, impacting over half of human infections through alterations in vector ranges and biodiversity, leading to emergence of difficult to treat pathogens. To mitigate the risks associated with climate change-related infectious events, proactive and aggressive measures are essential. The U.S. healthcare sector is a major contributor to greenhouse gas emissions and pollution, with a large portion being from pharmaceuticals. Improper disposal of antimicrobials disrupts ecosystems and increases environmental antimicrobial resistance. There are currently few tools available to help clinicians make more sustainable therapeutic choices to help alleviate these issues. A web-based clinical calculator was developed to provide clinicians with a practical tool to estimate plastic waste generated by common antimicrobial regimens. Antimicrobial doses, dosing frequency, and formulations were collected using commercially available package inserts. Compounding inputs required for dose preparation and administration were extracted from clinical compounding protocols. Weights of all inputs required to prepare both intravenous and oral doses were collected via direct weighing of individual components.

The antimicrobial sustainability calculator quantifies plastic waste generated by different antimicrobial regimens and incorporates clinically relevant factors including intravenous tubing, dosing frequency, and duration of therapy. Providers can input six selections including: antibiotic, dose, formulation, administration method, frequency, and duration. The calculator shows users the breakdown of waste generation during each step from preparation to administration and also allows for comparison to alternative antimicrobial regimens. While clinicians routinely consider efficacy, safety, convenience, and cost in their antimicrobial decision-making process, they are unlikely to think about sustainability. The development of this calculator offers insight into how different regimens contribute to plastic waste generation. Clinical application of this calculator will provide frontline clinicians with a novel tool that may lead to more sustainable clinical decisions without jeopardizing patient outcomes or safety.

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A peptide-drug conjugate targeting triple-negative breast cancer enhances drug uptake in mice tumors

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The lack of specificity of chemotherapeutic drugs for tumor sites has posed a major challenge in cancer treatment. A promising and emerging strategy to address this issue involves targeted delivery using agents like antibody-drug conjugates (ADCs) and peptide-drug conjugates (PDCs). Although these have shown increased therapeutic efficacy post-treatment in clinical and preclinical studies, there are limited data that report the comparison of actual concentration of drug in tumors (and in other normal tissues/organs), between conjugate and free drug alone. This knowledge is fundamental for predicting, assessing, and optimizing both the efficacy and safety profiles of these agents, to help minimize failure during clinical stages. Our group's objective was to determine the in vivo biodistribution of an *in vitro*-validated PDC targeting triple-negative breast cancer (TNBC), in mice. Mice bearing TNBC cell orthotopic tumors were injected with saline, free drug, or PDC for 4 weekly treatments. Twenty-four hours after the final treatment, mice were euthanized, and tumors and other organs were harvested and analyzed for drug concentration levels. The drug was found to be significantly elevated in the tumors of conjugate-treated mice by 7-fold, compared to those of free drug-treated mice. Additionally, up to 3-fold less drug was found to be accumulated in other organs, in the conjugate-treated mice, versus free drug-treated mice. These findings offer direct proof of our PDC's targeted accumulation at the tumor site, thereby improving its efficacy and safety in vivo, and highlighting it as a promising new approach for treating TNBC.

O1	**Modifying tryptophan and indole-derived compounds using engineered indole prenyltransferase enzymes** ***Ashley K. Alexander****, Diem N. Nguyen, Ahmed R. Aoun, Tae Ho Kim, Nagaraju Mupparapu, Sherif I. Elshahawi* Indole Prenyltransferase (IPT) enzymes are present in many microorganisms. They catalyze the transfer of prenyl moieties from natural pyrophosphate donors to tryptophan and other indole-derived small molecules. Prenylation alters the structure of small molecules, enhances their hydrophobicity, and subsequently alters their interaction with cell membranes and receptors. Prenylation of small molecules has been reported to increase cytotoxicity and antimicrobial properties. This suggests that generating enzymes that lead to diprenylation can lead to further improvement in compound properties. PriB is a C-6 IPT that uses dimethylallyl pyrophosphate as a native donor to prenylate tryptophan. PriB has shown broad substrate flexibility, allowing it to modify nonnative donor and acceptor substrates. Structural analysis of PriB active site suggested three key residues that play an important role in enzyme biocatalytic activity. Thus, site-directed mutagenesis of these three residues was performed, and the encoded enzymes were purified and screened. Our *in vitro* enzymatic reactions, coupled with HPLC-MS, kinetic data, in addition to 1- and 2D nuclear magnetic resonance spectroscopy, show that the three mutants are capable of catalyzing diprenylation reactions. This work highlights the crucial role of enzyme engineering in biocatalysis, demonstrating its ability to expand enzyme activity across diverse applications.

O2

Proximity-Dependent Proteomics Identifies Unique Interactomes of Adenylyl Cyclase Isoforms 6 and 9 in Human Airway Smooth Muscle Cells

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Despite the established role of cAMP in cellular signaling, little information is available about the mechanisms by which this second messenger functions within specific microdomains to regulate distinct cellular responses. The specific signaling effects are primarily due to the localization and activity of adenylyl cyclase (AC) isoforms that promote cAMP synthesis within these compartments. While multiple AC isoforms, such as AC6 in lipid rafts, are expressed in the human airway smooth muscle (HASM), how these isoforms are directed and anchor other complexes to specific membrane domains and their precise roles are not fully understood. We utilized BioID proximity-labeling to identify novel interactors with the two most highly expressed AC isoforms in primary HASM cells from normal patients, AC6 and AC9. This method enables studying protein-protein interactions with greater specificity and detailed spatial mapping. AC6 and AC9 isoforms were genetically fused to a biotin ligase MiniTurbo enzyme, which covalently biotinylates nearby proteins within a nanometer range. Biotinylated proteins were affinity purified with streptavidin coated magnetic beads for enrichment of the target proteins and proteomic analysis by LC-MS/MS. Equivalent and low-level expression of the AC6 and AC9 constructs was optimized by measuring cAMP production and immunoblot analysis. Proteomics data was generated for overexpressed AC6 and AC9 in three patient HASM cell lines. Of the 3,441 proteins identified across all cell lines, 29 were unique to AC6, 19 to AC9, and 28 were shared between the two, all significant at $p < 0.05$ after FDR adjustment by the Benjamini-Hochberg method. Unique AC6 interacting proteins were involved in pathways regulating inflammation and protein folding, while unique AC9 interacting proteins were from pathways involved in Rho GTPase signaling, Golgi vesicle formation and ERBB2 signaling. These findings provide new insights into the macromolecular complexes formed by different AC isoforms and how they shape unique spatial cAMP signaling and drive distinct physiological responses in human airway smooth muscle.

O3	**Backstage Passes to the Brain: A Minimally Invasive Enzyme Replacement Therapy for Angelman Syndrome** ***Barbara Bailus**, Delihla Correa, Rachel Stoub, Ty Johnson, Linna Han, Yara Al Mashriki, Moses Lee, Lisa Ellerby, Albert Keung* Angelman Syndrome (AS) is a rare neurodevelopmental disorder caused by the loss of UBE3A expression in the central nervous system (CNS). In the last fifteen years much progress has been made in both understanding the basic genetics of AS and developing tools for treating AS. However, one area that still needs further optimization is the method of delivery to the brain for these novel therapies. The brain still remains an extremely challenging organ to target for treatments, in a non-invasive manner. Multiple promising technologies, including ATFs, cDNA, CRISPR, and ASOs, have been successful in the rodent models of AS, but achieving widespread delivery of these therapeutics in a human brain remains elusive and is a major limiting factor in the effectiveness of these therapeutic approaches. Our study has focused on optimizing a novel delivery technology for delivering therapeutic proteins to the brain, based on various cell penetrating peptides. This system has previously achieved widespread delivery of several proteins from an intravenous injection, in a murine model. We are adapting this system for use with UBE3A which is the protein that is haploinsufficient in Angelman syndrome. The objective of this research is to create an enzyme replacement therapy for Angelman syndrome that allows for delivery of UBE3A to the brain by a peripheral intravenous injection, where the cell penetrating peptide allows the UBE3A to cross the blood brain barrier. Our presentation will highlight the progress we have made in optimizing and testing these proteins in cellular models, organoids and mouse models.

O4

Predictive Gene Expression Signatures for Alzheimer's Disease Using Post-Mortem Brain Tissue

***Ashley Duche**, Oliver Tran, Andrius Baskys, Rachita K. Sumbria, Moom Roosan*

Background: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by amyloid beta (Aβ) plaques and tau protein aggregates. These pathological features manifest in specific regions, but mechanisms rendering some areas more susceptible remain poorly understood. We developed predictive gene expression signatures to explore molecular mechanisms underlying regional vulnerability to AD pathology.

Methods: Post-mortem brain tissue from participants of the Religious Orders Study and Memory and Aging Project (ROSMAP), Mayo Clinic, and Mount Sinai Brain Bank (MSBB) were used to derive gene expression signatures from six brain regions affected at varying stages of AD progression. Differential gene expression analysis identified altered genes, which were used to develop predictive gene signatures using Adaptive Signature Selection and InteGratioN (ASSIGN) to predict pathway activity. Predictions were validated against known AD status across clinical markers, including Aβ plaque deposition, tau aggregates, cognitive assessments, and clinical diagnoses. Dysregulation of key biological pathways was analyzed using g:Profiler and ClueGO along with potential drug repurposing candidates identified using Connectivity Map (CMAP).

Results: Predictive gene expression signatures distinguished AD activity in control and AD post-mortem brain tissue, corresponding to clinical markers of disease severity. The signatures revealed common mechanisms of regional vulnerability, including upregulation of extracellular matrix (ECM)-related processes and downregulation of hormonal signaling pathways. Notably, S100A4 was consistently upregulated, while CRH expression was downregulated except in the cerebellum. Additionally, findings underscored the influence of APOE genotype and sex on disease progression. Drug repurposing analysis identified FGFR inhibitors, specifically oratinib and bromodomain inhibitors, as promising therapeutic candidates.

Conclusion: Molecular signatures underlying regional vulnerability to AD provide a framework for understanding genetic and systemic factors in disease progression. Findings highlight specific molecular pathways, including ECM-related processes and hormonal regulation, as key drivers of susceptibility. Identified drug repurposing candidates present promising therapeutic avenues for further investigation.

O5

The Impact of the Drug Addiction Treatment Act (DATA) Waiver Removal on Buprenorphine Prescribing and Access in California: A Geospatial and Trend Analysis (2022–2023)

***Elena Wu**, Harvey Duong, Ryan Stofer, Sherry Yun Wang*

Background: Removal of the Drug Addiction Treatment Act (DATA) waiver in Jan 2023 significantly altered buprenorphine prescribing patterns in California. Prior to this policy change, prescribers were required to obtain a special waiver to prescribe buprenorphine for opioid use disorder (OUD). The impact of this regulatory shift on prescriber behavior and patient access to buprenorphine treatment remains unclear. This study aimed to evaluate changes in the number and geospatial distribution of buprenorphine prescribers and patients in California between 2022 and 2023.

Methods: This study analyzed buprenorphine prescribing trends using state-level California's prescription drug monitoring program (PDMP) data from 2022 and 2023. We examined overall changes in prescriber counts, patient distribution, and regional accessibility across zip codes. Prescribers were categorized based on patient volume: (1) low-volume (<30 patients), (2) moderate-volume (30–100 patients), (3) high-volume (101–275 patients), and (4) very high-volume (>275 patients). Changes in geographic distribution were visualized using ArcGIS to assess any potential disparities in access.

Results: Between 2022 and 2023 in California, the number of buprenorphine prescribers increased, with a notable rise in low-volume prescribers (5,011 to 6,258; +1,247). However, the number of moderate-volume (205 → 199) and high-volume (40 → 38) prescribers slightly decreased, while very high-volume (101-205) prescribers remained rare (4 → 3). Geographic analysis showed an expansion of prescribers across multiple zip codes, particularly in urban and select rural areas. Despite these increases, patient distribution remained uneven, with some regions experiencing minimal patient coverage.

Conclusions: The elimination of the DATA waiver likely facilitated buprenorphine prescribing among new, low-volume providers, expanding access in certain areas. However, hesitancy among high-volume prescribers, along with persistent barriers such as stigma, insurance limitations, and geographic disparities, may have limited broader treatment accessibility.

O6

Spatiotemporal differential regulation of extrasynaptic GluN2B receptor subunits and PSA-NCAM in brain aging and Alzheimer's disease

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N-methyl-D-aspartate receptors (NMDARs) are critical for synaptic transmission, with GluN2B subunits playing key roles in synaptic plasticity. Extrasynaptic GluN2Bs (ES-GluN2Bs) activate long-term depression (LTD) pathways, potentially promoting dementia in Alzheimer's disease (AD). Polysialylation of neural cell adhesion molecule (NCAM) to PSA-NCAM by ST8-α-N-acetyl-neuraminide-α-2,8-sialyltransferase-4 (ST8Sia4) and UDP-N-acetylglucosamine-2-epimerase (UDP-E) regulates synaptic remodeling and inhibits ES-GluN2B activity physiologically. However, the spatiotemporal dynamics of ES-GluN2Bs and PSA-NCAM in brain aging versus AD, and how Aβ, a pathological hallmark of AD affects these proteins remain unclear. To investigate this, we examined expression levels of NMDAR subunits (GluN2A, GluN2B), ES-GluN2Bs, NCAM, and PSA-NCAM in young and old Tg2576 AD mice and wild-type (WT) controls across the cortex, prefrontal cortex, hippocampus, and midbrain using immunoblotting and pull-down assays. After this, we demonstrated the neurochemical effects of varying concentrations of monomeric Aβ treatment (0, 0.125, 0.25, 0.5, and 1 μM) on ST8Sia4, PSA-NCAM, and UDP-E expression via protein and mRNA quantification in IMR-32 neuroblastoma cells. Interestingly, our finding showed aging reduced overall GluN2B expression in both WT and AD mice (47–51%, n≥4) while increasing GluN2A expression (up to 85%, n≥4). ES-GluN2B levels were significantly elevated in AD mice (2–3-fold, n≥4), but unchanged in WT mice. PSA-NCAM expression was downregulated in AD mice (by 43–58%, n≥4), particularly in the hippocampus and prefrontal cortex, while increasing with normal aging (up to 2-fold, n≥4). Analysis of protein and mRNA expression levels following Aβ treatment in IMR-32 cells revealed significant downregulation (up to 60%) in ST8Sia4, PSA-NCAM, and UDP-E across all concentrations. Summarily, our findings demonstrate AD-specific increases in ES-GluN2B expression and a significant downregulation in PSA-NCAM levels, distinguishing AD from normal aging, potentially driven by Aβ-induced downregulation of biosynthetic enzymes ST8Sia4 and UDP-E. This underscores a potential link between PSA-NCAM expression and Aβ activity in AD, as well as possible therapeutic targets for AD intervention.

O7

Dose escalation of a blood-brain barrier traversing TNF-α inhibitor in a tauopathy (P301S) mouse model

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Background: Tumor necrosis factor-α (TNF-α) is a principal mediator of neuroinflammation, which is central to Alzheimer's disease (AD) pathogenesis. Biologic TNF-α inhibitors (bTNFIs) can attenuate the pathological manifestations of AD by inhibiting proinflammatory cytokine activity. However, their efficacy is limited by their ability to traverse the blood-brain barrier (BBB). To overcome this limitation, a bTNFI was fused to the mouse transferrin receptor antibody (TfRMAb); the latter drives the bTNFI across the BBB into the brain via receptor-mediated transcytosis. The fusion protein, designated as TfRMAb-TNFR, showed protective effects in female tauopathy mice with no effect in male tauopathy mice at a low 1.75 mg/kg dose. The current study aimed to investigate the effect of escalating TfRMAb-TNFR doses in male and female transgenic tauopathy mice.

Method: Nineteen-week-old male and female tau P301S mice (PS19) and age-matched wildtype littermates (n=12) were injected intraperitoneally with saline (n=11), TfRMAb-TNFR (2 and 5 mg/kg; n=9), and equimolar doses of TfRMAb (1.5 and 3.75 mg/kg; n=4) for 10 weeks. Mice received the lower dose for the first five weeks, followed by the higher dose for the next five weeks. Post-treatment assessments of locomotion and spinning behavior were conducted, and brains were collected for histological analysis of phosphorylated tau (Ser202, Thr205), total tau, and microgliosis. Protein levels of pro-inflammatory cytokines in the plasma and brains were quantified using Meso Scale Discovery (MSD). Terminal blood was collected for plasma diagnostic metabolic safety profiling.

Result: PS19 mice exhibited significant changes in locomotor activity ($p<0.05$) and spinning ($p<0.05$) and showed increased phosphorylation of tau (AT8, $p<0.01$) and total tau (HT7, $p<0.001$). Spinning was significantly reduced in PS19-TfRMAb-TNFR mice ($p<0.0001$) compared to PS19-saline mice. TfRMAb-TNFR treatment showed significant sex differences. TfRMAb-TNFR significantly reduced AT8 load in male PS19 mice ($p<0.01$) but increased AT8 load in female PS19 mice ($p<0.001$). An inverse effect was seen on microgliosis with TfRMAb-TNFR. Interestingly, TfRMAb-TNFR significantly reduced pro-inflammatory cytokine levels in the female PS19 mice brain ($p<0.01$) and in the plasma of the male PS19 mice $p<0.05$) compared to their respective sex-matched saline-treated PS19 mice. Total tau decreased significantly in both male and female PS19 mice with TfRMAb-TNFR compared with saline ($p<0.01$). No overt changes to the plasma metabolic panel or TfR expression were observed with TfRMAb-TNFR compared with saline in PS19 mice.

Conclusion: Male and female PS19 mice show differential responses to TfRMAb-TNFR, highlighting the sex-dependent therapeutic effects of escalating doses of TfRMAb-TNFR in this tauopathy mouse model. Future research should investigate the sex-specific effects of peripheral and brain inflammation on tauopathy.

O8

Tracking Stimulant Use with Concurrent Controlled Substances from Adolescence to Young Adulthood in California

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High rates of prescription drug misuse among adolescents and young adults have put renewed focus on ensuring judicious use of controlled medications to limit adverse outcomes related to misuse. This longitudinal study tracked ADHD stimulant usage and its association with other controlled substance use in young adults, using California's CURES database from 2019-2022 obtained from the Department of Justice. This study focused on adolescents who were 18 in 2019, following their controlled substance dispensing patterns into early adulthood. Descriptive statistics evaluated stimulant, opioid, and benzodiazepine use using the R statistical software. In 2019, 12,939 adolescents were dispensed stimulants, decreasing to 4,193 (32.4%) by 2022. Gender disparities were evident as males favored stimulant-only (61.8%) and stimulant-opioid combinations (55.3%), while females showed higher usage of stimulant-benzodiazepine combinations (51.6%). Those using all three substances showed equal gender distribution. Of the 11,473 stimulant-only prescriptions in 2019, only 27.9% remained on stimulants by 2022, 1.2% used stimulants and benzodiazepines, 2.2% used stimulants and opioids, and 0.2% used all three. The majority (68.5%) discontinued all three substances. Among those on stimulant benzodiazepine and stimulant-opioid combinations in 2019, most (65.3% and 58.7%) stopped all three by 2022, 12.9% and 2.6% continued the same combination, while 17.7% and 35.9% switched to stimulant-only therapy, respectively. Similar trends were seen in those using all three substances, with 58.8% discontinuing all by 2022. These findings highlight evolving substance use patterns as adolescents transition to young adulthood, revealing a significant shift towards discontinuation of stimulants and combined controlled substance use. Continuous monitoring and targeted interventions are essential for mitigating substance misuse risks.

O9

Role of PGRMC2: Insights from a Cardiomyocyte-Targeted Knockout Mouse Model

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Cardiac diseases, including coronary artery disease, heart failure, and arrhythmias, remain leading causes of morbidity (disease) and mortality (death) worldwide. Genetic factors significantly influence both the development and progression of these diseases. Our previous transcriptomic studies indicated that progesterone receptor membrane component 2 (PGRMC2) is involved in cardiomyopathy.

In this present study, we investigated the effect of the PGRMC2 gene on cardiac disease using a targeted knockout (KO) mouse model. Wild-type and PGRMC2 KO mice were compared for their cardiac functions and molecular characteristics. The presence of PGRMC2 in lysed heart cells was evaluated using Western blot analysis, with GAPDH serving as a loading control. PGRMC2 expression was confirmed in wild-type (WT) mice, while the KO mice showed a marked reduction in PGRMC2 expression. The genotyping was conducted using the MYH6-Cre system, which specifically targets the heart, allowing us to assess the effects of PGRMC2 KO solely in cardiac tissue. In addition to heart tissue, kidney lysates were analyzed via Western blot analysis to confirm the tissue-specific knockout.

Magnetic resonance imaging (MRI) of the hearts revealed structural and functional changes in the animals with the PGRMC2 KO. More specifically, the analysis of cardiac output and ejection fraction demonstrate significant cardiac dysfunction in the PGRMC2 KO mice under hypoxic conditions. The KO mice exhibited reduced right ventricular ejection fraction, stroke volume, and cardiac output, alongside increased pulmonary artery pressure and resistance, indicating right heart failure associated with pulmonary arterial hypertension. In addition, left ventricular dysfunction was observed with elevated LV end-systolic volume and decreased ejection fraction, particularly under hypoxia. MRI revealed ascites, pulmonary congestion, and portal congestion, all indicative of congestive heart failure. Elevated levels of heart failure biomarkers, such as atrial natriuretic peptides, brain natriuretic peptides and troponin, further confirmed the presence of heart failure in the KO mice with both left and right heart congestion. The KO group also exhibited fluid accumulation in the abdomen, a characteristic sign of heart failure. These findings suggest that the absence of PGRMC2 in the heart leads to significant cardiac dysfunctions.

This study highlights the critical role of PGRMC2 in cardiac functions and suggests that its absence may contribute to the development of congestive heart failure. Our results provide valuable insight into the molecular mechanisms underlying cardiac diseases and the potential for targeting PGRMC2 as a therapeutic approach for heart failure.

O10	**Function of Phosphodiesterase Isoforms in Human Airway Smooth Muscle Cell cAMP Signaling Compartments** ***Jordyn Margolis**, Isabella Cattani-Cavalieri, Eric Gebski, Rennolds Ostrom* Isoproterenol (ISO) and Prostaglandin E2 (PGE2) induce cyclic adenosine monophosphate (cAMP) production via activation of ß2-adrenoreceptors (β2AR) and EP2/4 receptors (EP2/4R), respectively to induce airway smooth muscle relaxation and bronchodilation. β2AR agonists are approved therapies for managing airway hypercontractility in asthma and chronic obstructive pulmonary disease (COPD), but EP2/4R are not. Different G protein-coupled receptors (GPCRs) elicit compartmentalized cAMP signaling responses in lipid raft or non-raft domains. Phosphodiesterases (PDEs) are vital regulators of cAMP compartmental signaling due to their ability to metabolize cAMP to adenosine monophosphate (AMP). The aim of this study is to understand how different PDE isoforms are expressed in human airway smooth muscle (HASM) cells and how PDEs might regulate β2AR and EP2/4R signaling. HASM cells were transduced with a mammalian baculovirus expressing various forms of the cADDis biosensor using centrifugal force. cADDis reports cAMP levels in real time via changes in fluorescence and can be altered to target to different subcellular locations. We expressed cADDis in lipid rafts (cADDis-FMP), non-raft plasma membranes (cADDis-FS15), or the cytosol (cADDis-OG, non-targeted) and measured the change in fluorescence after drug addition. Responses were normalized to a maximal concentration of forskolin (FSK, 10 µM). Each of these biosensors were stimulated with either ISO or PGE2 with and without either 10 nM cilostazol (CIL; PDE3), 10 nM rolipram (ROL; PDE4), or 100 nM PF-04957325 (PF; PDE8). We observed increased ISO-stimulated cAMP detected by cADDis-FMP upon addition of ROL, suggesting PDE4 is functional in lipid raft domains. cADDis-FS15 detected an increased PGE2-stimulated cAMP following addition of PF, suggesting PDE8 is functional in non-raft domains. Addition of CIL reduced cAMP levels in all conditions tested, implying a non-specific effect of this inhibitor. PDE isoforms appear to have specific effects in HASM cell cAMP compartments.

O11

Development of Pharmaceutical Inhibitors Targeting nNOS for Melanoma Treatment

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Interferon gamma (IFN-γ) in the melanoma tumor microenvironment plays opposing roles, orchestrating both pro-tumorigenic activity and anti-cancer immune responses. Our previous studies demonstrated the role of neuronal nitric oxide synthase (nNOS) in IFN-γ-stimulated melanoma progression. However, the underlying mechanism has not been well defined. This study determined whether the nNOS/NO and COX-2/PGE2 signaling pathways crosstalk and augment the pro-tumorigenic effects of IFN-γ and how nNOS inhibition impacts the immune response in melanoma. Bioinformatic analysis of proteomic data was conducted to identify proteins of interest associated with IFN-γ treatment in melanoma. Changes in protein expression were determined using various analytical techniques including western blot, flow cytometry, and confocal microscopy. The levels of PGE2 and nitric oxide (NO) were analyzed by HPLC chromatography and flow cytometry. *In vivo* antitumor efficacy was determined utilizing a human melanoma xenograft mouse model. Changes in mouse T cells were identified using flow cytometry. Our omics analyses revealed that the induction of COX-2 was significantly predictive of IFN-γ treatment in melanoma cells. In the presence of IFN-γ, PGE2 further enhanced PD-L1 expression and amplified nNOS induction, which increased intracellular NO. Cotreatment with celecoxib effectively diminished these changes induced by PGE2. In addition, nNOS blockade using a selective small molecule inhibitor (HH044), efficiently inhibited IFN-γ-induced PGE2 and COX-2 expression levels in melanoma cells. Furthermore, celecoxib was shown to enhance HH044 cytotoxicity *in vitro* and effectively inhibit human melanoma tumor growth *in vivo*. HH044 treatment also significantly reduced tumor PGE2 levels *in vivo*. Immunophenotyping of mouse peripheral blood mononuclear cells (PBMCs) after prolonged HH044 treatment showed significant increases in CD4+PD-1+ and CD8+PD-1+ T cells. Our study demonstrates the positive feedback loop linking nNOS-mediated NO signaling to the COX-2/PGE2 signaling axis, which further potentiates the pro-tumorigenic activity of IFN-γ and that nNOS inhibition markedly impacts the immune profile in melanoma.

O12

Structural Insights into the Pharmacological Modulation of KCa3.1 Channels by SKA-111 and DHP-103 Revealed by Cryo-EM

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The intermediate-conductance Ca2+-activated K+ (KCa3.1, also called SK4) channel mediates K+ efflux in response to elevated intracellular calcium concentration in many cell types including red blood cells. Gain-of-function mutations of KCa3.1 located either in the calmodulin (CaM)-binding region of KCa3.1 (e.g. S314P, A322V, R352H) or at the inner gate of the ion conduction pathway (e.g. V282M) cause hereditary xerocytosis, a hemolytic anemia, in a subset of patients. A KCa3.1-selective blocker, 1,4-dihyropyridine 103, blocks mutant channels S314P and R352H with equal potency as wild-type KCa3.1 (IC50 ~6 nM), while the A322V mutant is less sensitive. Here, we used cryogenic-electron microscopy (cryo-EM) to determine two structures of the KCa3.1 channel, one bound to 1,4-dihydropyridine 103 at ~3.45 Å resolution (103_KCa3.1), and the other to a subtype-selective positive gating modulator (SKA-111) at 3.09 Å resolution (SKA-111_KCa3.1). In the 103_KCa3.1 structure, the cryo-EM density of 1,4-dihydropyridine 103 is seen in the water-filled central cavity of the channel pore sandwiched between the innermost K+ in the selectivity filter and an additional K+ in the central cavity where it directly impedes ion permeation. In the drug-bound SKA-111_KCa3.1 structure, SKA-111 is positioned between the N-lobe of CaM and the S4-S5 linker of the KCa3.1 channel, consistent with previous results using site-directed mutagenesis and patch clamp. Widening of the inner gate by SKA-111 represents a potential mechanism for its positive gating modulation of the KCa3.1 channel. These cryo-EM structures help elucidate modulatory mechanisms by pharmacological agents that target the KCa3.1 channel and shed light on the gating mechanism of KCa3.1.

O13

Comparison of Statin Use for ASCVD Prevention in People with HIV at a Federally Qualified Health Center

Shaien Rivers, *Jerika Lam*

Introduction: Current guidelines recommend statin therapy for people with HIV (PWH) with high 10-year atherosclerotic cardiovascular disease (ASCVD) risk scores or after nonpharmacological interventions have failed. While statins traditionally aim to benefit high-risk populations (i.e., have clinical ASCVD, diabetes mellitus), recent studies report promising reductions of ASCVD-related events by extending primary prevention to lower risk estimates (ASCVD score of 5-10%). By evaluating the impact of statin use, clinical pharmacists can assess the efficacy of primary ASCVD prevention intervention for PWH. This study aims to further establish necessary statin therapy optimization for PWH who have low-to-moderate 10-year ASCVD risk.

Methodology: A chart review will be conducted between 2020 to 2023 comparing PWH who are prescribed a statin medication and PWH who have low-to-moderate 10-year ASCVD scores of 5-10% and are not prescribed a statin medication at the AltaMed clinic, a Federally Qualified Health Center, in Anaheim, California. Comparison between the two patient groups will allow for an evaluation of the efficacy of primary ASCVD prevention intervention for PWH. Efficacy will be assessed via determining the calculated 10-year ASCVD risk scores at baseline and during treatment, particularly laboratory biomarkers (e.g., cholesterol panel, viral load, CD4+ counts, transaminases, and renal function), weight and BMI, comorbid health conditions, types of statins taken, and concomitant medications including antiretroviral treatments.

Results: pending

Conclusion: pending