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Scientific Session Abstracts

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Advanced development of a novel synthetic Mincle Adjuvant, UM-1098, in combination with a clinical stage mycobacterium tuberculosis antigen (M72) to induce robust protective Th1/Th17 immunity against TB

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The urgent need for safe and effective Th1/Th17-inducing adjuvants is critical for advancing vaccines against bacterial and fungal pathogens, including *Mycobacterium tuberculosis* (*Mtb*), *Bordetella pertussis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and others. Approximately one-fourth of the global population is latently infected with tuberculosis (TB), with a 10% risk of developing active TB. In 2022, TB was the second deadliest infectious disease after COVID-19, causing twice as many deaths as HIV/AIDS. The World Health Organization's 2015 End TB Strategy aims for a 90% reduction in TB incidence by 2035. Despite global and domestic efforts to develop prevention strategies and treatments for TB, challenges such as drug-resistant strains and the variable efficacy (0-80%) of the only licensed TB vaccine, BCG persist. Ongoing research is needed to develop additional safe and effective TB vaccines that prevent both infection and disease. Effective Th1 and Th17 responses are essential for TB protection, yet adjuvants and delivery systems that induce robust Th1 and Th17 immunity are lacking. Thus, developing next-generation vaccine adjuvants that provide broad immune protection against emerging bacterial and fungal pathogens is a critical unmet need. Our research aims to advance a novel synthetic Th1/Th17-inducing Mincle ligand, UM-1098, toward human clinical trials. We have developed a simple but effective strategy for co-delivering Mincle agonists with the recombinant *Mtb* fusion antigen, M72, using tunable silica nanoparticles (SNP). This adjuvant formulation demonstrated safety and efficacy in mice, pigs, and non-human primates across multiple antigen/pathogen platforms, including *Mtb*. In a virulent *Mtb* challenge model, vaccination with M72 adjuvanted with UM-1098/SNP significantly reduced lung bacterial burden compared to unvaccinated mice, providing protection without pulmonary inflammation. These findings support further development of the UM-1098 adjuvant formulation for immunization against TB and other diseases where Th1/Th17 immunity contributes to protection.

Measuring the effects of pharmacy closures on medication adherence

Kelly Anderson, PhD
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OBJECTIVES: Pharmacy closures in the United States have been well-documented, however the effect of pharmacy closures on patient outcomes are not well understood. In this study, we examine effects on anticonvulsant medications, which are a “protected class” of drugs for Medicare Part D plans. Nonadherence to anticonvulsants has been linked to increased mortality and increased emergency department visits for patients with epilepsy.

METHODS: We identified our cohort using 2018-2022 Colorado All Payer Claims Database (CO APCD) for ages 18-89. Pharmacy type and closure date were identified using National Council for Prescription Drug Programs (NCPDP) dataQ. From this data, we identified anticonvulsants, defined

based on IQVIA's therapeutic class classification system. We defined exposure to a pharmacy closure as filling a medication at a location that closed in the subsequent 6 months. To measure the effects of pharmacy closures, we constructed time-varying difference-in-differences models.

RESULTS: Prior to pharmacy closures, patients filled an average of 0.94 prescriptions and 31.24 days' supply monthly for anticonvulsants. Parallel trends assumptions were met in the pre-period. In the difference-in-differences analyses, we found pharmacy closures reduced monthly fills per patient by 0.17 fills (17.9%)(p-value: <0.001) and days supplied by 3.82 days (12.3%)(p-value: <0.001). When excluding mail-order fills, pharmacy closures reduced monthly fills per patient by 18.6% (p-value: <0.001).

CONCLUSIONS: Studying the effects of pharmacy closures on anticonvulsant use, we found significant reductions in number of fills and days' supply for anticonvulsants. The reduction in days' supply (12.3%) was smaller than the reduction in number of monthly fills (17.9%) indicating some patients shift to filling larger volume prescriptions in response to pharmacy closures. As the reduction in fills is larger when excluding mail order fills, this suggests some patients shift from filling their prescriptions from regular retail to mail-order, but the effect is relatively small.

Extreme heat and wildfire smoke exposure in the western U.S.: A geospatial analysis

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Climate change is an urgent public health challenge with wide reaching effects across the globe. In the Western United States, the increasing frequency and intensity of wildfires and extreme heat events pose a significant risk to human health. Evidence suggests that exposure to wildfire smoke alone or exposure to extreme heat alone can each increase the risk of morbidity and mortality, but relatively little is known about the health effects of concurrent exposure to wildfire smoke and extreme heat, particularly for those with underlying cardiovascular disease. Empirical evidence on the health effects associated with exposure to these hazards is needed to inform the implementation of clinical care and public health interventions that ameliorate the deleterious effects of wildfire smoke and extreme heat to population health. This presentation will provide an overview of current research characterizing exposures to wildfire smoke and extreme heat during the summer of 2021 and the associated health outcomes for those with cardiovascular disease.

Advancing pediatric treatment options in children with HIV: Insights from the IMPAACT 2019 study

Kristina Brooks, PharmD
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IMPAACT 2019 was an international, open-label, dose confirmation study to evaluate the pharmacokinetics, safety, and efficacy of a new child-friendly, dispersible fixed dose combination formulation for the treatment of children with HIV. Kristina Brooks, PharmD is the lead pharmacologist for this study, and her laboratory is supporting analyses of pharmacokinetic samples and data from these investigations. She will speak about the design, analysis, and ongoing research efforts within this study, and how these collective efforts with the IMPAACT Network supported the availability of this new formulation across the globe.

Projected cost savings from optimal medication adherence in cardiovascular disease patients requiring lipid lowering therapy: a multi-national economic evaluation study

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Poor adherence to chronic cardiovascular medications can impede the achievement of targeted clinical outcomes. Given the increasing demand for interventions to improve medication adherence and the recent development of digital technologies as potential solutions, it is crucial for policymakers to understand the benefits and economic impacts of these interventions.
This study estimated the potential benefits of improving adherence among cardiovascular disease (CVD) patients requiring secondary prevention in Mexico, Thailand, and China using a Markov model simulation from both healthcare system and societal perspectives. We compared two scenarios: (1) optimal adherence based on a meta-analysis of 51 randomized controlled trials (RCTs) and (2) the status quo as reported in the literature for each country. The association between adherence and CVD outcomes was derived from a dose-response meta-analysis involving 4,051,338 patients.
Outcomes included the total number of CVD events and associated costs in 2022 USD, life-years, and quality-adjusted life years (QALYs). It was estimated that achieving optimal adherence could prevent 40 CVD events in Mexico, 34 in Thailand, and 63 in China among a hypothetical cohort of 1,000 patients over a lifetime horizon. The incremental effectiveness per patient was 0.6 life-years in Mexico, 0.68 QALYs in Thailand, and 0.93 QALYs in China. From the societal perspective, the total cost savings associated with optimal adherence were $412 in Mexico, $316 in Thailand, and $700 in China. The results of cost savings remained robust in both deterministic and probabilistic sensitivity analyses. Our study indicates that achieving optimal adherence among CVD patients requiring lipid-lowering therapy can save costs and improve health outcomes in Mexico, Thailand, and China. These findings support the consideration of strategies to enhance adherence in these countries.

Phenoconversion in drug transporter function provides a novel strategy to diagnose MASH

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Fewer than 1% of patients with metabolic dysfunction-associated steatohepatitis (MASH) have been identified by liver biopsy, even though new therapies are available to treat this inflammatory fibrogenic condition. Screening methods to identify patients with MASH including imaging techniques and lab tests using endogenous biomarkers are generally less effective due to a lack of sensitivity or specificity, cost, availability, and other concerns. We have demonstrated that progression to MASH results in changes to three separate drug transport processes which combine to result in the decreased biliary efflux of the metabolite of our exogenous probe drug (EZE-Gluc), and the retention of the metabolite in the blood, and subsequently urine. Hence, these transporter changes potentiate the accumulation of the exogenous biomarker in the blood and urine of MASH patients that increases with disease severity. Our preliminary data in humans demonstrate a disease-specific transporter expression pattern, a selective biomarker substrate for those transporters, and an exciting proof of concept in MASH patients. Reported data indicates a 70% increase in mild, 400% increase in moderate, and 600% increase in patients with severe hepatic impairment. Our patent shows that plasma and/or urine levels of EZE-Gluc following a safe ($1/10^{th}$ of the normal therapeutic dose of EZE) can be used as a diagnostic screening tool to identify patients with MASH that could potentially include disease severity. We anticipate that the altered disposition of EZE-Gluc in MASH patients will serve as a specific, non-invasive exogenous biomarker capable of diagnosing patients with MASH. This simple screening test can be quickly and widely used to identify patients for subsequent therapy for MASH.

Using 'designer' chromatin to profile interactors of acyl modifications

Katharine Diehl, PhD
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Histones serve as the scaffold for the eukaryotic genome, and these proteins are highly post-translationally modified to regulate access to the DNA. While many histone modifications, such as acetylation, have been studied now for decades, recent mass spectrometric evidence has shown that there are a variety of other acyl groups that modify histones. This finding has led to the hypothesis that the presence of specific acyl modifications on chromatin connect the metabolic state and the genome, since each acyl group is derived from the corresponding acyl-CoA. This idea has led to many questions about how these different acyl marks are regulated and how each one leads to differential gene regulation. To get at these questions, we used protein semisynthesis to produce site-specifically acylated chromatin that we then used to investigate the interactome of that acyl modification. So far, we have identified a novel eraser enzyme of histone lactylation as well as several putative readers of

this modification. These findings provide a critical starting point for understanding how lactylation connects lactate metabolism and transcriptional regulation in cells.

Disabling polarity switches to combat cancer metastasis

Martin Golkowski, PhD
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Metastasis and associated therapy resistance remain the principal cause of cancer-related death. We discovered that hepatocellular carcinomas (HCC) that have transdifferentiated to a metastatic phenotype systematically rewired their kinome to enable polarity switching and directed cell migration, exposing a possible vulnerability for combatting HCC metastasis. Solid cancers like HCC can highjack diverse developmental and stress pathways, which in concert with genetic and epigenetic alterations, allow them to acquire phenotypic plasticity. Plastic cancer cells can trans-differentiate to a mesenchymal phenotype through the epithelial-mesenchymal transition (EMT), promoting an elongated morphology, increased motility and invasiveness, and enhanced resistance to apoptosis. Systematic transcriptional and post-transcriptional rearrangements underly the EMT. This includes switching from the apical-basal polarity of epithelial cells to the front-rear polarity of mesenchymal-like cells, a perquisite for directed cell migration. Accordingly, targeting polarity switching may help prevent metastasis. To identify pharmacological targets for disabling polarity switches in HCC, we applied our mass spectrometry (MS)-based proteomics pipeline for kinome activity profiling to epithelial HCC lines that were stimulated to undergo the EMT. This revealed the increased activity of a sub-network of kinases that control endocytosis, vesicle trafficking, the centrosome-microtubule axis and cell adhesion. Inhibiting one of these kinases, death-associated protein kinase 3 (DAPK3), completely blocked mesenchymal HCC cell migration. We hypothesize that DAPK3 controls polarity switching through centrosome re-positioning during the EMT, and that inhibiting DAPK3 blocks HCC cell metastasis.

Structural mapping of mitochondrial co-translational import in cells

Danielle Grotjahn, PhD
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Despite containing their own distinct genome, mitochondria rely heavily on the nucleus to encode 99% of the proteins necessary for mitochondrial function. Most of these proteins are synthesized by cytoplasmic ribosomes before targeting and import to mitochondria. However, a subset of proteins is imported co-translationally, with their synthesis and import occurring simultaneously. Although evidence of co-translational import into the mitochondria was discovered nearly five decades ago, the molecular mechanisms mediating this elusive process have remained unclear and somewhat debated. Our lab harnessed state-of-the-art imaging and computational tools to provide a new molecular perspective to this elusive process. We show that cytoplasmic ribosomes engaged in co-translational import make multiple contacts with the mitochondrial outer membrane. We show that ribosomes

primed for import exhibit a high degree of clustering on the mitochondrial surface in an arrangement that suggests the formation of polysomes. Interestingly, these ribosomes localize at sites of local constrictions of the outer and inner mitochondrial membrane, suggesting that local membrane remodeling may facilitate efficient protein import into the distinct mitochondrial compartments. Our work sets the stage for enabling future studies to identify molecular mechanisms mediating mitochondrial co-translational import.

Insulin prices and manufacturer discounts: implications for patients and policy reform

Inma Hernandez, PhD
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Importance: Despite the political salience of insulin prices, no study has quantified trends in insulin prices that account for manufacturer discounts (rebates).
Objective: To describe trends in list prices and net prices of insulin products in 2012-2019, and to quantify total discounts provided by manufacturers for insulin products.

Design: Longitudinal analysis of Medicare, Medicaid, and SSR Health data.

Setting/Participants/Exposures: US sales of insulin products.

Main Outcomes and Measures: We estimated net prices for insulin products as list prices minus manufacturer discounts negotiated with payers (rebates). We quantified total discounts as the difference between gross and net sales for each product and year. From this figure, we isolated rebates using a peer-reviewed algorithm.

Results: Net prices of long-acting insulins increased at an annual growth rate of 23.6% from 2012-2014 but decreased at an annual rate of 8.3% driven by increased rebates following the introduction of new products Toujeo, Tresiba, and Basaglar in 2015. Net prices of short-acting insulins increased at an annual growth rate of 5.6% from 2012-2017 but decreased in 2017-2018 following the introduction of Fiasp and Admelog. In 2012-2019, rebates increased from 22.7% to 64.8% for long-acting insulins and from 37.9% to 66.1% for short-acting insulins. Rebates for the four leading insulin products (Lantus, Levemir, Humalog, and Novolog) increased from $$3.5 billion in 2012 to $16.4 billion in 2019.

Conclusions and Relevance: Insulin list prices have grown substantially since 2010, but net prices have declined since 2015 because of rising manufacturer discounts. These diverging trends result into an increasingly large difference between list and net prices of drugs, often called “the gross-to-net-bubble”, which may exacerbate inequities in access, as patient cost-sharing is based on list price.

Discovery and characterization of microbial protein nanocompartments encoded in natural products gene clusters

Jesse Jones, PharmD
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Encapsulins are recently discovered self-assembling protein nanocompartments capable of selectively encapsulating dedicated cargo proteins, including enzymes involved in iron storage, sulfur metabolism, and stress resistance. Recently, they have also been found within natural product gene clusters, potentially presenting a novel process for natural product biosynthesis. Here, we discuss the bioinformatic analysis leading to the discovery of encapsulins residing within natural products gene clusters, as well as the preliminary work conducted to characterize the related natural product biosynthetic gene products, with a particular emphasis on the potential encapsulin nanocompartments themselves.

Pharmacological adaptation of proteostasis to ameliorate neurodegenerative diseases

Jeffery Kelly, PhD
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The cellular protein homeostasis, or proteostasis network regulates proteome function by controlling ribosomal protein synthesis, chaperone- and chaperonin-mediated protein folding, protein trafficking, proteasome and lysosomal-directed protein degradation, and related processes. Stress-responsive signaling pathways match proteostasis network capacity with demand in each subcellular compartment to maintain or alter cellular homeostasis. The beginning of the seminar will focus on how a protein homeostatic deficiency leading to neurodegeneration and/or organ deterioration in an aging-associated amyloid disease can be stopped or slowed utilizing small molecule kinetic stabilizers. The second part of the talk will focus on how we discovered drug candidates that adapt proteostasis by enhancing lysosomal flux via a high throughput screen. One of these compounds extends lifespan and healthspan in *C. elegans*, while also clearing the alpha-synuclein aggregates in neurons, a process that is thought to cause Parkinson's disease, studies performed in collaboration with the Laushel laboratory. Another of these mTOR inhibitor-independent autophagy activator hits reduces cytotoxic axonal mutant prion protein aggregate levels within endosomes of murine primary hippocampal neurons and normalizes axonal trafficking deficiencies, studies performed in collaboration with the Encalada Laboratory. In addition, a subset of hits from the screen robustly clear phosphorylated and insoluble tau, while reducing tau-mediated neuronal stress vulnerability in an iPSC-derived neuronal familial tauopathy model, studies carried out in collaboration with the Haggarty/Silva laboratories.

Mining nature's chemistry from the ocean to improve human health

Brad Moore, PhD
University of California San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences

The ocean covers about 70% of our planet and is home to diverse species that make thousands of bioactive natural products. Despite supply challenges associated with rare marine organisms that live in the deep sea, there are over 20 approved pharmaceuticals based on marine natural products. We have developed a program to mine the genomes of life from the sea to discover new drug leads and evade marine toxins. This talk will highlight our progress on developing genome mining platforms to the phase III glioblastoma drug salinosporamide A and the common seafood neurotoxin domoic acid.

Skin reconstruction device for austere environments

Monica Serban, PhD
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Austere environments in which access to medical facilities, medical personnel, or even water and electricity is limited or unavailable pose unique challenges for medical device product design. Currently existing skin substitutes are severely inadequate for the treatment of severe burns, chronic wounds, battlefield injuries, or work-related injuries in resource-limited settings. To address these unique needs, our group prototyped a biomaterials-based device specifically designed for use in low-resource circumstances. Our results indicate that this prototype is mechanically robust, is cytocompatible, protects from wound-specific oxidative stress damage, is self-adherent and does not require medical skills for deployment, is capable of topical drug delivery for infection and/or pain management, and promotes tissue repair.

Mechanisms of accumulation of nano-drugs and nanoparticles in the skin

Dmitri Simberg, PhD
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences

The skin is the body's largest organ and plays a crucial role in immune function. However, the use of nanosized drug delivery systems can often result in skin toxicity. For instance, PEGylated liposomal doxorubicin (PLD) is known to cause severe skin toxicity known as palmar-plantar erythrodysesthesia (PPE). Despite this, there has been limited research into the mechanisms behind the skin accumulation of nanoparticles. Our study utilized ex vivo fluorescent imaging and skin flap confocal microscopy to demonstrate that systemically injected nanoparticles and liposomes tend to accumulate in the mouse skin, particularly in areas subject to mechanical stress and pressure (1-3). Through experimental

physiology approaches, we were able to show that the extravasation in these areas is passive and does not require energy or transcytosis (3). Additionally, optoacoustic in vivo imaging and transcriptomic analysis of mouse skin indicated that proinflammatory responses to accumulated doxorubicin further increase vascular permeability and enhance the accumulation of liposomes, creating a detrimental feedback loop. Confirmation of the pathophysiological mechanisms underlying this phenomenon in patients can help develop strategies to mitigate the toxicities associated with nanoparticles.

Accelerating drug discovery with artificial intelligence

Travis Wheeler, PhD
University of Arizona, R. Ken Coit College of Pharmacy –

Deep Learning techniques have produced remarkable breakthroughs across a diverse space of challenging problems‡. Based on such successes, it is natural to expect that Deep Learning methods will similarly lead to dramatic advances in the accuracy of methods for rapidly predicting the interaction potential of a target protein and a drug candidate. In my talk, I will discuss some advances along these lines, and work that we are performing to gather massive new data sets to train the next generation of Deep Learning methods for virtual screening.
*Note: I asked an AI chat tool to create a haiku describing my research. It gave me the following ... then provided the second as a bonus.

Protein worlds unfold,
AI guides through vast landscapes,
Cures within our grasp.

Simulations dance,
Molecules in vibrant waltz,
Discovery awaits.

Accelerating antimalarial drug discovery

Elizabeth Winzeler, PhD
University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences

Malaria is an often-fatal parasitic disease spread by mosquitos. Despite decades of effort focused on control and elimination, the number of worldwide malaria cases has stagnated. In 2022, there were an estimated quarter billion cases of malaria. There is no protective vaccine that can be used to fully protect the 3 billion people at risk, and malaria is both prevented and treated by antimalarial medicines. New approaches and new medicines will be needed if case numbers are to be reduced, especially in Sub-Saharan Africa where resistance to current therapies are emerging. We are using a

collaborative, multifaceted and multi-institutional approach to develop new treatments and new solutions to the malaria problem. These include discovering new drug targets, understanding drug resistance liabilities and exploring new therapeutic modalities with a focus on strategies that could potentially replace vaccines for malaria prevention and malaria elimination.

Developing papain-like protease (PLpro) inhibitors as broad-spectrum coronavirus treatments

Rui Xiong, PhD
University of Arizona, R. Ken Coit College of Pharmacy

Coronaviruses, a family of viruses causing respiratory illnesses, have become a significant public health concern, particularly with the SARS-CoV-2 pandemic. Despite available vaccines and antivirals, the emergence of new variants necessitates ongoing drug development. The papain-like protease (PLpro), an essential viral protease highly conserved among coronaviruses, presents an attractive target for antiviral drug development. However, there are currently few potent and validated PLpro inhibitors. This scarcity is largely due to the featureless binding pockets at the gly-gly recognizing P1 and P2 substrate-binding sites, which pose a significant challenge in developing potent inhibitors. In our previous research, we identified a series of potent PLpro inhibitors through co-crystal structures, some of which bind to a newly discovered region on the PLpro, known as the "BL2 groove". Building on these findings, we've now designed a series of covalent inhibitors targeting the "BL2 groove" and mimicking the "gly-gly" sequence. These novel compounds show high potency against SARS-CoV-2, with some demonstrating similar or superior efficacy to nirmatrelvir. Moreover, some molecules exhibit strong activity against MERS-CoV, which has a 30% mortality rate upon infection. Collectively, our design represents a promising strategy for developing broad-spectrum coronavirus treatments, addressing the urgent need for effective therapeutics against both current and potential future coronavirus threats.

In silico and in vivo phenotypic drug screening for mitigating noise-induced hearing loss

Danny Xu, PhD
Idaho State University, L.S. Skaggs College of Pharmacy

In 2022, the American Public Health Association (APHA) designated noise as a public health hazard. (Banks & Fink, 2022) Noise exposure is the leading cause of acquired hearing loss, a significant global health burden affecting nearly 500 million people worldwide. (WHO, 2018) Overexposure to hazardous levels of noise is estimated to account for 30% of all hearing loss, making noise exposure the leading preventable cause of hearing loss. (Rabinowitz, 2000) Noise-induced hearing loss (NIHL) is also the most prevalent occupational disease in the world, with an estimated 1.3 billion people suffering from hearing loss due to noise overexposure. (Vos et al., 2012). The National Institute for Occupational Safety and Health (NIOSH) estimates that 22 million American workers are exposed to

hazardous noise levels every year at work. In particular, firefighters are at heightened risks of hearing impairment due to long-term exposure to excessive occupational noise from sirens, water pumps, saws, and other power equipment. (Hong, Samo, Hulea, & Eakin, 2008) Noise overexposure often results in permanent hearing impairment with associated auditory symptoms such as tinnitus. Despite of the high societal economic burden and impact on quality of life, there are no FDA-approved pharmacological interventions for hearing protection. Noise-induced hearing loss remains a significant, life-altering medical issue among a large high-risk worldwide population, creating an urgent need for finding new effective otoprotective therapies. In this talk, we will describe new in silico and in vivo approaches to screen for novel otoprotectants and discuss the translability between zebrafish and rodent models.

Bench to bedside development of cancer immunotherapies at Calibr-Skaggs

Travis Young, PhD
Scripps Research, Skaggs Graduate School of Chemical and Biological Sciences

The development of cancer therapies has reached an inflection point with the advent of immunotherapies. These approaches, based on redirecting a patient's own immune system to recognize and eliminate tumor cells have been transformative for patients, resulting in curative responses in otherwise highly treatment refractory diseases for which no other options existed. At Calibr-Skaggs we have built a pipeline of differentiated immunotherapy approaches that are at the forefront of this wave of innovation and leverage our experience in bench to bedside translation. This includes a gene and cell therapy called a "switchable" chimeric antigen receptor (CAR)-T cell therapy that allows precision control of genetically engineered cells that enables them to seek and destroy cancer cells within patients. Thus far this platform as shown excellent activity resulting in complete responses in patients with lymphoma that had failed up to 8 prior treatments, with an improved safety profile compared with conventional CAR-T cell approaches. This platform is progressing forward into breast cancer and autoimmune conditions this year. In another approach, we have developed trispecific antibodies that build on the concept of redirecting a patient's T cells to target cancer using biologics. These highly engineered antibodies use multiple arms to engage the T cell, inducing improved anti-tumor immunity compared with existing approaches. We have also initiated programs to develop *in situ* based gene therapies in which viral vectors can be directly delivered to patients to reprogram immune cells to recognize tumor cells. These approaches complement our cancer portfolio which includes small molecules, antibody drug conjugates, novel immuno-oncology targets and reflect our commitment to developing the next generation of cancer therapies for patients.

Targeting cyclin-dependent kinases (CDKs) in cancers: from CDK inhibitors to cyclin degraders

Solomon Zeleke, PhD
Idaho State University, L.S. Skaggs College of Pharmacy

The cyclin-dependent kinase (CDK) family of proteins play a critical role in transcription, mRNA processing and cell cycle regulation, making them attractive targets for cancer treatment. Our research has identified clinical-stage CDK4/6 inhibitors that effectively impede aberrant cell cycle progression in various cancers, including those affecting the central nervous system. We have also developed inhibitors that specifically target CDK12. Interestingly, studies show that these CDK12 inhibitors not only inhibit CDK12 activity but also induce cyclin K degradation. This finding provides a novel approach to addressing CDK dysregulation in cancer. Our progress is supported by a comprehensive medicinal chemistry campaign focused on optimizing CDK4/6 and CDK12 inhibitors. Through iterative design and synthesis, our goal is to improve the effectiveness of these compounds in selectively targeting cancer.