MAKING LAB-BASED DISCOVERIES INTO TRULY PERSONALIZED TREATMENT

DRUG DISCOVERY AND NANOMEDICINE RESEARCH PROGRAM
AT JOHN WAYNE CANCER INSTITUTE & PACIFIC NEUROSCIENCE INSTITUTE

The Drug Discovery and Nanomedicine (DDNM) Research Program at JWCI fosters the development of novel, safe and effective therapeutics for both oral and intravenous delivery, to address the unmet disease needs in oncology and the neurosciences.

The DDNM research program utilizes a unique, two-pronged approach, **combining drug discovery tools and nanotechnology tools** to circumvent existing clinical problems. The DDNM research program plays a critical role in JWCI and PNI's clinical and translational research efforts to facilitate the transition of basic science discoveries into translational research by providing drug discovery and nanotechnology core expertise.

With the mission of improving the quality of patient life leading to meaningful health outcomes, the DDNM research program collaborates with both internal and external groups of talented and experienced scientists and clinicians. We aim to develop tomorrow's therapeutics for wide range of human disorders including a wide range of drug discovery and nanotechnology projects in oncology and neurosciences.

GOALS & OBJECTIVES

1. Identification of new small molecules therapeutics for clinically relevant targets/biomarkers through various drug discovery methods
2. Assay development for drug target ID validation and selection of hit compounds
3. Preclinical ADME-guided lead optimization for drug-like small molecules
4. Drug repurposing screening for rare and neglected diseases
5. Exploring potential nanoparticle-based therapeutics to overcome clinical barriers of existing drugs
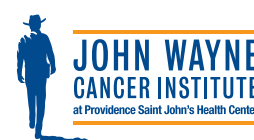
DRUG DISCOVERY TOOLS

- Virtual screening
- Medicinal chemistry
- Discovery biology
- Pre-clinical ADMET/efficacy studies in design and optimization of novel small molecule drugs in oncology and neuroscience

Our research is mainly focused on developing targeted novel drugs for clinically important biomarkers/targets, and translating lab-based discoveries into the clinic more efficiently.

NANOTECHNOLOGY TOOLS

In order to improve safety and minimize toxicity of preclinical and clinically active drugs and biologics, we encapsulate our compounds into biodegradable nanoparticles such as liposomes, polymeric micelles, lipid-polymer hybrids, albumins, and so on, for both targeted and non-targeted delivery of therapeutics in oncology and neuroscience applications.

The Nanomedicine Lab houses advanced instrumentation to design and characterize nano-formulations. Preclinical model validation is through collaborative partnerships. We believe our pioneering multidisciplinary approach has the potential to lead to better therapies for patients, combating a range of diseases and overcoming critical clinical challenges associated with existing drugs such as toxicity and resistance.

PACIFIC NEUROSCIENCE INSTITUTE ℠

Saint John's Health Center
PROVIDENCE Health & Services

JOHN WAYNE CANCER INSTITUTE
at Providence Saint John's Health Center

VENKATA MAHIDHAR YENUGONDA, MPhil, PhD

Director, Drug Discovery and Nanomedicine Research Program; Assistant Faculty Member, Providence Health and Services; Associate Professor, Translational Neurosciences and Neurotherapeutics, John Wayne Cancer Institute

A 2018 recipient of the JWCI independent Investigator grant, Dr. Yenugonda has over a decade of experience in drug discovery and nanomedicine (DDNM) research. He is a medicinal chemist with experience in a wide range of therapeutic areas (i.e. Oncology, Neuroscience, Immunology, Anti-Cholesterol and Rheumatology) and has led multiple interdisciplinary projects, ranging from target identification to clinical proof of concept IND applications. Through these projects he has identified several preclinical leads, which remain at various stages of development.

He has authored over 25 scientific publications, and is also co-inventor of several US patents and provisional patent applications. He is a fellow of the National Academy of Inventors, a reviewer of scientific journals of high repute, and a scientific advisor of several biotech startup companies. Dr. Yenugonda's long-standing interest is in developing novel small molecule

therapeutics and nano-formulations to maximize the therapeutic index of treatments for patients with cancer, neurological disorders and neurodegenerative diseases. He believes that a deeper understanding of the complexity of human biology early in the drug discovery process, and application of precision therapeutics, will replace the traditional "blockbuster model" and will greatly improve the design of effective drug therapies.

His unique perspective and experience in the field of drug discovery and nanomedicine will advance the ongoing translational drug discovery projects at the John Wayne Cancer Institute. Additionally, he works in collaboration with Pacific Neuroscience Institute's medical specialists to devise and implement novel therapeutic strategies for treating brain cancer and other neurological diseases.

MAJOR ACTIVITIES

The DDNM program is staffed with full time scientists and technicians most of whom are seasoned experts in various aspects of drug discovery and nanomedicine research. Our program was designed to complement the strength of academic research by bridging the gap between basic and translational applications. Our program is part of the Department of Translational Neurosciences and Neurotherapeutics on the 2nd floor of JWCI. We have strong support from chair of the department, Santosh Kesari, MD, PhD, and his team who help with some assay development in lead optimization. The 1,050 square-ft lab is designed for drug discovery and nanomedicine research operations and allows multi-disciplinary collaboration under one roof fostering a teamwork-based approach. Our laboratories are fully equipped with the most advanced instruments to maximize the quality and productivity of our operations for many drug discovery and nanomedicine research activities. In addition, our program partners with best-in-class CRO companies and academic institutions to perform other specific drug discovery and development activities.

VIRTUAL SCREENING

We apply various modern *in silico* methods such as ligand- and structure-based drug design strategies to search libraries of small molecules of protein receptor or enzyme interest. Our DDNM program collaborates with computational scientists at Molsoft LLC, San Diego, CA, and the University of Tennessee, Knoxville, TN, to execute computational drug design projects. JWCI has CDA agreements with those companies.

Ligand-Based Drug Design
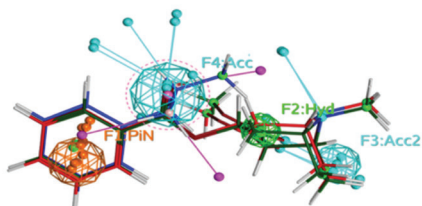
Structure-Based Drug Design
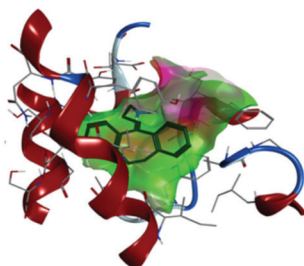
MEDICINAL CHEMISTRY

Equipment: The drug synthesis lab contains, a large chemical hood plumbed with air and vacuum, buchi rotovapour, drying oven, Agilent 1260 II HPLC (ELSD), Biotage isolera flash purification, explosion proof refrigerator with -20 freezer, melting point apparatus, 1310 Perkin Elmer IR, molecular device UV spectrometer and two Mettler balances.

Partnerships: The analytical characterization of analogs will be taken at UCLA's chemistry and biochemistry department and any special synthesis will be performed at Dr. Ohyun Kwon's chemistry lab at UCLA. DDNM program has collaborated with international CRO companies such as Syngene, Anthem and Dr NS labs for large scale synthesis and analog synthesis of small molecules.

ASSAY DEVELOPMENT AND SCREENING ASSAYS

The Tissue Culture and Discovery Lab contains all standard modern biological equipment including two tissue culture hoods, microscope, two incubators, cell counting machine, western blot apparatus, centrifuges, and RT-PCR. We also have full access of JWCI's core equipment and our department equipment. We have strong support from our department team scientists and technicians to help on various biological experimentation in drug target ID engagement studies.

DRUG METABOLISM, PHARMACOKINETICS AND EFFICACY STUDIES

In process of identifying drug-like small molecules, pharmacokinetics (PK) and pharmacodynamic (PD) studies are the key experiments to understand the drug safety and efficacy profile. We will perform these studies in collaboration with various CRO companies and discuss results with expert team members to select lead small molecules for further preclinical IND applications.
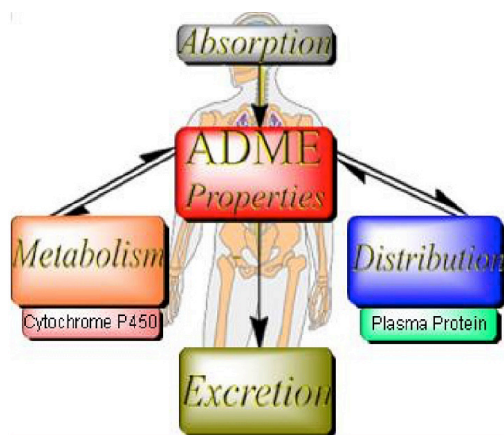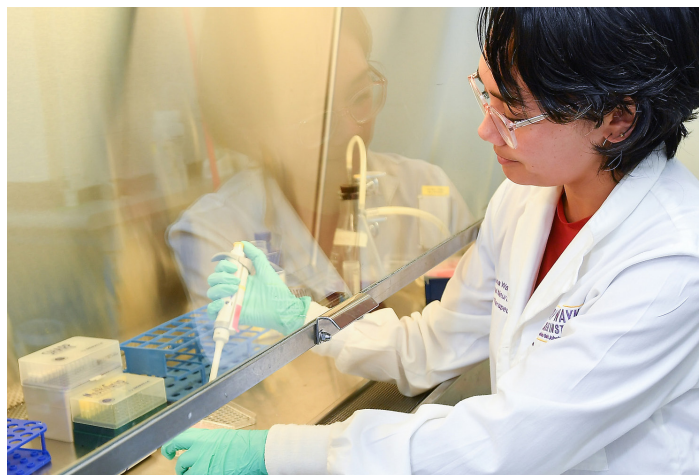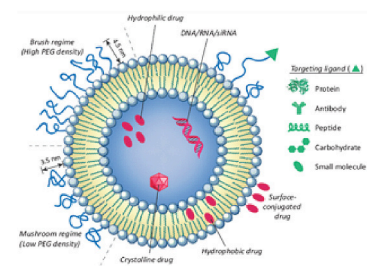

NANO DRUG FORMULATION

Systemic administration of therapeutic agents (TA) and biologics (proteins/ siRNA) for treatment of cancer and neurodegenerative diseases is a common practice. However, their presence in normal tissues leads to adverse toxicities, limiting the administered dose and the resulting treatment efficacy. This undue toxicity can potentially be avoided if the TA remains encapsulated or inactive until exposed to the intended organ within a well-defined volume. In order to improve safety and minimize toxicity of preclinical and clinically active drugs and biologics, we are encapsulating our compounds into biodegradable nanoparticles such as liposomes, polymeric micelles, lipid-polymer hybrids, albumins, and so on, for both targeted and non-targeted delivery of therapeutics in oncology and neuroscience applications.

We have state-of-the-art equipment at our Nanomedicine Lab at JWCI to design and characterize nano-formulations and validate them using cell and pre-clinical animal models.

By applying all the above major activities, our DDNM Program will optimize small molecules and nano formulations to create drug-like agents with intellectual property which can be transfered to startup companies/collaborators for further pre-clinical IND-enabling studies.
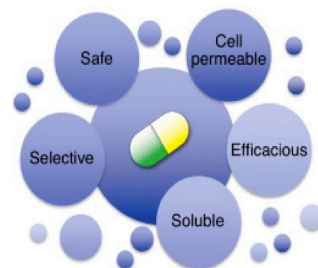
We will follow the following checkpoints to identify leads:

- Highly selective and specific
- Minimize toxic side effects
- Favorable drug metabolism and pharmacokinetics
- Orally bioavailable
- Brain penetrant (CNS drugs)
- Preclinical efficacy (LD50/ED50>10)

RESEARCH PROJECTS

Our DDNM research program is engaged in range of scientific areas with diversified collaborations. We present some of our active projects here.

Project 1: Development of novel Cell Cycle Kinase Inhibitors (CDKi) for treatment of cancer and neurodegenerative diseases

Disease models: Cancer: Triple Negative Breast Cancer, Prostate Cancer, Medulloblastoma and Glioblastoma

Neurodegenerative Disease: Alzheimer's Disease

Participating Collaborative Universities/ Institutes:

John Wayne Cancer Institute, Georgetown Lombardi Cancer Center, UT Southwestern Medical Center and UCLA

Project 2: Development of novel chemo and radio sensitizers for cancer therapy

Disease models: Head & Neck Cancer, Pediatric & Adult Brain Cancer

Participating Collaborative Universities/ Institutes: Georgetown Lombardi Cancer Center and UT Southwestern Medical Center

Project 3: Introduction to Drug repurposing for Rare and Neglected Diseases

Disease models: CNS Diseases (Cancers and Neurodegenerative Diseases)

Participating Collaborative Universities/ Institutes:

John Wayne Cancer Institute, Children's National Health Systems, Washington DC and UT Southwestern Medical Center

Project 4: Developing Novel therapeutics for Neurodegenerative and Neurological Disorders caused by substance abuse

Disease models: Alzheimer's Disease, Depression, Drug abuse

Participating Collaborative Universities/ Institutes: Pacific Brain Health Center, Barrow Neurological Institute, Duke University, Georgetown University and UT Southwestern Medical Center

Project 5: Development of nanocarriers for cancer-targeted drug delivery

Targeted Ligands: Transferrin, PSMA and Folic Acid

Disease models: Triple Negative Breast Cancer, Prostate Cancer and Glioblastoma

Participating Collaborative Universities/ Institutes: John Wayne Cancer Institute

DDNM TEAM

Anubhab Mukherjee, PhD, Postdoctoral Research Fellow

Dr. Mukherjee develops novel nano-formulations using several nanotechnology platforms, including liposomes, polymeric micelles, lipid-polymer hybrids, and albumins for both targeted and non-targeted delivery of therapeutics.

Ariana Waters, BS, Research Assistant

Ariana's major focus is to assist in drug discovery biology for lead optimization.

FUNDING

The DDNM program has strong support from the following sources to generate proof of concept data on various pilot projects. This is for the purpose of securing additional grants from both private as well as public agencies (National Institute of Health and Department of Defense/CDMRP).

- Saint John's and JWCI Foundation
- Department of Translational Neurosciences and Neurotherapeutics
- Associates for Breast and Prostate Cancer Studies (ABC's)
- Fashion Footwear Association of New York (FFANY)

COLLABORATION

The DDNM research program is constantly seeking new collaboration opportunities in drug discovery and nanomedicine research in a wide range of therapeutic areas. We welcome informal discussions with faculty of JWCI and PNI on basic and translational research ideas into novel therapeutics. We will consider several check point criteria such as clinical significance, druggability of identified targets/biomarkers, fundability, matches with our expertise and capabilities in order to consider the project.

In addition, we are always looking for talented and enthusiastic individuals at all levels who are interested in becoming a part of our team developing new therapeutics for unmet medical needs

If you would like to join our team, please send us your cover letter and curriculum vitae.

To initiate collaboration discussions with our team, please contact us at **VMY@JWCI.ORG.**

For more information contact us at:

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