DIVISION OF PHARMACEUTICAL SCIENCE
JAMES L WINKLE COLLEGE OF PHARMACY

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE students

FOR APPLICATION YEAR: 2025

PROJECT TITLE: Metabolism-based interactions among commonly used COVID-19 medicines

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Project Description

COVID-19 (coronavirus disease 2019) remains a global health crisis, driving unprecedented efforts to develop therapeutics. Key examples include molnupiravir, nirmatrelvir, and remdesivir, which operate through distinct mechanisms: nirmatrelvir inhibits SARS-CoV-2 replication by targeting the viral main protease (Mpro), while molnupiravir and remdesivir target RNA-dependent RNA polymerase (RdRp). Molnupiravir induces lethal mutagenesis, and remdesivir halts viral replication through chain termination.
Pharmacokinetically, nirmatrelvir is a substrate of cytochrome P450 3A4 (CYP3A4) and is inactivated by oxidation. Molnupiravir and remdesivir, as prodrugs, require activation via hydrolysis by carboxylesterase-2 (CES2) and carboxylesterase-1 (CES1), respectively. Remdesivir also irreversibly inhibits CES2, while molnupiravir downregulates CYP3A4 expression. This project hypothesizes that the efficacy of these drugs depends on metabolism-based interactions and delivery strategy. The Specific Aims are to: (1) elucidate their metabolic interactions, and (2) develop organ-targeted nanoformulations.
The student will learn advanced laboratory techniques, including cell culture, enzymatic activity assays, and drug metabolism analysis using high-performance liquid chromatography (HPLC). They will synthesize lipid-coated calcium phosphate nanoparticles and assess drug incorporation, cellular uptake, and retention using fluorescence microscopy and spectroscopic methods.. Additionally, the student will analyze single-cell RNA sequencing data (scRNAseq) for the expression of drug-metabolizing enzymes and drug. This innovative research uncovers pharmacological synergies and provides a framework for optimizing antiviral drug efficacy, with broad implications for addressing future pandemics.