Project 1

Doxorubicin-induced Disruption of Cardiac Extracellular Matrix Homeostasis

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Project description:

Doxorubicin is a highly effective chemotherapeutic used to treat many adult and pediatric cancers, such as solid tumors, leukemia, lymphomas and breast cancer. However, its use is limited due to a dose dependent cardiotoxicity, which can lead to lethal cardiomyopathy. Cardiac fibroblasts are the main cell type responsible for the synthesis, deposition, and degradation of cardiac extracellular matrix (ECM). Cardiac ECM not only provides structural support for cardiac cells, but also plays important roles in electrical signaling, secretion of growth factors and cytokines, and potentiating blood vessel formation. In contrast to the extensive research efforts on toxic effects of doxorubicin in cardiomyocytes, data on the effects and mechanisms of doxorubicin on cardiac fibroblasts and ECM homeostasis are limited. **We hypothesize that doxorubicin alters the function of cardiac fibroblasts. Such alteration in turn adversely affects the function and survival of cardiomyocytes via ECM disruption and cell-cell communication between fibroblasts and cardiomyocytes.**

In this study, we will investigate what role of fibroblasts plays in doxorubicin-induced cardiotoxicity. The major goals are to elucidate whether doxorubicin adversely affect the function of cardiac fibroblasts which in turn disrupt the homeostasis of cardiac ECM and effects of doxorubicin on key fibrogenic signaling pathways in cardiac fibroblasts. Results from this project will advance our understanding of the role of cardiac ECM in doxorubicin-induced cardiotoxicity, and generate valuable preliminary data to guide future studies which may lead to novel treatment or preventive approaches to manage doxorubicin-induced cardiotoxicity.

To achieve our goals, we propose two specific aims. **Aim 1** is to investigate doxorubicin cytotoxicity and its effects on key signaling pathways of ECM homeostasis in cardiac fibroblasts. Fibroblasts will be isolated from neonatal mouse heart tissue and cultured. The gene expression profiles for TGF-β and ROS signaling pathways involved in cardiac fibrosis (TGF-β, NADPH oxidases, plasminogen activator inhibitor-1, SMAD), and MMPs involved in collagen degradation and remodeling (MMP1, MMP2, MMP3, MMP9, TIMP1, TIMP2) will be examined using real time PCR. **Aim 2** is to examine the direct intercellular signaling between doxorubicin treated fibroblasts and cardiac myocytes. In this aim, fibroblasts will be pre-treated with doxorubicin for 24 hours to induce alteration and release of the soluble cell signaling molecules such as cytokines and chemokines, etc. Cardiac myocytes will subsequently co-cultured with the doxorubicin pre-treated fibroblasts for 24 hours without the presence of doxorubicin. The proliferation of myocytes will be examined. The global gene expression changes in myocytes will be evaluated using RNA-seq technology.

Mentoring: This summer research opportunity will provide the skills, knowledge and experience to prepare the student to conduct biomedical research independently. The PI will be closely mentoring the student via training in experimental techniques, regularly scheduled one-on-one meetings to review progress and gather feedback, and lab meeting presentations.

Skills that can be acquired: include mammalian cell culture, protein extraction, protein detection using Western Blotting, gene expression measurement using Quantitative PCR (qPCR), microscopy imaging, data analysis, and manuscript writing, etc.

Need for funding: Funding is needed to purchase materials and supplies for fibroblast cell culture, Western Blotting, and mRNA extraction.

ICOM Summer 2021 Internship Opportunities at the *Montrose Translational Health Lab - Boise State University*

The Montrose Translational Health Lab at Boise State University aims to translate basic science into practical clinical and community solutions. Dr. Luke Montrose is an environmental toxicologist with research interests in public health, exposure assessment and chronic illness, particularly as it relates to vulnerable and understudied populations. As an Assistant Professor in the Department of Community and Environmental Health at Boise State University, Dr. Montrose is positioning himself to work collaboratively across the region with relevant stakeholders to enhance community resilience through research on the health effects of wildfire smoke exposure. Dr. Montrose has two projects and is seeking one ICOM student for each project.

Project 2

We are seeking a summer intern student to contribute to a project titled "Building Community Resilience with an Air Quality Communication Strategy Aimed at Enhancing Elder Care." This study is aimed at improving community resilience by empowering the people responsible for the health of our most vulnerable community members to make timely and informed decisions related to wildfire smoke events. While data indicates that skilled nursing facility administrators perceive wildfire smoke exposure as a hazard to their residents, limited access to actionable data that is specific to their building's air quality (inside and outside) hinders risk mitigation. Thus, the objectives of this project are to generate a community-driven data communication strategy by surveying Idaho skilled nursing facility administrators, and then to implement and evaluate this communication strategy during a wildfire season by partnering with two Boise-area skilled nursing facilities.

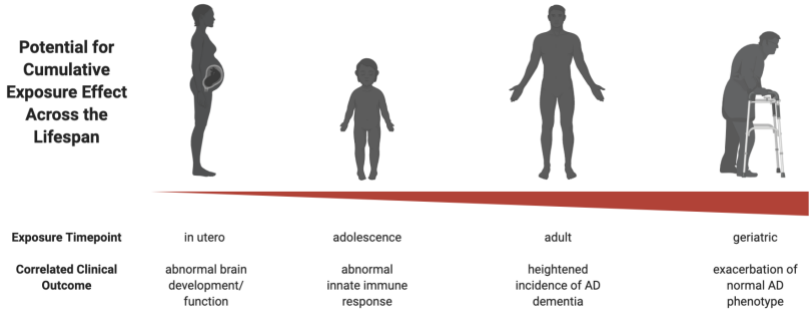
The ICOM summer intern will be directly involved in survey development for this pilot project. They will communicate and coordinate with stakeholders (skilled nursing facility administrators) and researchers in the community health field (Drs. Montrose and Sarah Toevs) as well as the field of social work (Dr. Royce Hutson) to develop and refine 15-30 quantitative and qualitative survey questions aimed at addressing best practices for dissemination of air quality data, to include content and depth of data as well as timeliness and frequency of delivery. In doing so, the ICOM summer intern will be exposed to air quality data collection and analysis procedures, and become familiar with health implications of wildfire smoke among at-risk populations. Dependent on the outcome and time investment necessary for the survey development, an ambitious student may also have an opportunity to help deploy the survey via phone to the 82 skilled nursing facilities in the state of Idaho. For the development and deployment of the survey instrument, the ICOM summer intern will need to cultivate soft skills such as cultural competency and interpersonal communication. The intern will be invited to participate in weekly lab meetings and work directly with the PI and laboratory technician on this pilot project. As this project is supported by the Boise State Hazard and Climate Resilience Institute (HCRI), the intern will also be invited to monthly HCRI meetings and work directly with institute members who are contributing to the pilot project (e.g., HCRI director Brittany Brand). A student with medical interests in community or family medicine would gain insight into an emerging public health issue - wildfire smoke exposure. The funds for this project would go toward the purchase of research equipment including low-cost air monitors.

Project 3

We are seeking a summer intern student in a project to optimize a novel piece of laboratory equipment: the ProteinSimple Wes platform. This platform has revolutionized the ability to quantify protein using traditional immunoblotting principles that have been manipulated to allow high sensitivity and low sample input volume while drastically increasing assay speed. The ProteinSimple Wes platform has many clinical applications, including being used in many labs to test for presence of SARS-CoV2 IgG antibodies in serology. Other applications include immuno-oncology (tumor microenvironment), biomarker detection, and gene/cell therapies. In our lab, this equipment will be employed to study the extra-pulmonary effects of environmental exposure to wildfire smoke by assessing pathological phenotypes. Specifically, we are interested in examining the effects of wildfire smoke exposure on brain health, including potential to modulate risk or progression of Alzheimer's disease. We hypothesize that this may occur via changes in epigenetic patterns, chiefly differential DNA methylation.

A summer intern can look to gain exposure to molecular techniques including protein extraction from tissue, total protein concentration, and specific protein quantification using the ProteinSimple Wes platform. A highly motivated student may also have the opportunity to gain exposure to the following workflow: DNA extraction, bisulfite treatment, PCR amplification, and targeted pyrosequencing analysis to examine DNA methylation profiles. In addition, our lab will include this summer student in laboratory meetings (weekly), including discussion of relevant literature, and conceptualization/progression of the student's project. A good fit for our lab would be someone who has an interest in laboratory medicine, pathology, or neuroscience and has some experience with basic laboratory techniques (ex. pipetting, following written protocols). The $1500 will be used on Wes supplies and reagents to accommodate the training. Primary mentorship for this project will come from the PI, but daily activities will be supervised by a rising 2nd year Biomolecular PhD student and laboratory technician.

Project Relevance:



Working hypothesis relating woodsmoke exposure to observed health outcomes based on existing epidemiologic literature.