Career Exploration Program Exit Presentation

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Pharmacology Discipline

SPACE LIFE SCIENCES SUMMER INSTITUTE

Background

- Clear Lake High School
- Career Exploration Program
- CSA Internship Extension
- Interests in biochemistry – how can we change the chemistry of the body using medications?

The Pharmacology Discipline

"Risk of Clinically Relevant Unpredicted Effects of Medication"

- Medication usage
- Medication stability
- Spaceflight and pharmacokinetics
- Spaceflight and pharmacodynamics
- Spaceflight and antimicrobials

Project Involvement Highlights

- Pharmacology Risk Evidence Book Update
- FeRad Experiment
- Research Proposal
- Current status of therapies to treat or prevent radiation damage

Pharmacology Evidence Book

- What is the evidence book?
- Update using the most recent literature.
- Learning how to understand and critically evaluate scientific literature

Evidence Report: Risk of Therapeutic Failure Due to Ineffectiveness of Medication

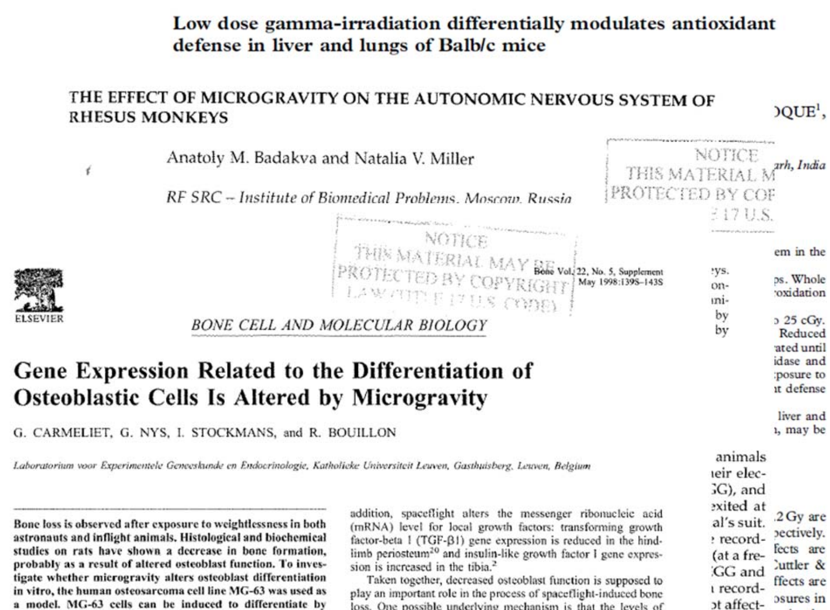
I. **PRD Risk Title: Risk of Therapeutic Failure Due to Ineffectiveness of Medication**

Description: Given that terrestrial medical practices, including therapeutic medications, must be used as the basis for therapeutic use on missions, there is a possibility that medications used will be less than ideal for the actual circumstances encountered on missions.

II. **Executive Summary**

It is possible that the actions of administered drugs on crewmembers during spaceflight are different from their actions on Earth, but even after more than 40 years of spaceflight experience, most questions about medication use during missions remain unanswered. Use of medications with insufficient knowledge about their actual activities may result in inadequate treatment and may even reduce performance and well-being in some circumstances. There is evidence that this has already occurred during and immediately after spaceflights. The spaceflight pharmaceutical activity knowledge base must be improved to enable flight surgeons and crewmembers to make better-informed decisions about using pharmaceuticals during flight.

The spaceflight environment induces changes in human physiology, and these changes have been the subject of much study over the past few decades. These studies are confounded by the small number of potential subjects, as well as by the inability to separate the different stressors of spaceflight (radiation exposure and microgravity, for example) from each other. In every physiological system, the details of spaceflight-induced physiological changes are not completely understood. Despite this fact, crewmembers are treated with pharmaceuticals to reduce or prevent medical problems, with little information about drug function in their altered physiological systems.

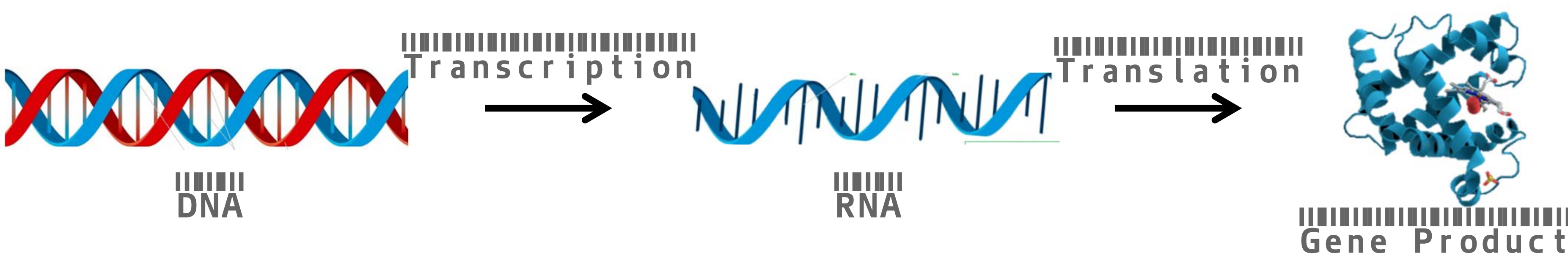


FeRad Experiment – Introduction

- Mouse liver cells on short-term shuttle flights (STS-135) have been shown to exhibit changes
- By replicating aspects of spaceflight in the laboratory, we can conduct experiments without impacting mission resources
- Astronauts are on a high-iron diet during spaceflight
- Galactic Cosmic Rays (GCRs) and Solar Particle Events (SPEs) are ionizing radiation sources that can alter physiological functions
- Preliminary medication usage data from the International Space Station (ISS) crew shows that the most common reasons for using medications in space are the same for healthy people on earth

FeRad Experiment – Gene Expression

- The process by which genetic information is used to create a functional gene product, mainly proteins
- Environmental factors like radiation can change the amount of gene product
- Changes in gene product can result from changes in transcription, translation, or other functionally specific intermediate steps
  - Example: increase in amount of RNA transcribed
- A change in expression high in the chain does not guarantee a change in gene product expression



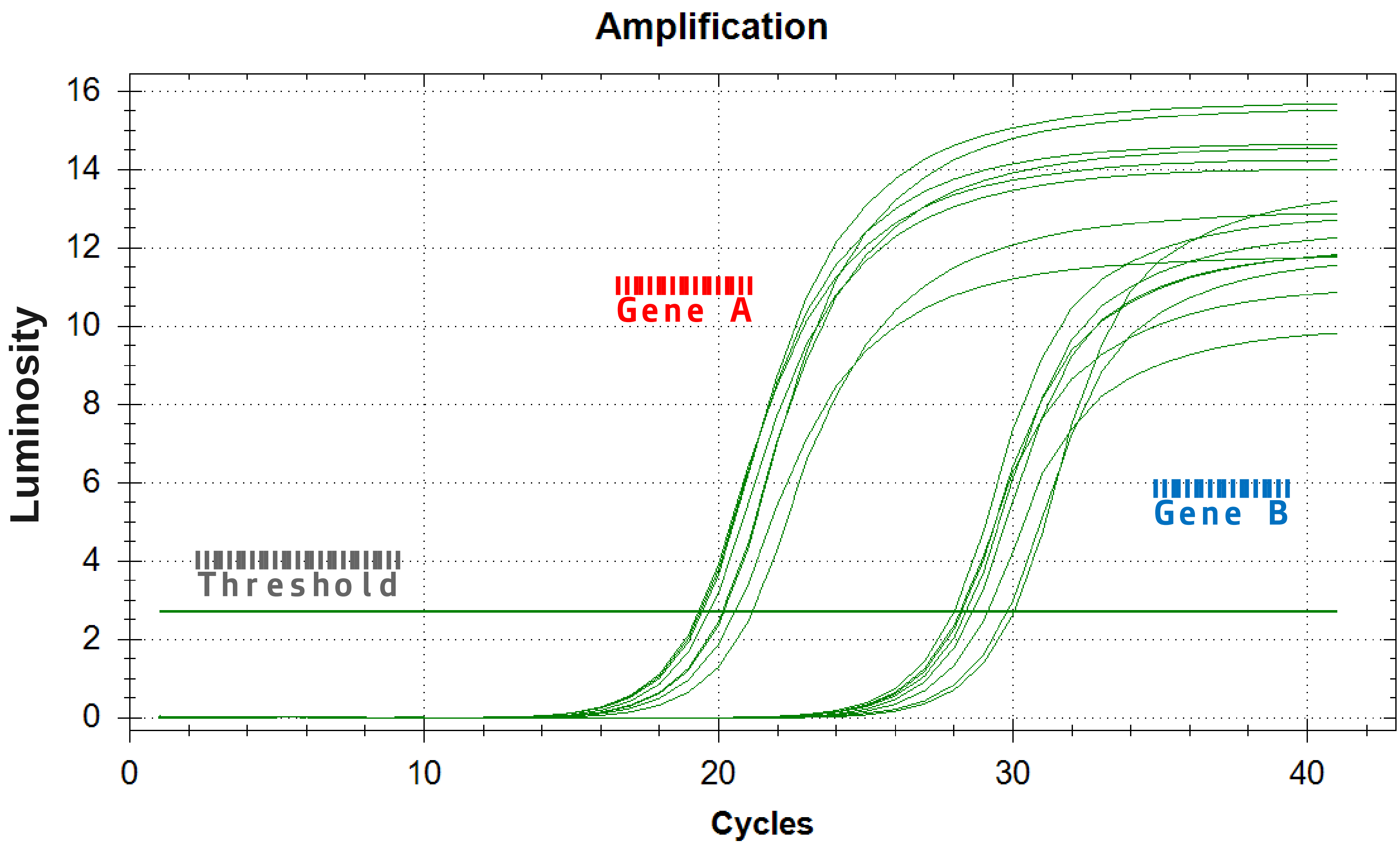
FeRad Experiment – Drug Metabolism

- Enzymes are a type of protein that act as highly selective catalysts for biological reactions
- Medications are generally metabolized by enzymes in the liver – leading to their activation or inactivation
- The largest group of drug metabolizing enzymes is the Cytochrome P450 enzyme superfamily
- The substrates, or reactants of the P450 superfamily includes metabolic intermediates (lipids and hormones) and xenobiotics (drugs and other chemicals)

FeRad Experiment – Polymerase Chain Reaction

- Used to determine whether there was a change in RNA expression of a gene
- Multi-step process
  - Total RNA Isolation
  - Conversion of all RNA to cDNA
  - Use of primers to ensure only one gene is copied during duplication cycles
  - Addition of fluorophore that glows in the presence of double-stranded DNA
  - Repeated duplication of one gene sequence in the thermocycler

FeRad Experiment – Polymerase Chain Reaction

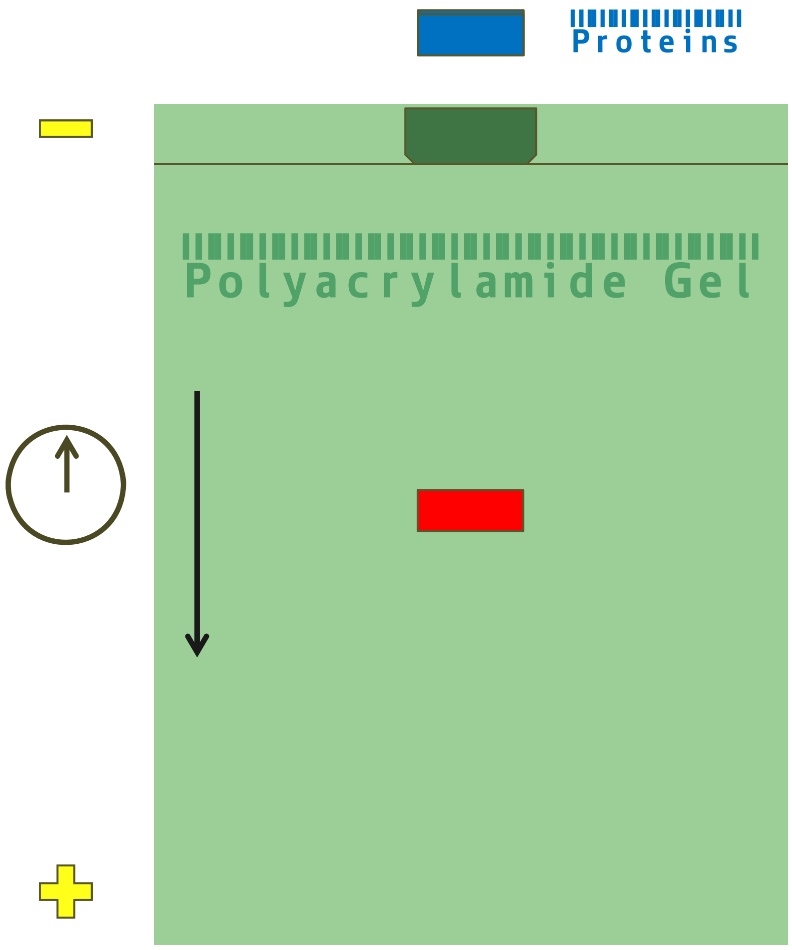


The initial presence of more cDNA copies of Gene A causes it to reach the lumonisity threshold ~10 cycles before Gene B.

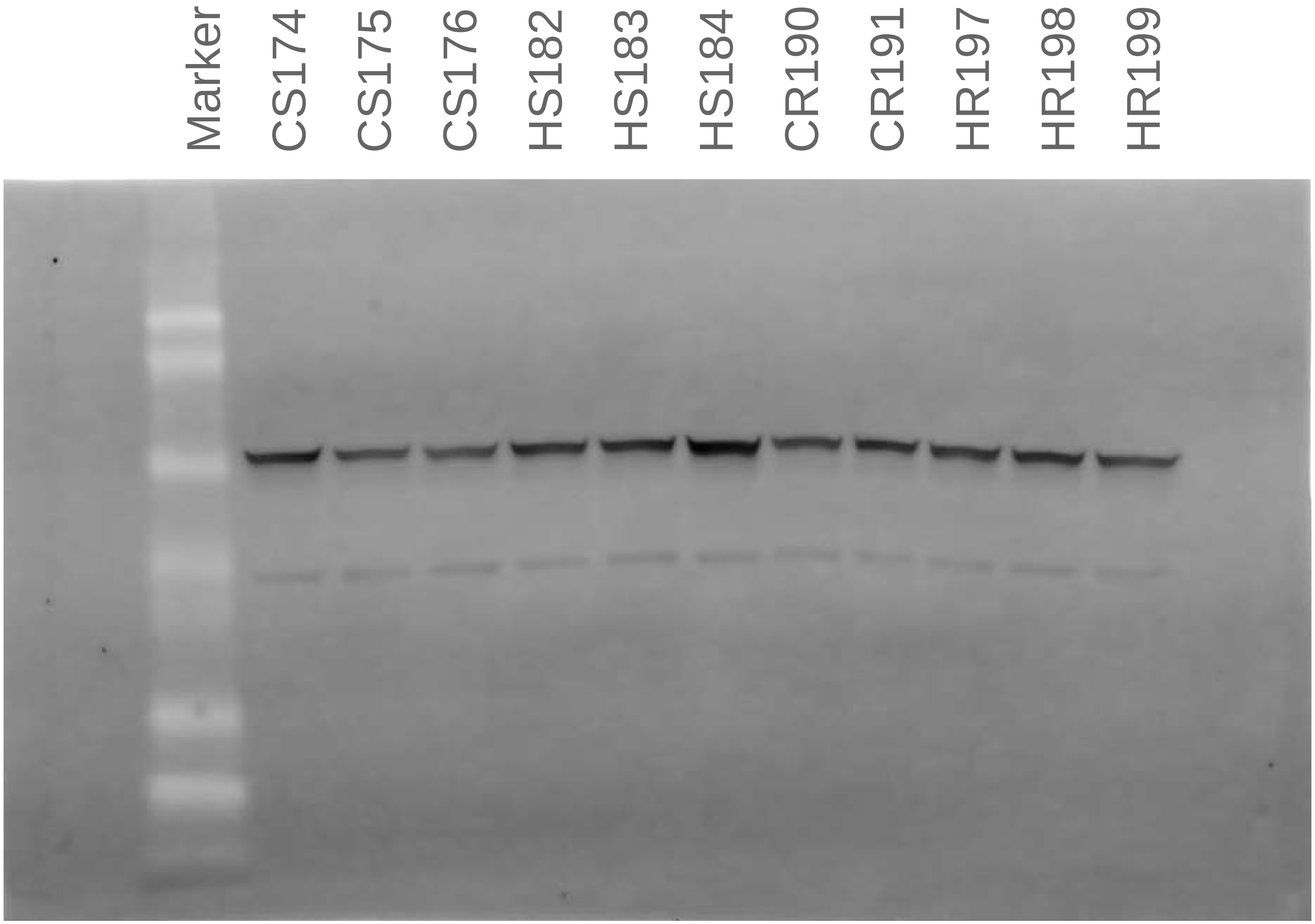
This implies there was more RNA for Gene A expressed than there was for Gene B.

FeRad Experiment – Western Blotting

- Use of gel electrophoresis to separate out all of a cell's proteins by molecular weight
- Proteins are then transferred to a less-fragile nitrocellulose membrane
- The membrane is rinsed with antibodies that bind only to the protein of interest
- A fluorophore is bound to the antibody
- The membrane is scanned, and the light of the fluorophore is measured



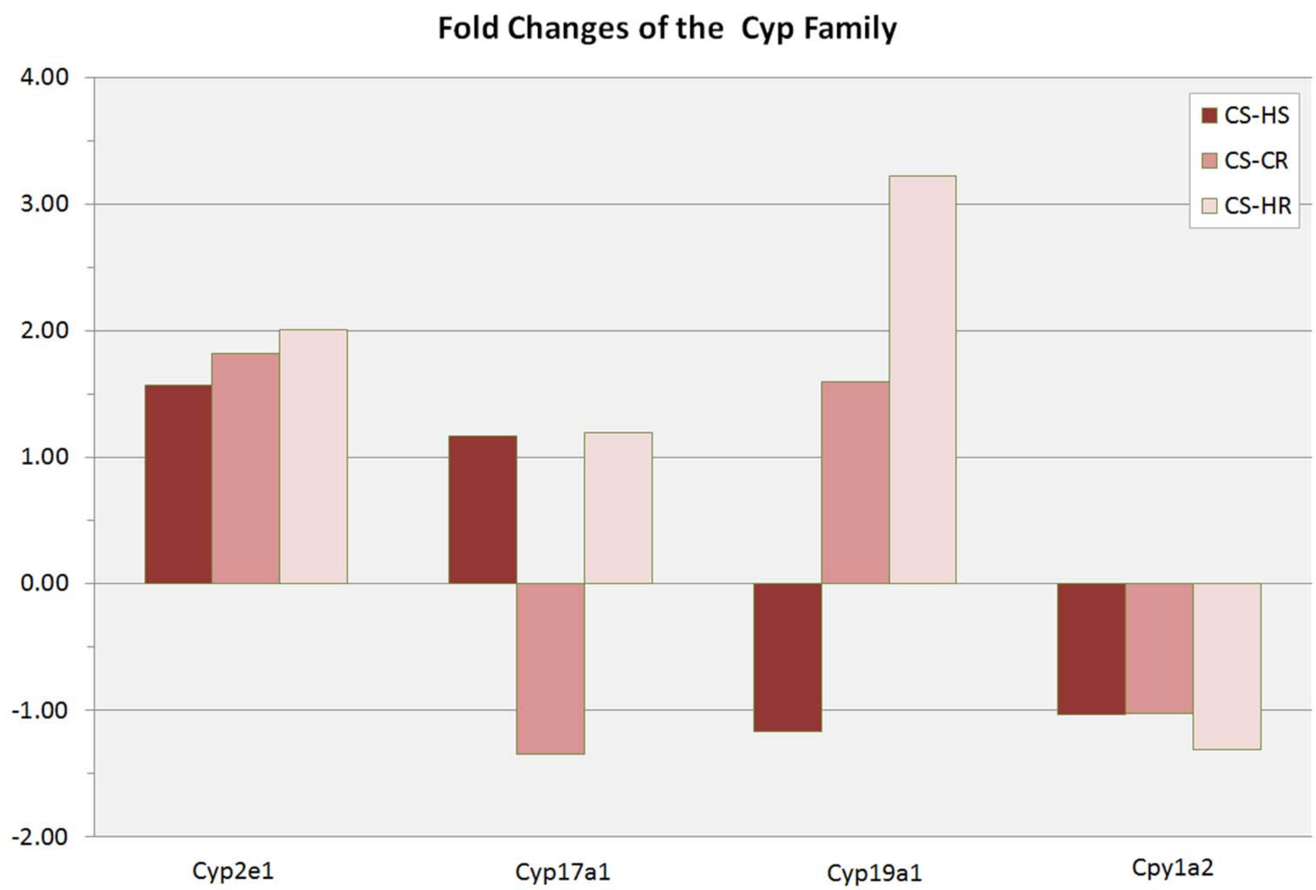
FeRad Experiment – Western Blotting



Western blot for the drug metabolism protein Cyp2e1. Molecular weight marker is on the leftmost lane.

FeRad Experiment – Initial Results

- Some (but not all) of the enzymes that metabolize medications are found in far greater quantities in the liver after exposure to radiation and/or high iron.



Research Proposal – Introduction

- Wrote a proposal to study the effects of radiation and a high-iron diet on oxidative stress in tissues of differing metabolic rates
- Better understanding of scientific design
- Was able to apply knowledge gained from shadowing Kami Faust on the FeRad experiment

Determining if Tissue Metabolic Differences Results in Differential Radiation-Induced Oxidative Stress

Introduction

Reactive oxygen species, or ROS, are a byproduct of normal aerobic metabolic function. With the majority being formed in the mitochondria, ROS are molecules that contain oxygen, and are highly chemically reactive – some examples include peroxides (such as hydrogen peroxide) and oxygen ions (commonly known as 'free radicals'). These byproducts form in the mitochondria

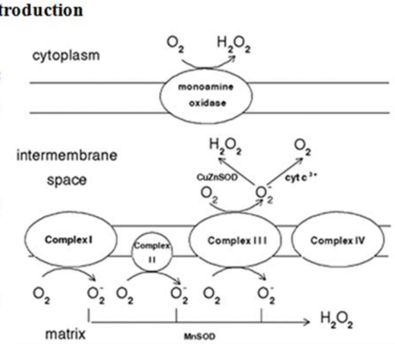


Figure 1, The formation of ROS (Balaban et. al., 2005)

of a cell (see figure 1), and leak out into the cytoplasm, where they can react with and damage vital molecules and proteins, such as DNA, RNA, and enzymes. While certain metabolic functions (and therefore the creation pathways of ROS) are universal to all cells and tissues

Research Proposal – Overview

- Made use of existing samples
- Determine the differences (if any) in oxidative stress responses of tissues of differing metabolic activity
  - High glycolytic – fast twitch muscle fibers
  - Intermediate – liver tissue
  - Low glycolytic – slow twitch muscle fibers

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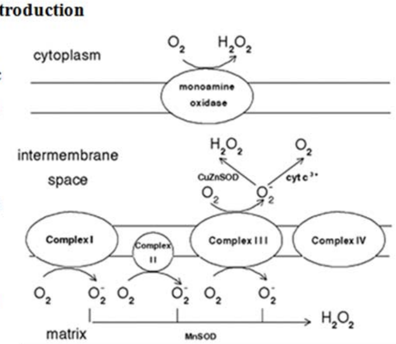

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JSC Experiences

Human Research Program Conference

CEP Award Ceremony

Summer Intern Collaboration

Future Plans

- Grand Valley State University
- B.S. in Chemistry
- Undergraduate research
- Graduate School
- Work in pharmaceutical industry

Thank You!

- Dr. Virginia Wotring
- Kami Faust
- Ashley Kappenman
- Carolyn Snyder
- Missy Matthias
- Nick Gardner
- Dr. Lauren Merkle
- Jacqueline Reeves
- Cristi Richardson
- Beth Marshall
- Victoria Hood
- Allen Hood

NASA