Presbyterian College

Undergraduate Summer Research Symposium

Presentation Abstracts

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Targeted Delivery of Carbon Monoxide: Enhancing Therapeutic Potential Against ROS-Mediated Diseases

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Direct inhalation of carbon monoxide (CO), an endogenously produced signaling molecule naturally present in micromolar concentrations in the body, is currently in various human clinical trials. There are several issues associated with inhaled CO as a mode of delivery in the clinical settings such as storage issues, reliance on trained personnel, and dependence on the pulmonary capacity of patients for effective delivery, among many others. Thus, CO-in-a-pill strategies wherein development of stable, drug-like organic CO surrogates that will release CO in response to specific stimuli is a growing area of research. In this project, we designed a chemical system that responds to high levels of reactive oxygen species (ROS), such as hypochlorite and hydrogen peroxide. We have synthesized twelve potential CO prodrugs with an oxidizable pyrrole ring linked to an alkyne arm. In the presence of high levels of ROS, we hypothesize that the pyrrole ring is converted to a dienone which reacts with a strategically placed alkyne arm via a Diels Alder-reverse Diels Alder reaction cascade ultimately leading to release of CO. Using a reaction-based fluorescent probe for detection of CO, we found that several of the synthesized CO donors indeed release CO in response to ROS such as hypochlorite. Structure-CO release activity relationship study is currently underway as a guide for us to design new CO prodrugs. Concurrently, cell culture studies are ongoing to evaluate the cytotoxicity of these prodrugs. Successful development of this targeted CO delivery system could have significant implications for future therapeutic strategies addressing diseases such as osteoarthritis, chronic inflammation, atherosclerosis, lung and gastric cancer.

Inducing Fluidization in Granular Materials via Magnetic Fields

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PC Summer Fellows

Granular materials are a growing focus of study relating to discrete, macroscopic, solid particles and their interactions; this includes substances such as sand, grain, and coal. Granular materials can act as solids, like sand on the beach, or as fluids, like sand in an hourglass, depending on external forces. This transition between solid and fluid phases is known as jamming and unjamming and occurs due to changes in these external forces. For example, friction causes poured cereal to jam in a box, and tapping the side of the box will cause it to unjam. The jamming and unjamming transition can be harnessed and utilized in soft robotic grippers, using granular materials in the fluid state to flow around an object, and then jamming the granular material to get an adaptable, solid grip around a given object. Currently, these robotic grippers use vacuums to jam dry granular material, or magnets to jam fine iron particles suspended in oil. This experiment looks at the physics behind using magnetic fields to induce the jamming and unjamming transition in dry granular material. By attaching a strong neodymium magnet to a motor and suspending it below a sample of iron filings, a magnetic granular material, we can change between inducing direct and alternating magnetic fields. At rest, the neodymium magnet will induce a direct magnetic field, which forces the iron filings to jam. When the motor is turned on, the neodymium magnet will rotate, inducing an alternating magnetic field, which will apply a changing force on the iron filings, causing them to fluidize. This method will provide a new way of manipulating magnetic granular materials that can be applied to the robotic gripper design for applications in prosthetics, drones, and industrial automation. Future development would include experimenting with solenoids for greater control over duty cycles used for the unjamming transition, as well as experimentation with different magnetic granular materials for better control.

The Identification of Bacteria for Mutagenesis Capability

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Despite the ease and affordability of gene sequencing, there is still much unknown about the functions of many conserved genes (McFall-Ngai et al., 2015). One method of discovering linkages between bacterial genes and their functions is using forward genetics, such as transposon mutagenesis. Transposons are DNA sequences that have the ability to move to different locations within the genome (Babakhani et al., 2018). The specific purpose of this study is to identify strains of bacteria that are able to successfully mate with *E. coli* to generate gene mutations via transposon mutagenesis, a critical first step to linking genes to their function. We used TN5, a transposon on the pRL27 plasmid, which carries a gene for resistance to the antibiotic kanamycin. Different bacterial strains were mated with *E. coli* strain BW20767 which carries the pRL27 plasmid. Mutants were generated and first identified by their resistance to kanamycin and by Gram staining, then via 16s gene sequencing. These mutants will be further characterized via DNA sequencing to confirm the mutation and then phenotypic screens performed to determine effects of the mutations on function.

Liberalism and Conservatism: A Study of Ideological Change in 21st-Century American Politics

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Since the Great Depression, ideological conflict in the United States has largely been characterized by disagreements over the power of the federal government and its role in the economy. Some of the first research into liberalism and conservatism in the 1960s adhered to this traditional conceptualization but found that many Americans did not exhibit similar attitudes. Therefore, researchers concluded that only a minority of the electorate could be considered true ideologues. However, recent studies have highlighted the increasing importance of social and moral issues for respondents in their conceptualizations and self-identifications, suggesting that these issues now represent a new, legitimate dimension of ideological conflict. This study seeks to determine the extent to which social issues now influence ideological self-identifications, which will reveal how prominent they have become in relation to traditional ones and, therefore, whether or not conceptualizations of liberalism and conservatism (and the conflict between them) have changed as a result. To answer these questions, survey data from the American National Election Studies from 1992 to 2020 was analyzed. Variables reflecting fundamental positions on the size of government, the government's role in the economy, and social values were first correlated with measures of ideological self-identification, and a linear regression was then conducted to compare the significance of each variable in impacting those identifications. Initial results show that, although governmental issues remain significant overall, social issues appear just as influential in formulating self-identifications. These preliminary findings suggest that, over time, social issues have become equally important to governmental/economic ones in the conceptualization and operationalization of ideological labels and conflict in the United States.

Displacement-Based and De Novo Construction Approaches for Fluorescent Carbon Monoxide Detection and Monitoring

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Fluorescent CO probes are useful tools in the study of biologically relevant concentrations of CO. Various designs of these probes have been described in the literature, for example HFCO-1 and CODP-102. HFCO-1 is a palladacycle based turn on probe which relies on CO binding to Pd and subsequently releasing benzimidazole benzoic acid, a fluorescent molecule. CODP-102, another Pd-based probe, relies on a de novo construction of fluorophores. In this project, HFCO-1 and CODP-102 were synthesized, characterized, and compared. HFCO-1 was synthesized via two steps while CODP-102 was synthesized via five steps. Based on the fluorescence studies, both probes were turned on in the presence of CO. However, CODP-102 was more sensitive and exhibited lower background fluorescence. Furthermore, CODP-102 required a higher excitation wavelength and exhibited green fluorescence, indicating that CODP-102 will be more appropriate for biological purposes. With these findings, CODP-102 will be utilized for evaluating a small library of potential hypochlorite-activated CO prodrugs designed for CO targeted delivery.

Understanding the Coordination Chemistry of Tellurium Supported by Redox-Active Ligands

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SCICU

Tellurium (Te) as a central atom was studied and observed because its bonding nature is not fully realized. Tellurium is classified as a metalloid because of how it has the properties of both metals and nonmetals. The use of redox-active ligands with Te(IV) ions has recently been proven to aid in the separation and isolation of Te from a mixture of other metals. Experiments and laboratory methodologies were undertaken, including the isolation and purification of both inorganic and organic substances, alongside the handling of air-sensitive materials. This research will bring a greater understanding of tellurium as the central atom in inorganic complexes. These were carried out by inorganic and organometallic techniques and characterized using nuclear magnetic resonance (NMR) and infrared (IR) spectroscopies. The research presented in this study has elucidated certain behaviors of tellurium when interacting with redox-active ligands, specifically 3,5-di-tert-butylcatechol. In most experiments, noticeable color changes was observed because of the movement of electrons within the complex, specifically the ligand. In the primary experiment, 3,5-di-tert-butylcatechol was used in toluene to synthesize an orange Te(dtbc)2 complex. This in total has led to more knowledge and ideas of how tellurium behaves as a central atom with redox ligand.

Specific Histone Arginine Methylation Sites Identified by Histone Proteomic Profiling are Depleted Through Dual p53 and PTEN Deletion in Metastasis-Transformed MCF10A Breast Cells

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Additional support for this project was provided by the Cancer Research Center of Lyon (Lyon, France) and the Karmanos Cancer Institute of Wayne State University (Detroit, Michigan).

Metastatic potential in basal-like breast cancers typically is initiated by genetic alterations that lead to a process known as epithelial-mesenchymal transition (EMT). However, the transition between these genetic alterations and the epigenetic switches that help drive the invasive EMT phenotypes in breast cancers is still not well defined. With this attempt to better connect epigenetic modifications in breast cancer invasiveness, we performed a DIA-based mass spectrometry of isolated histones from an isogenic panel of MCF10A breast cell lines where tumor suppressor genes *TP53* and *PTEN* were silenced to induce EMT. From approximately 72 histone modifications identified and annotated from our mass spectrometry results, we identified 5 histone events differentially altered in our MCF10A cell line panel. Two events of note were histone H3 lysine-14 acetylation (H3K14ac) significantly increasing and histone H4 arginine 55 dimethylation (H4R55me2) significantly decreasing in our EMT-transformed MCF10A p53-/PTEN- cell lines when compared to the parental, non-tumorigenic MCF10A cell line. Additionally, significant arginine demethylation of H4R55me2 & H3.1R83me in the EMT-transformed MCF10A p53-/PTEN- cell lines corresponded with JMJD6, an established histone arginine demethylase, being overexpressed in basal-like breast cancer cell lines as well as in basal-like breast cancer patients from The Cancer Genome Atlas (TCGA) and METABRIC datasets. Through histone proteomic profiling of our isogenic EMT model, the loss of specific histone arginine methylation events corresponding with JMJD6 overexpression could highlight the potential for a targetable epigenetic mechanism in breast cancer metastasis.

Predicting Orthologous Groups of Proteins/Domains with Graph-Based Clustering Algorithm

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Comparative evaluation of amino acid sequences is a well-known method used for evolutionary analyses, functional annotation, phylogenetic reconstructions of proteins, and assistance in distinguishing between deleterious and benign mutations in proteins. This type of analysis heavily relies on the detection of homologous proteins that share an evolutionary ancestry. Within the family of homologous proteins, one may distinguish orthologs (if derived from a common ancestor by means of a speciation event) and paralogs (if derived from a common ancestor by means of a duplication event and thus represent gene copies) [1]. While the function of orthologs is likely retained due to selective pressure, paralogs diverge faster and, as a result, might acquire new functions or become dysfunctional [2, 3]. Throughout the current proposal, to an automated algorithm was built with the purpose of efficiently distinguish “allowed” non- synonymous amino acid substitutions (benign mutations) vs. “non-allowed” substitutions (likely pathogenic mutations) in proteins through the separation of orthologous sequences to the query protein sequence from a total set of homologs with graph-based clustering analysis. We hypothesize that by removing paralogs to the query sequence from the list of homologous sequences, we increase the accuracy of prediction of the effect of single amino acid substitution on protein activity. Four codes were written to achieve this goal. The first of which focused on the finding of homologous sequences through NCBI’s BLAST Database. The second worked with Multiple Sequence Alignment (MSA) in order to assign a percent identity to each sequence. The third code will focus on Cluster Analysis to find clusters of orthologs and separate these sequences from paralogous sequences. The final code will build a phylogenetic tree through the realignment of ortholog clusters and a bootstrap analysis. While certain results are still pending, it is confirmed that homologous sequences and MSA assist in confirming the conservation of amino acids in a protein, directly correlating to the effects of a single nucleotide substitution.

Utilization of Magnetically Induced Jamming in a Universal Gripper

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There is a worldwide need for low cost, highly functional, upper limb prosthesis. Currently, an upper limb prosthesis can cost upwards of $30,000, and replacement is common for individuals such as athletes who put heavy usage on their prosthesis and children who quickly outgrow fitted limbs. The cost after all of these considerations can get extremely high, creating a large need for a more accessible and affordable option. To address this need, we created a high functioning, low cost, prosthetic gripper. We designed and built a gripper that utilizes a rigid three prong mechanism to grasp an object, analogous to an arcade claw machine. However, similar to the claw machine, the grippers' rigid edges alone will not be able to grasp all types of objects. This basic rigid gripper design was enhanced using pillow-like cushions attached to the end of each arm. The addition of cushion like pads will allow the gripper to increase hold strength on the object being gripped. The cushion-like pads used for our prototype consist of iron filings encapsulated by rubber membranes; the iron filings can be jammed and unjammed with the utilization of an external magnetic field. The operation of this gripper is as follows: when the object comes into the grasp of the gripper it will indent into the soft cushion of the unjammed pads, which will then be jammed into a rigid state via an external magnetic field produced by a solenoid, and secures the object into the prosthesis' grasp. This design will allow for a strong and secure grasp on the object being gripped allowing for complete movements such as picking up and putting down objects of various sizes and shapes, as well as the ability to complete tasks such as turning open a doorknob. Through this project we will increase the accessibility of a low cost and accessible gripper with high functionality.

α-Ketothioesters: Novel Approach for Carbon Monoxide Release for Therapeutic Applications

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Over the past few decades, CO has been studied as an alternative therapy to traditional cancer treatments with several recent clinical trials administering CO through inhalation. Despite promising results, a significant obstacle facing this therapy is the precise measurement of dosage, as there is a clear risk for excessive inhalation of CO. Thus the concept of "CO-in-a-pill" emerged, wherein small organic molecules with well-defined CO-release chemistry and kinetics are being used as surrogates to CO gas inhalation. While well-known decarbonylation chemistries have been extensively studied to this end, new chemical strategies need to be developed to address critical limitations of current CO donors. Based on the molecular logic of an unprecedented chain editing reaction of α-keto thioesters in the ketosynthase domain of a protein in the assembly line of barbamide, we developed new chemical scaffolds with imposed constraints that will lead to cyclization followed by a decarbonylation to release CO. Various synthetic strategies were explored to install the ketoester functionality on ortho-positioned nucleophilic groups. We found that activation of the carboxylic acid with oxalyl chloride followed by nucleophilic attack is superior compared to carbodiimide coupling. Because of the unstable nature of 1,2-benzenethiols, it was extremely challenging to isolate the target product. Therefore, we set out to explore various substrates. A series of eight reactions were set up and monitored with the two periods of running overnight to ensure a thorough mixture. The polar nature of the final compounds often required dual purification utilizing silica gel column chromatography. All of the reactions were conducted under an inert gas atmosphere. The final confirmed products will be evaluated for CO release using CO fluorescent probes. These initial synthetic studies are important in building lead compounds that can be modified for biological applications, eventually paving the way for advancements in drug delivery systems for CO-release in therapeutic applications.

Combating Loneliness and Fostering Connection Among Today's College Students

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In recent decades, research has repeatedly demonstrated serious physical and psychological health complications correlated with loneliness. In fact, the mortality risk of loneliness is greater than that of other significant health concerns, such as smoking and obesity (Holt-Lundstad et al., 2017). In the post-pandemic world, loneliness has become even more prevalent, and maintaining genuine connections has become increasingly difficult. In response, governments around the world have identified loneliness as a bonafide public health crisis; a 2023 U.S. Surgeon General's advisory called loneliness a national epidemic (Public Health Service, 2023). Among today's college students, this epidemic is especially prevalent, correlating with persistence in continuation of college and overall mental health (Gopalan & Brady, 2019). Further, loneliness in this population is exacerbated by the constant influence of social media, which has contributed to higher levels of loneliness and depression among adolescents and emerging adults under experimental conditions (Hunt et al., 2018). One well-documented response to this epidemic of loneliness has been priming for connection and gratitude via tasks as seemingly simple as journaling (Emmons & McCullough, 2003). However, with the rapid changes of the 2020s, further research is needed to explore similar strategies among today's college students. This Fall, we will conduct exploratory research with a limited sample of Presbyterian College Psychology students. Participants will be evaluated on perceived loneliness, perceived campus belonging, and self-reported social media use. Over 4-6 weeks, participants will (1) write brief, weekly journal entries reflecting on their strongest and most meaningful connections and (2) document their average daily social media use. This design will provide updated and campus-specific data while exploring the feasibility and utility of implementing self-led interventions with the potential to expand to broader student populations on resource-strapped college campuses.

Open Chromatin Regions Identified by ATACseq Correspond with Overexpression of Metastatic Drivers in Dual p53/PTEN-Deleted Metastasis-Transformed MCF10A Breast Cells

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Metastatic potential in basal-like breast cancers typically correspond with increased enrichment of aggressive progenitor-like populations called cancer stem cells (CSCs), typically identified by the loss of epithelial markers EpCAM and CD49f. In our MCF10A breast cell line model, deletion of p53 and PTEN lead to tumorigenic transformation and cancer stem cell expansion. With these observations that reflect cell dedifferentiation as a mechanism of oncogenic transformation, it was important to better detail the epigenetic events that correspond with breast CSC progression. With this in mind, we performed Assay for Transposase-Accessible Chromatin sequencing (ATACseq) on our isogenic panel of MCF10A breast cell lines where tumor suppressor genes *TP53* and *PTEN* were silenced to drive breast CSC expansion. Furthermore, we performed gene expression analysis of isolated EpCAM-/CD49f- CSCs from MCF10A p53-/PTEN- cells to determine which genes differentially upregulated in CSCs corresponded with open chromatin in our ATACseq data. Based on this analysis, we identified 96 genes with open chromatin that were also significantly overexpressed in our isolated CSCs. Such examples of transcripts include cell markers like *PECAM1* (i.e. CD31), *NCAM1,* and *IL6R,* protein kinases like *FYN* and *ROR2,* and transcription factors like *NPAS2 and KLF15.* Additionally, several identified transcripts are also significantly upregulated in basal-like breast cancers from The Cancer Genome Atlas (TCGA) breast cancer dataset. Collectively, this work provides an overview of open chromatin sites that contribute to oncogene overexpression in breast cancer and provide rationale for targeting these transcripts via chromatin targeting-based therapies (ex: BET bromodomain inhibition).