Biomarkers of Exposure to Hazardous Substances (2017-2022)

The UC Davis Superfund Research Center conducts research to:

a) Improve understanding of the mechanisms by which hazardous chemicals produce adverse health affects,

b) Develop, validate and integrate novel methods to evaluate chemical exposures, levels of contamination, and health risks, and

c) Develops innovative remediation strategies to reduce hazardous substance exposure and toxicity.

These activities improve the ability of the National Superfund Program to address legacy and emerging contaminants and associated transformation products to more comprehensively protect the U.S. population from health risks posed by hazardous substances.

Biomarkers of Exposure to Hazardous Substances

Project	PI
1. Optimizing Bioremediation	Tom Young, Frank Loge
2. Nanosensing Platforms	Tingrui Pan
3. Immunochemical BioMarkers	Natalia Vasylieva
★ 4. Cardiac Toxicity	Nipavan Chiamvimonvat
5. Endoplasmic Reticulum Stress	Fawaz Haj, Christophe Morisseau

In response to intensive forestry management and illegal marijuana groves, collaborative research with the Yurok Tribe Environmental Program (YTEP) will:

- Conduct environmental sampling to identify contaminants and their concentrations
- Implement field deployable assays for use by YTEP partners
- Collaboratively identify culturally and ecologically appropriate remediation strategies

Community Engagement Core - Dr. Beth Rose Middleton, PI

The Community Engagement Core works to develop meaningful bi-directional communication strategies between university and tribal researchers and community partners to apply UCD Center research to address community concerns.

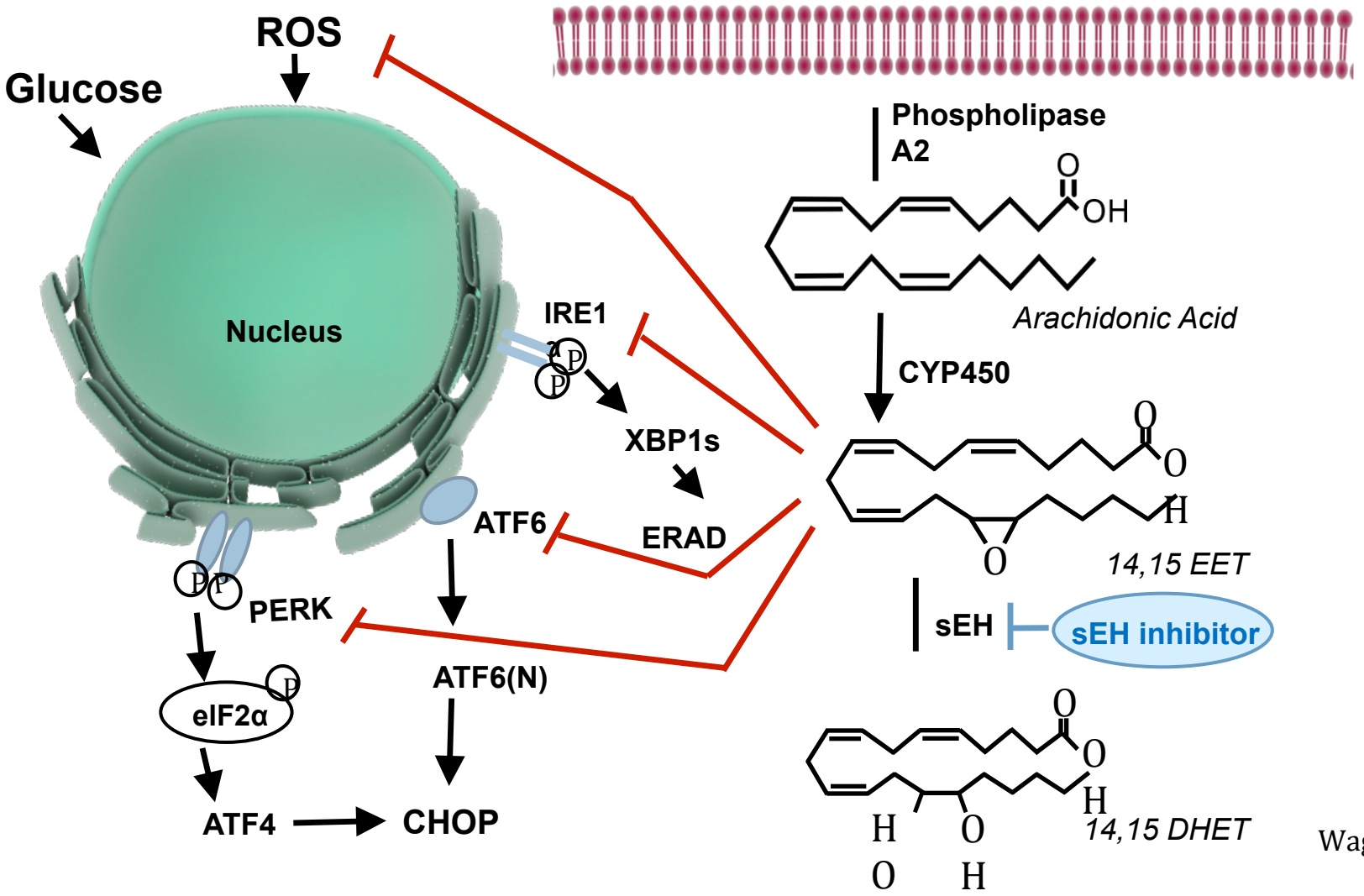
Broadly, the chemical detection technologies, remediation strategies and training opportunities aim to provide communities with autonomous methods for addressing environmental health problems within their community while training scientists on developing equitable, respectful, and responsible projects with community partners.

Develop analytical methods to detect hazardous chemicals for the variety of UCD-SRP projects.

Validate alternative analytical methods such as:

- Immunoassays
- Cell-based assays

sEH inhibition and EpFA block Endoplasmic Reticulum Stress (ER Stress)



Wagner et al. 2017

Investigate new mechanistic insights into the effects of chronic exposure of Superfund (SF) chemicals on endoplasmic reticulum (ER) stress.

Effects of SF chemicals on ER stress by

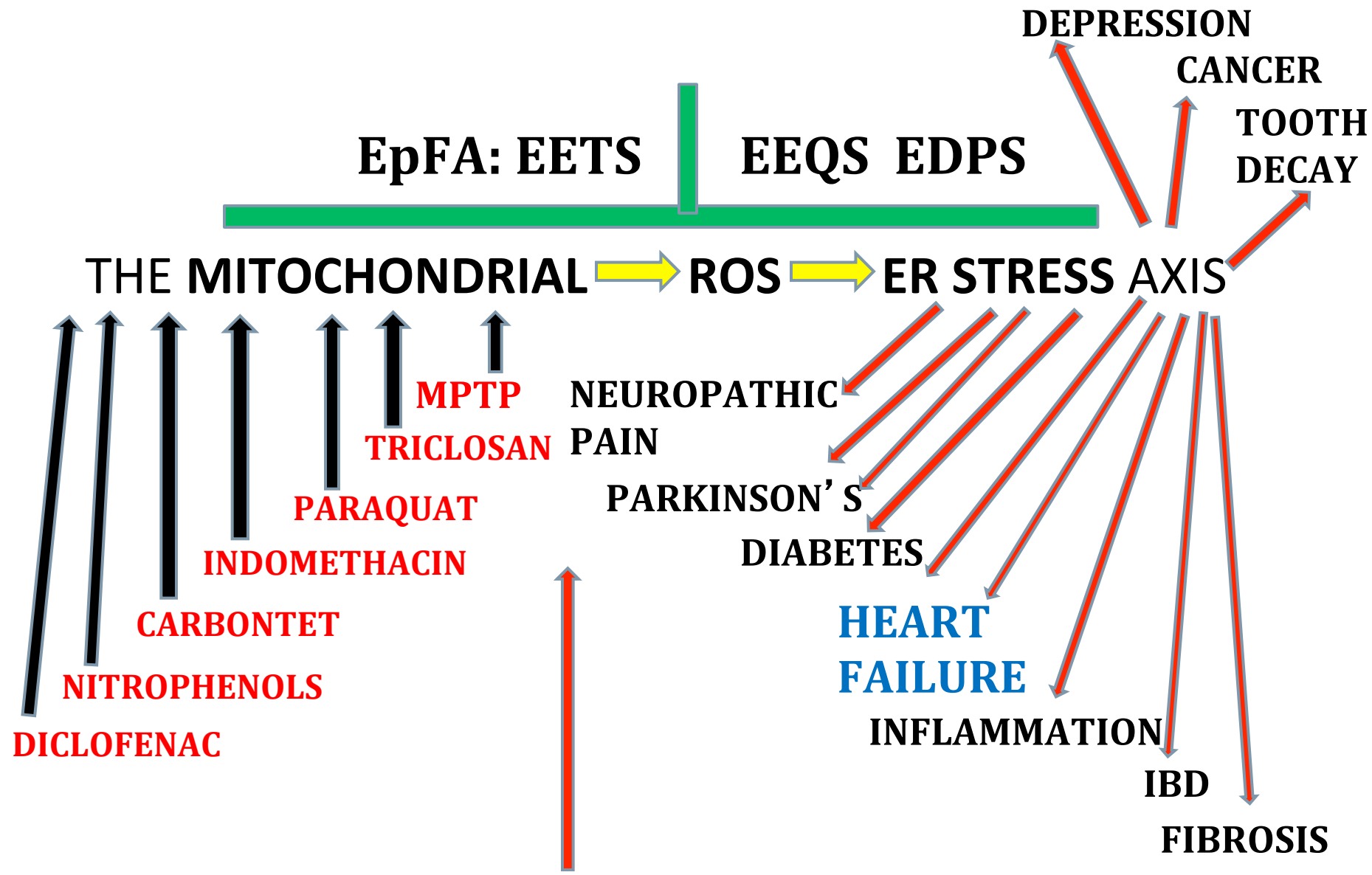
- Altering gene expression
- Inhibition
- Competition for catalysis
- Increasing reactive oxygen species
- **BLOOD AND URINARY BIOMARKERS OF DISRUPTION OF THE ER STRESS PATHWAY TO MONITOR XENOBIOTIC EXPOSURE AND POSSIBLY DRIVE THERAPEUTIC INTERVENTION.**

Investigate molecular mechanisms of chronic exposure to Superfund chemicals on mitochondrial oxidative stress (MOS) and proteasome dysfunction

Target Analytes:

- Pesticides
- Antimicrobials
- HaHs/PaHs
- Commercial Chemicals
- Pharmaceuticals
- **CELL, BLOOD AND URINARY BIOMARKERS OF DISRUPTION OF MITOCHONDRIA TO MONITOR XENOBIOTIC EXPOSURE AND POSSIBLY DRIVE THERAPEUTIC INTERVENTION.**

DEVELOP BIOMARKERS TO DETECT FUNDAMENTAL PROCESSES OF TOXICITY



Project 4 - Monitoring Mitochondrial Oxidative Stress and Cardiac Toxicity Caused by Chronic Exposure to Chemicals

Dr. Nipavan Chiamvimonvat, Project Leader

Dr. Aldrin Gomes, Co-Leader

Overall aims

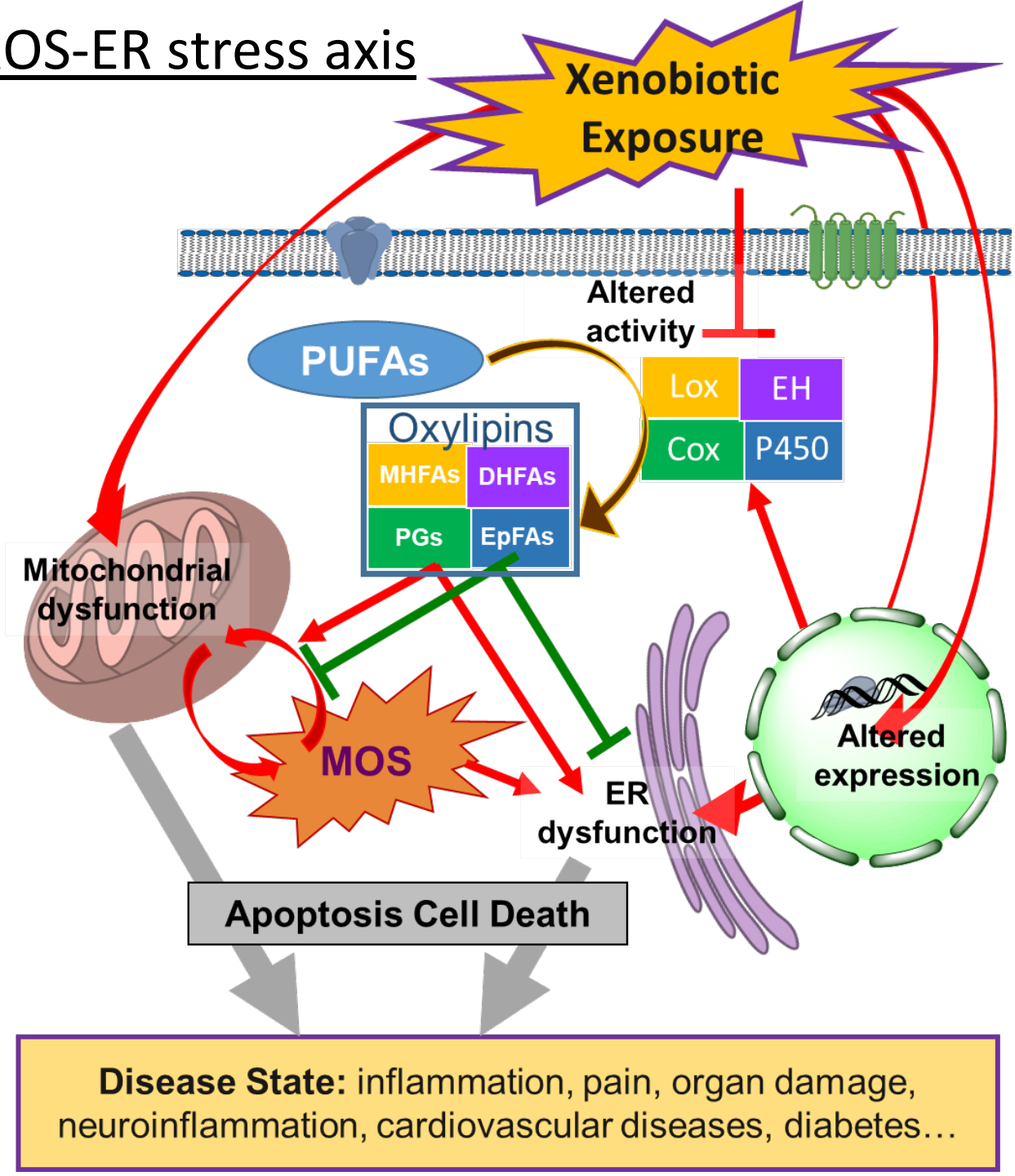
Hypothesis: chronic exposure to xenobiotics and/or non-steroidal anti-inflammatory drugs (NSAIDs) leads to mitochondrial oxidative stress (MOS) that results in proteasome dysfunction, apoptosis, tissue fibrosis and cardiac toxicity.

Focus: Heart health related diseases.

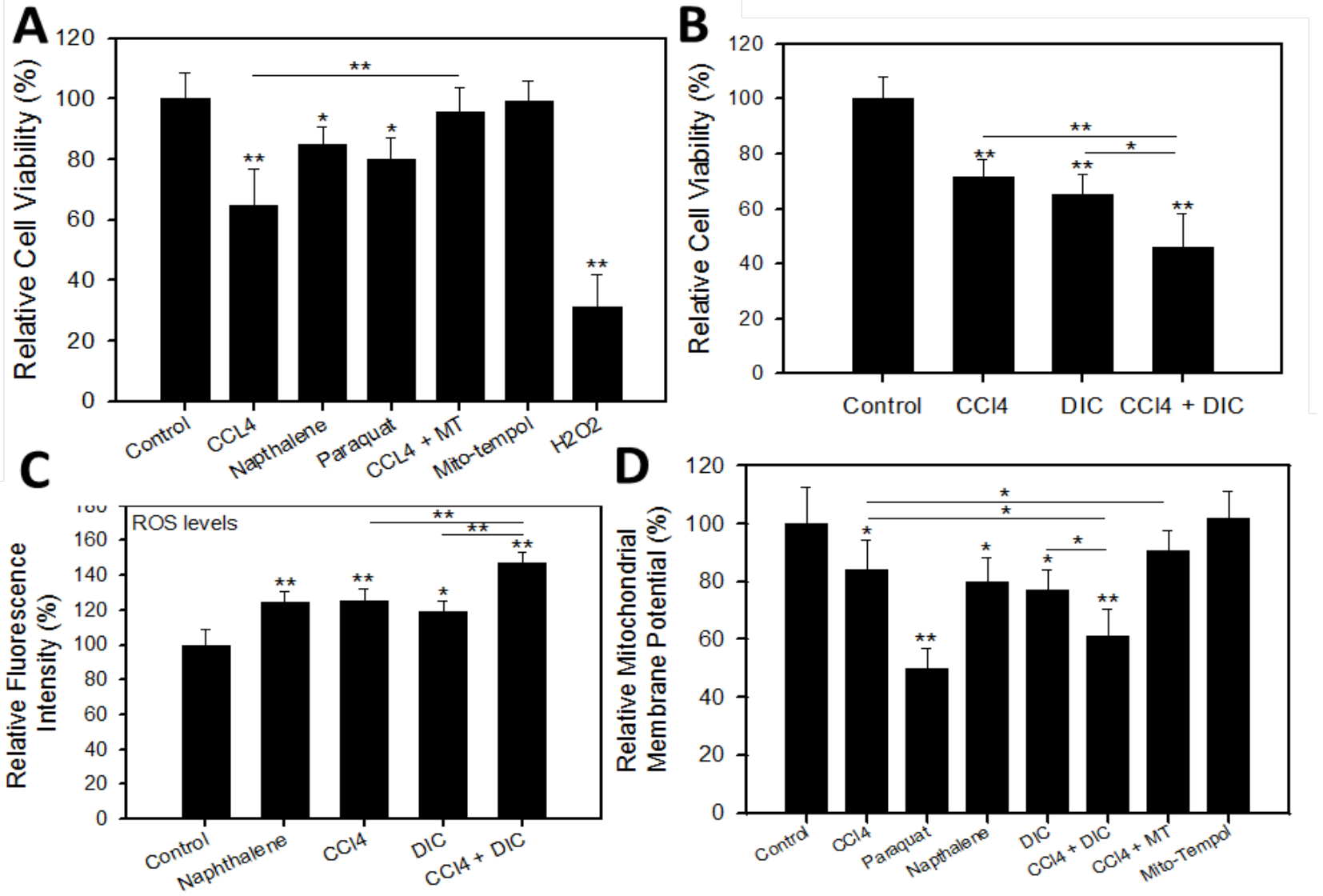
Approach: used cell based assay and in vivo models to test effect of exposure to SF chemicals and/or NSAIDs on mitochondrial stress, proteasome dysfunction, apoptosis, fibrosis and associated alterations of cell, plasma and urine profile as a biomarker.

Deliverable: Easier methods to monitor mitochondrial oxidative stress as a marker of xenobiotic exposure.

The MIT-ROS-ER stress axis

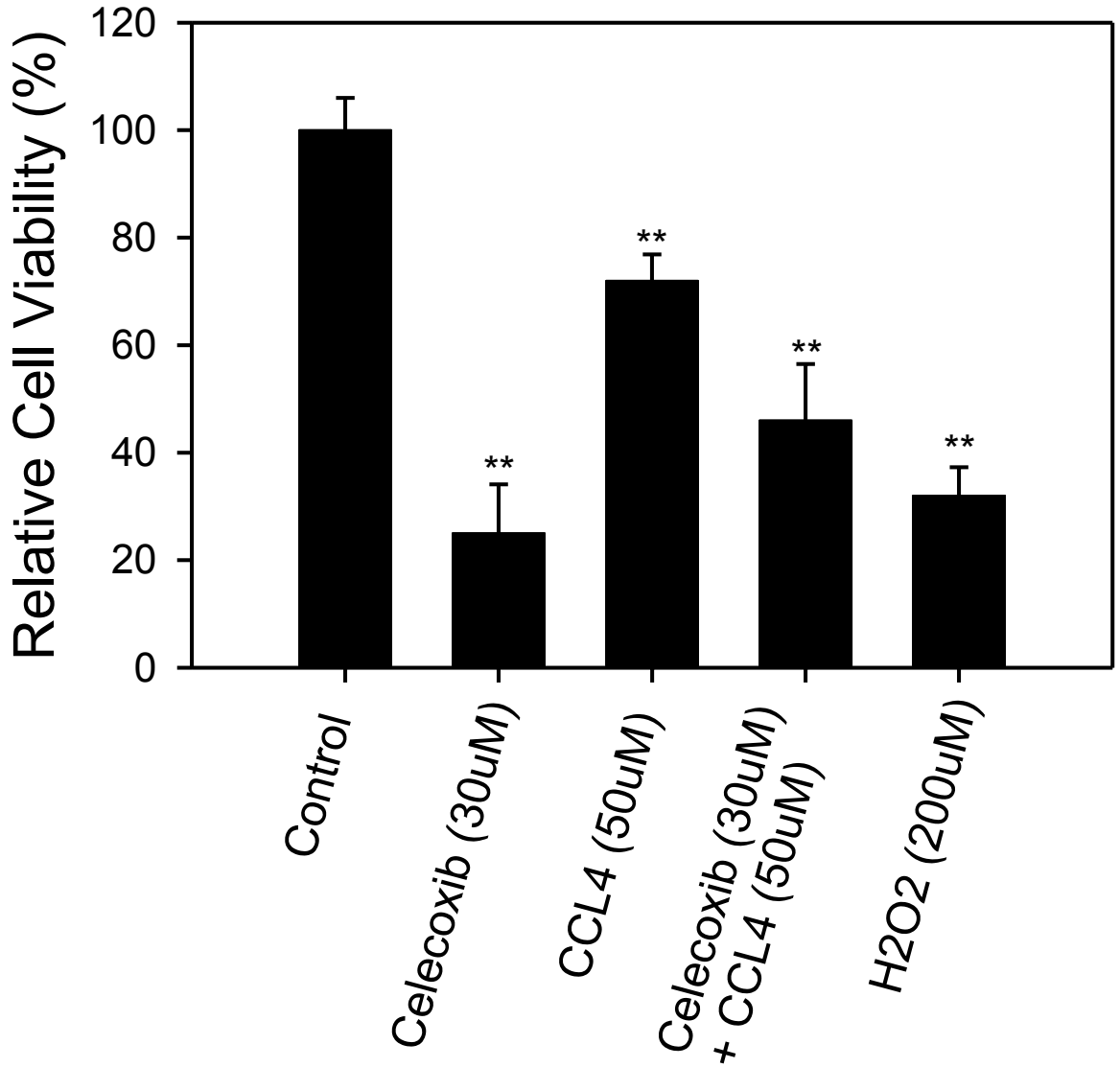


Effect of xenobiotics on cell viability, Reactive Oxygen Species (ROS) production, and mitochondrial membrane permeability (MMP)

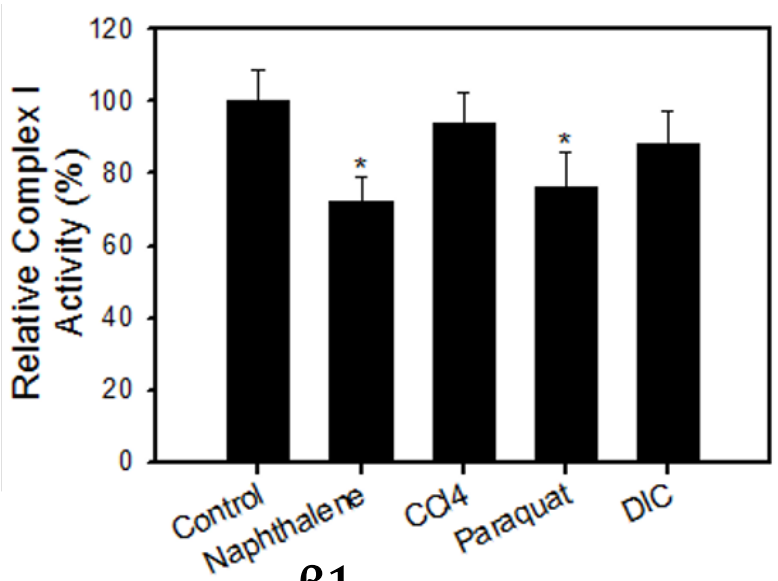


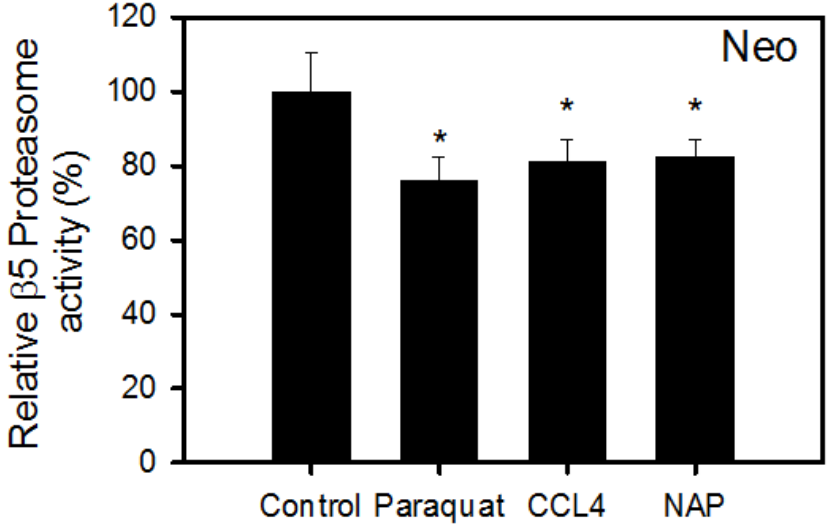
Cell viability in H9c2 cardiac cells incubated with 50μM CCl_4, 100μM paraquat, 20μM naphthalene, 10 μM diclofenac (DIC) for 24 h. Pre-treatment with 20μM mito-Tempol (MT) prevented reduced cell vitality caused by CCl_4. H_20_2, 200 μM.

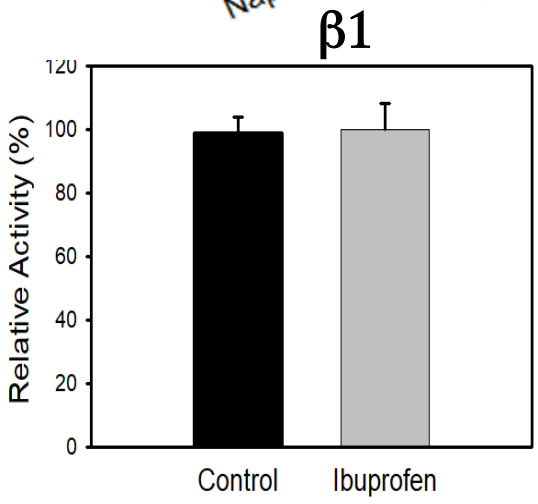
Effect of xenobiotics on Cardiac Cell Viability

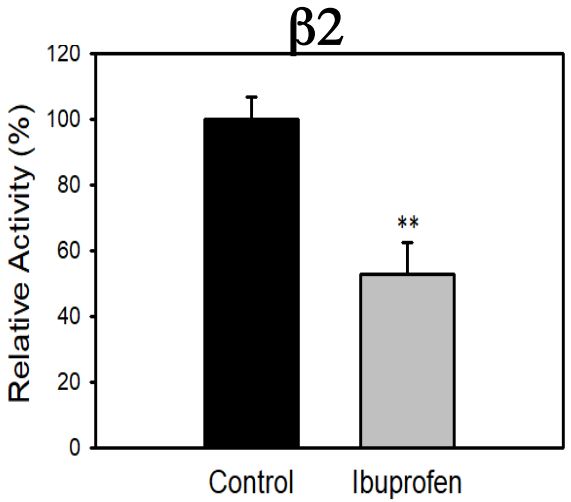


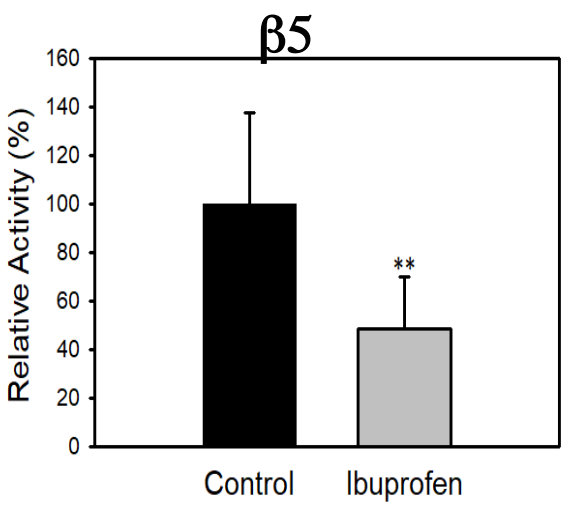
Xenobiotic exposure affects mitochondrial electron chain transport activity and proteasome activity





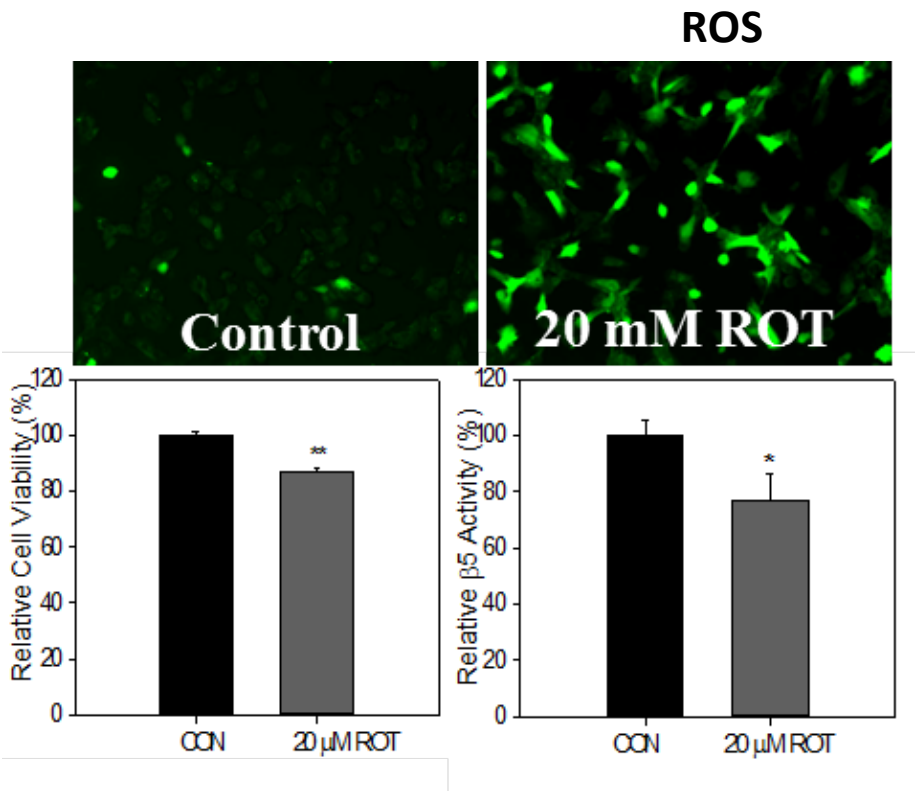




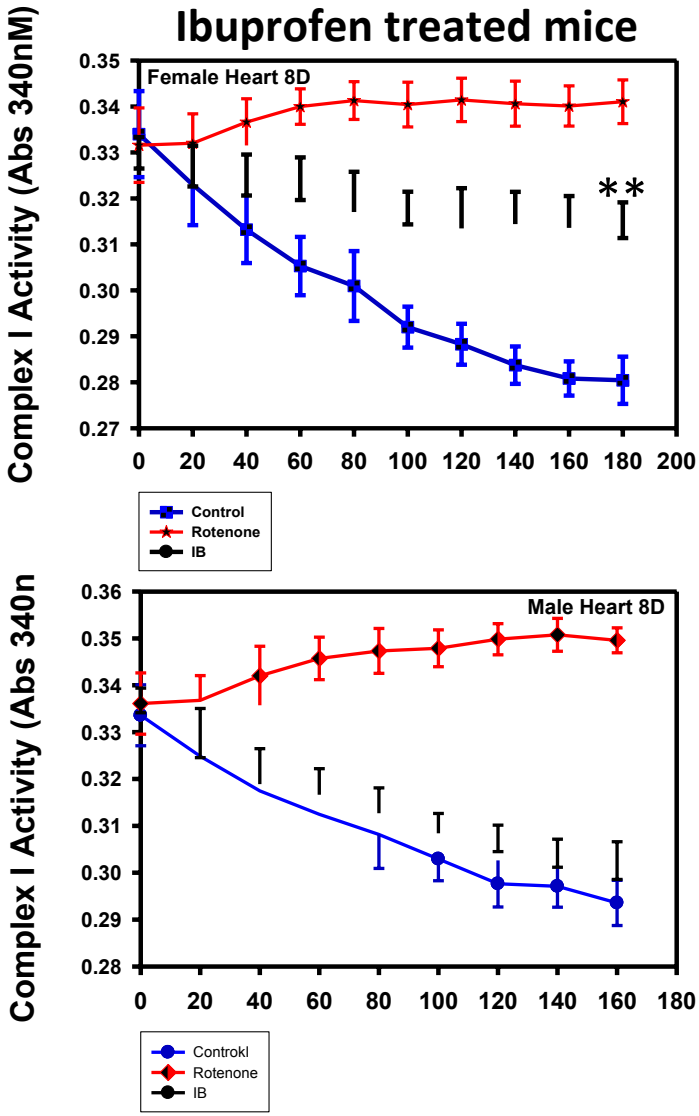


Mitochondrial complex I activity is decreased by naphthaline (20 μM) and paraquat (100 μM) but not CCl4 (20 μM) or DIC (20 μM). Lower figures show proteasome dysfunction occurs in hearts of ibuprofen treated mice

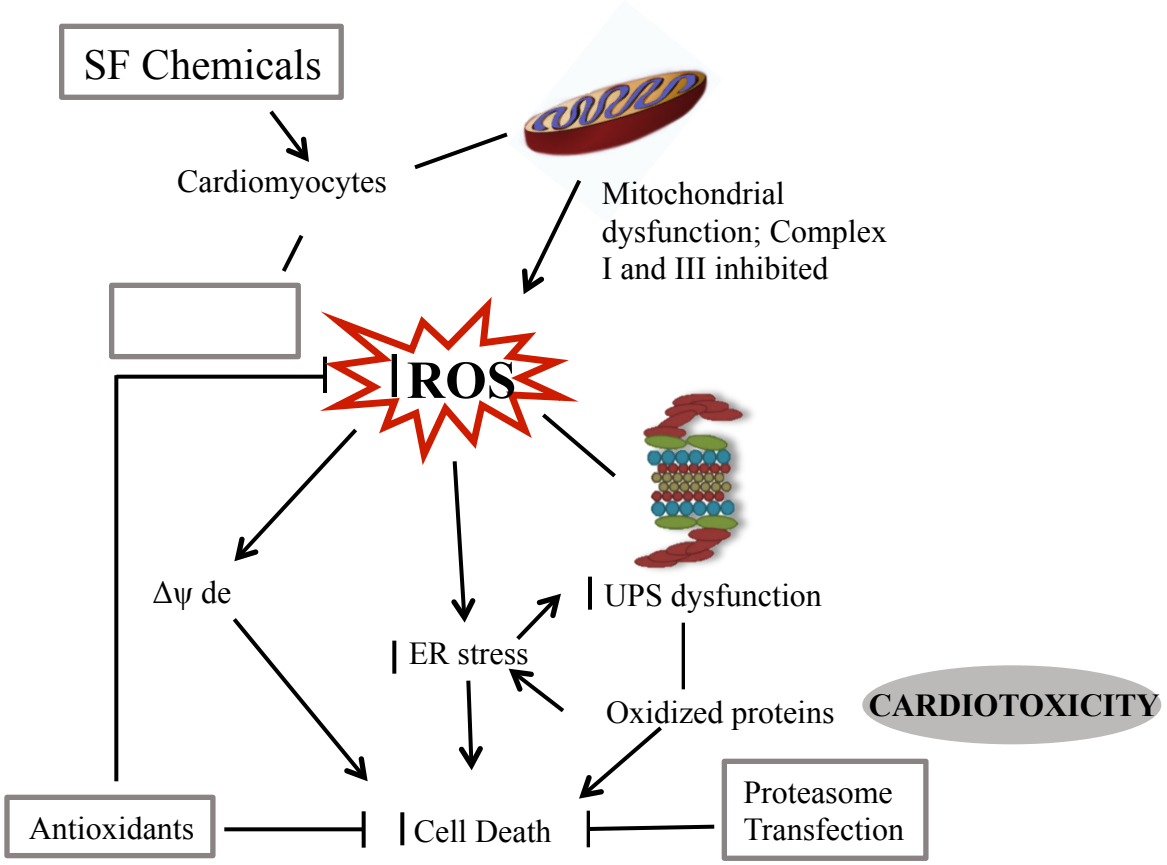
Reducing mitochondrial electron transport chain activity increases ROS and reduces cell viability



ROT – Rotenone (a Complex I activity inhibitor)



Current Model



Conclusions

- CCl_4 naphthalene, paraquat induces cardiac toxicity, mitochondrial stress and proteasome dysfunction.
- Mitochondrial-stress is induced by other xenobiotics: diclofenac, ibuprofen, naproxen.

Future Directions

- Expand target analysis (Pesticides, HaHs/PaHs, Commercial Chemicals and Pharmaceuticals).
- **Determine cell, blood and urinary biomarkers of mitochondrial dysfunction to monitor Xenobiotic exposure and possibly drive therapeutic intervention.**

Acknowledgements

- Bruce Hammock
- Natalia Vasylieva (project 3)
- Fawaz G. Haj (Project 5)
- Christophe Morisseau (Project 5)
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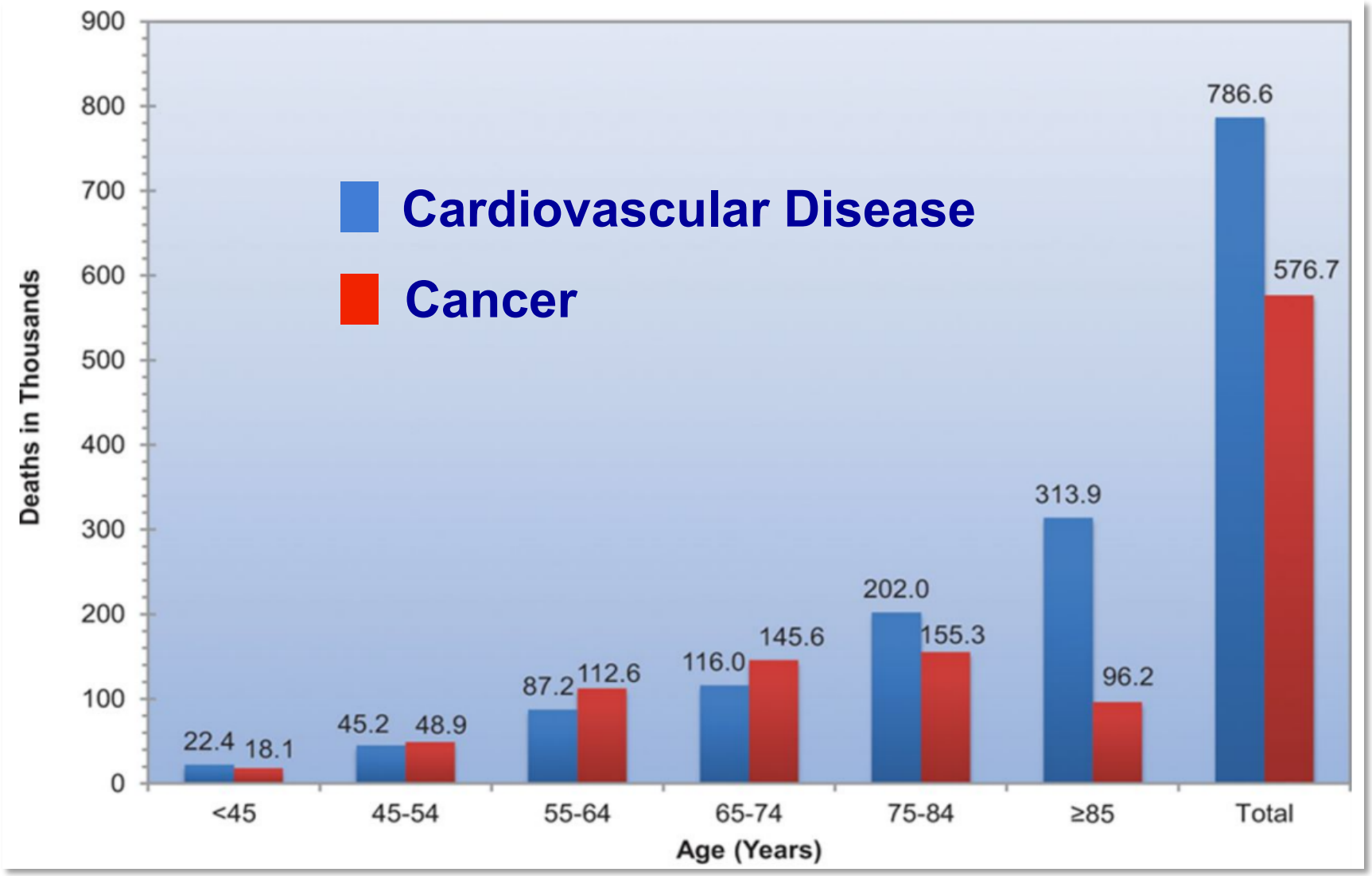
- Daniel Tancredi (core B)

Funding from: NIEHS/Superfund Research Program P42 ES004699

Project 4 - Monitoring Mitochondrial Oxidative Stress and Cardiac Toxicity Caused by Chronic Exposure to Chemicals

Nipavan Chiamvimonvat, MD
Division of Cardiovascular Medicine

Mortality rate of cardiovascular disease surpasses that of cancer

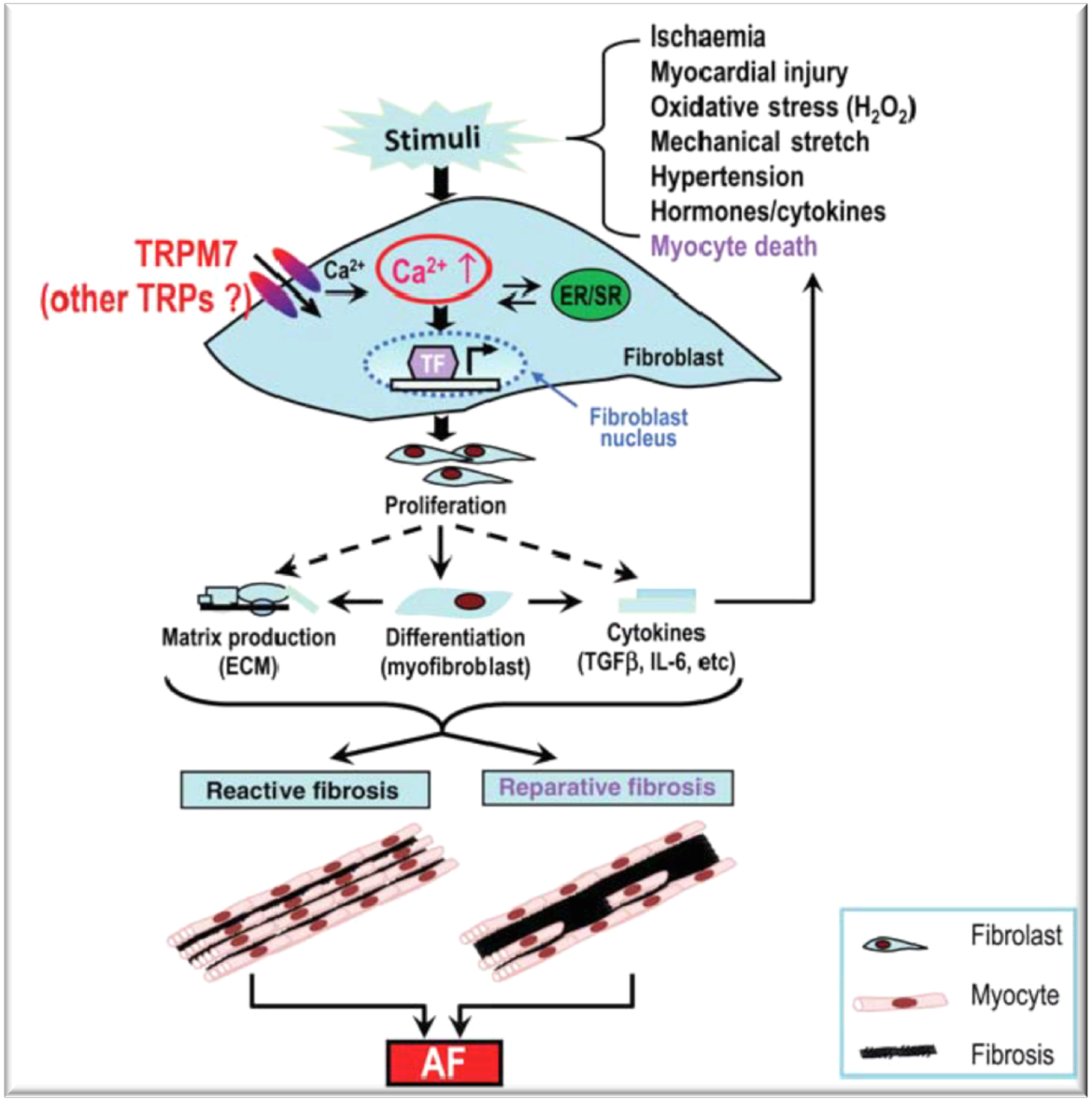


Circ 131(4): e29-322, 2015

Cardiac fibroblasts

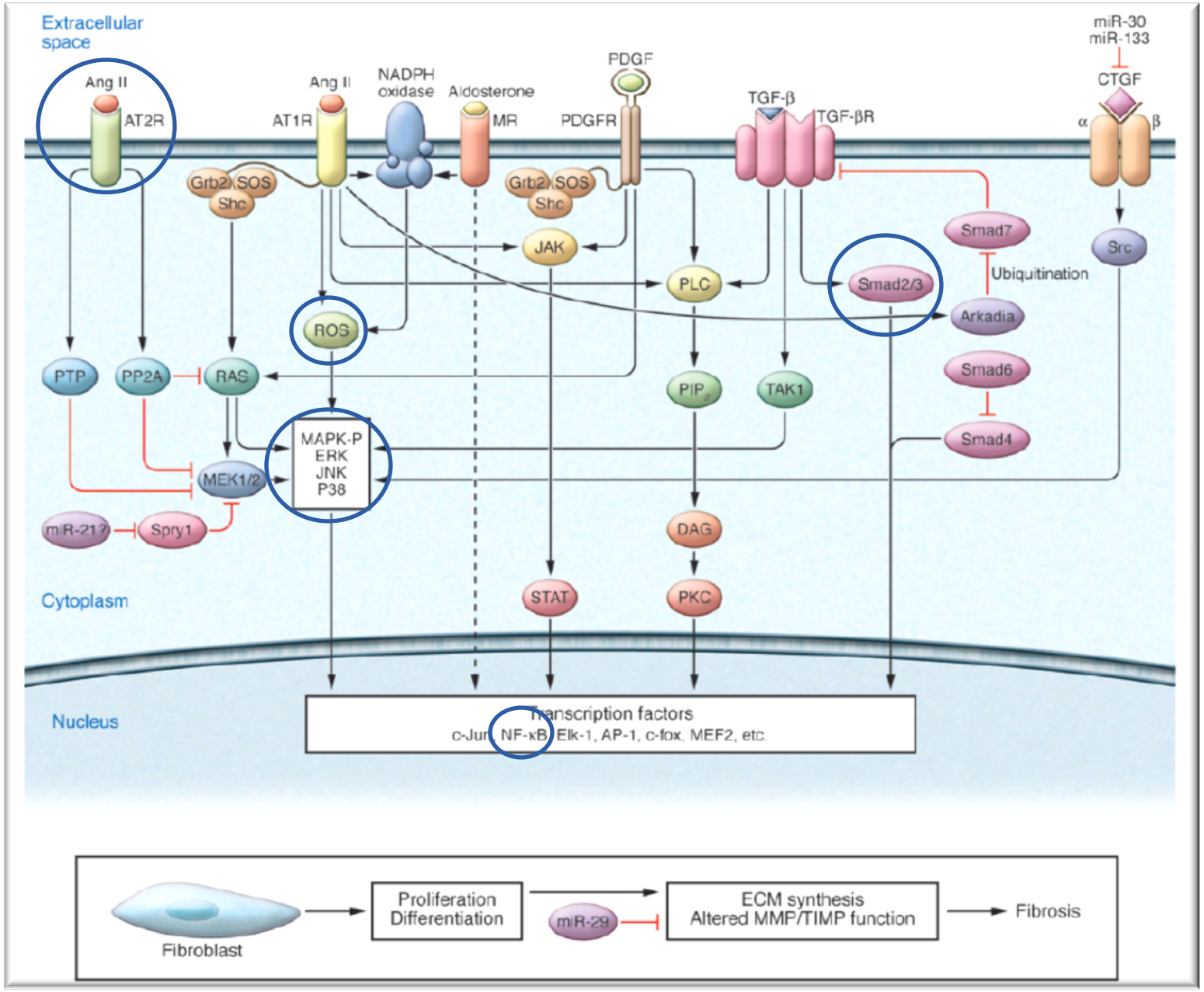
- Cardiac fibroblasts account for ~75% of all cardiac cells, but contribute only ~10-15% of total cardiac cell volume.
- The principal sources of extracellular matrix (ECM) proteins.
- A heterogeneous population.
- Derived from various distinct tissue niches including resident fibroblasts, endothelial cells, and bone marrow sources.

Roles of cardiac fibroblasts



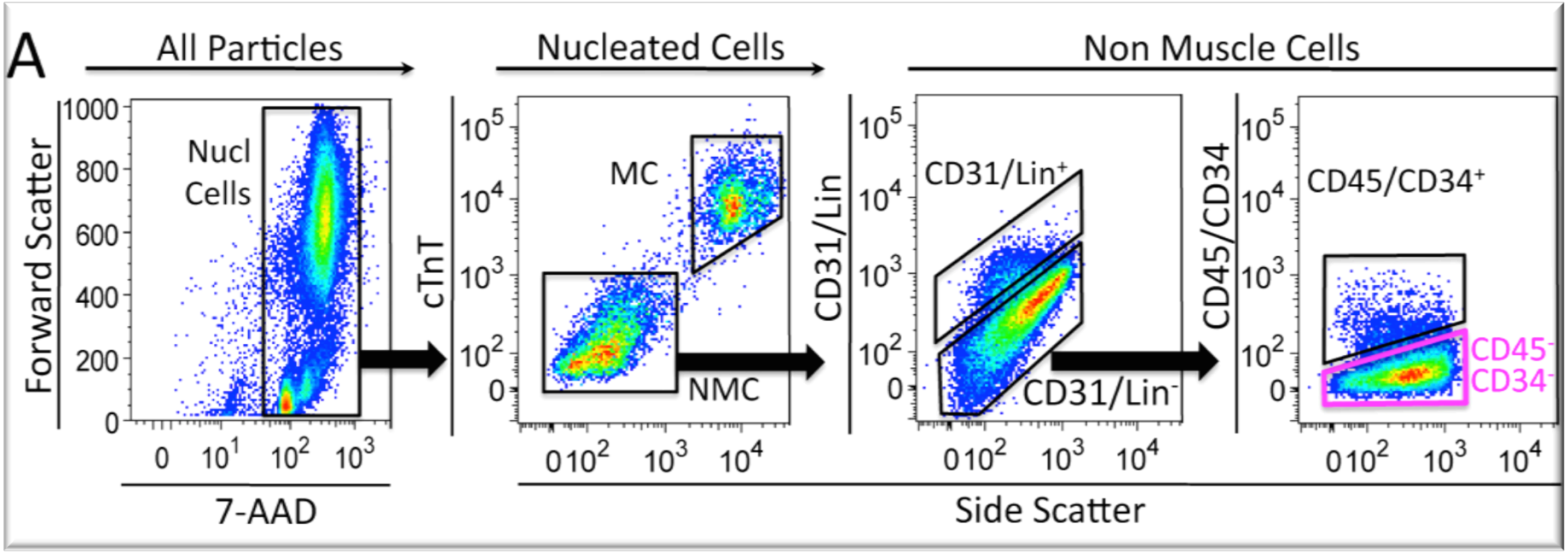
Yue *et al*, Cardiovascular Res 2011

Molecular mechanisms leading to cardiac fibrosis

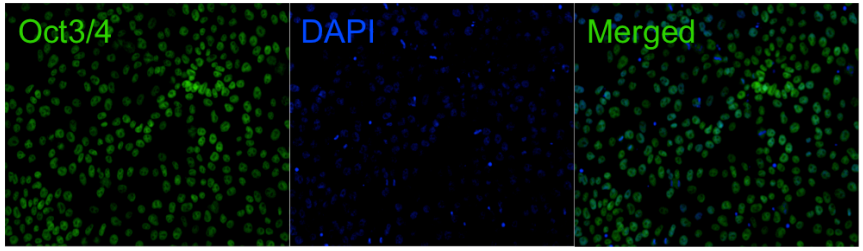


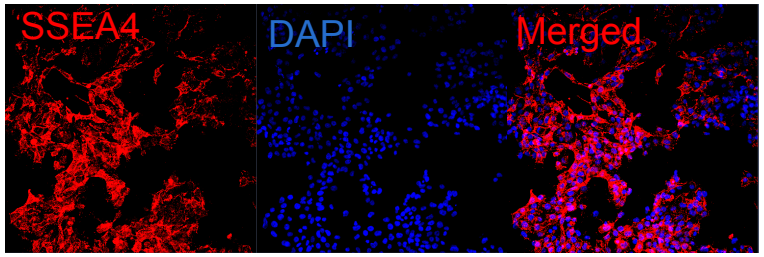
Wakili *et al*, 2011

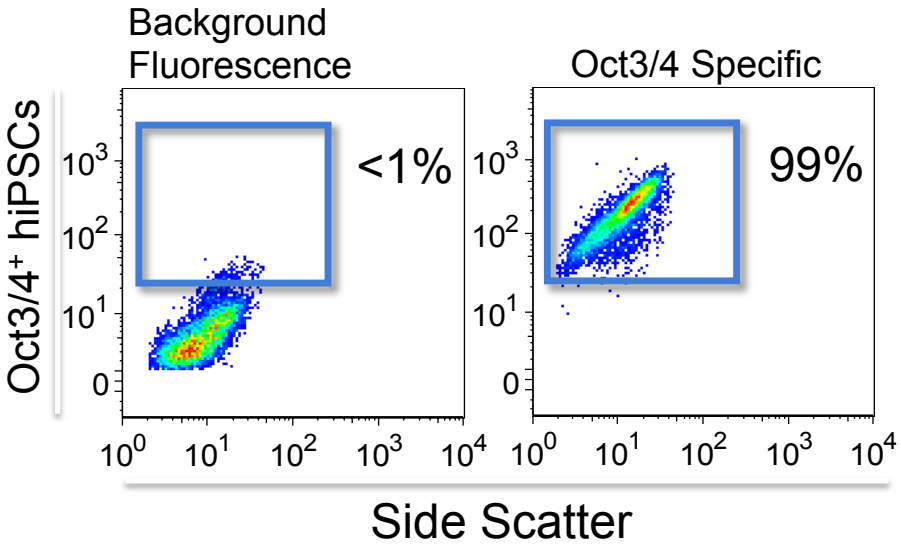
Flow cytometric analysis of the isolated cells from mouse hearts

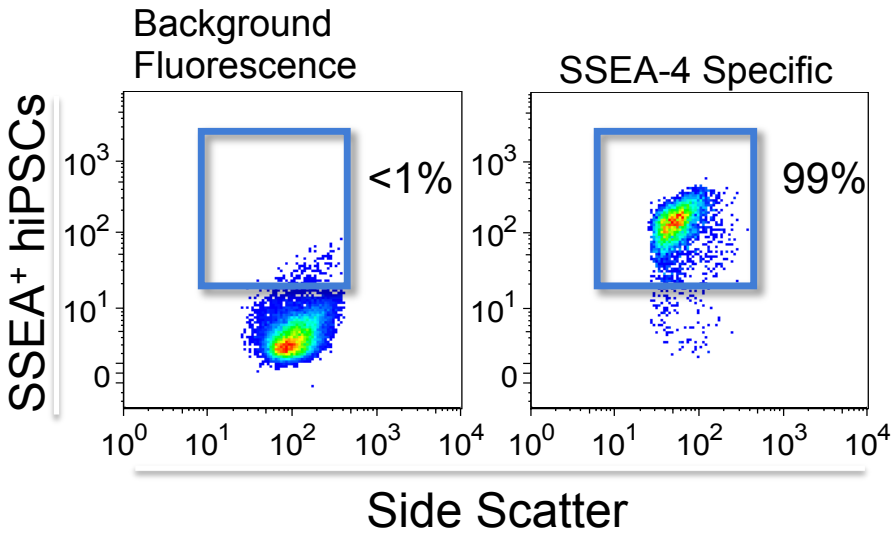


Recreating disease in a dish
hiPSCs and hiPSC-CMs

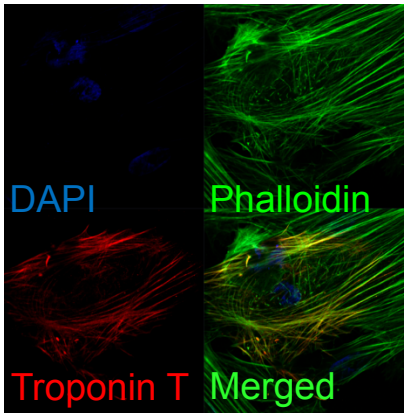




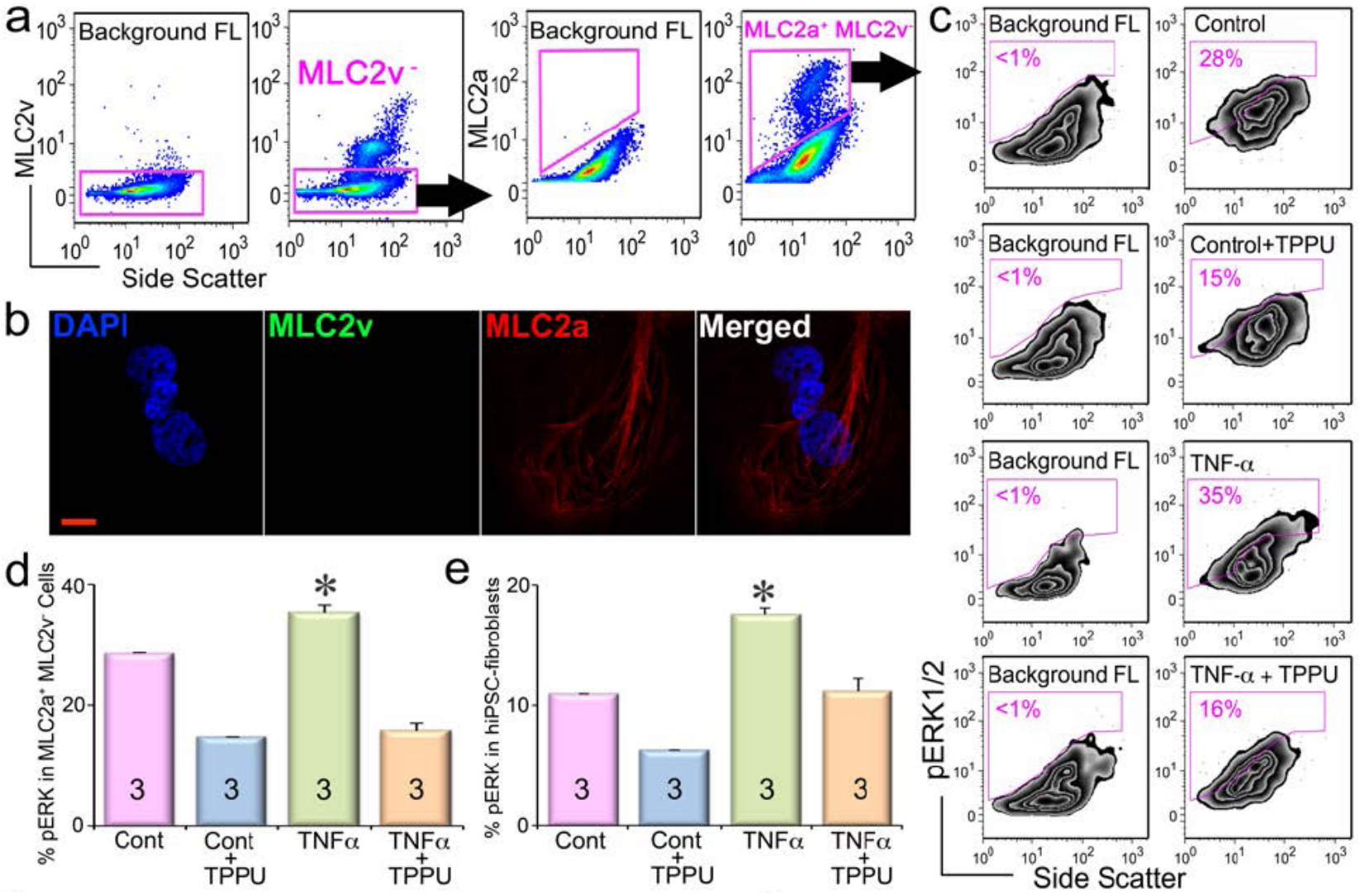




hiPSC-CMs

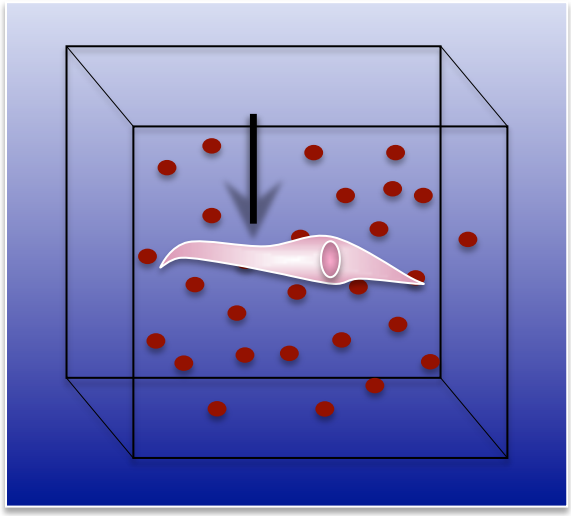


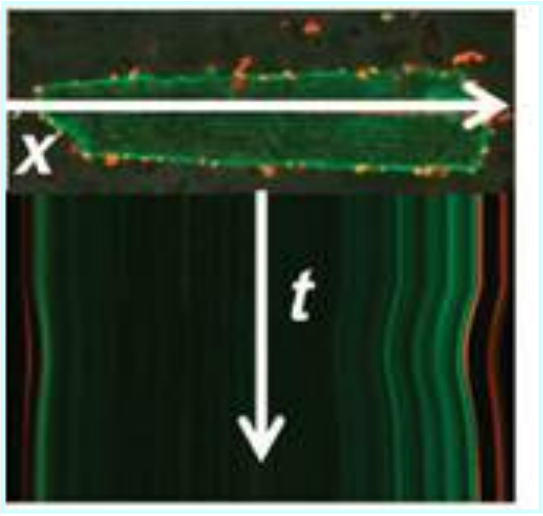
Activation of MAPK in hiPSC-CMs and hiPSC-fibroblasts by TNF-α

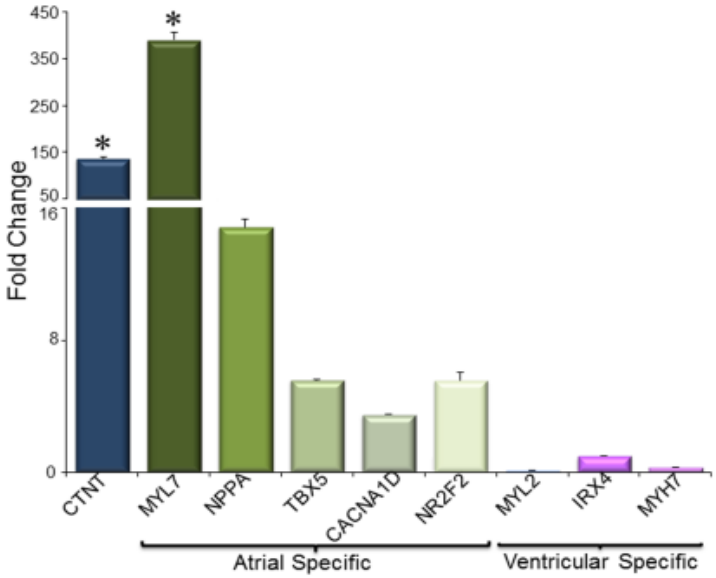


Novel Cell-in-Gel Platform

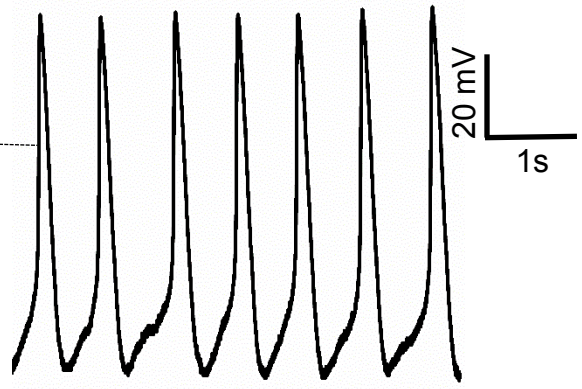
Novel 3D Cell-in-Gel



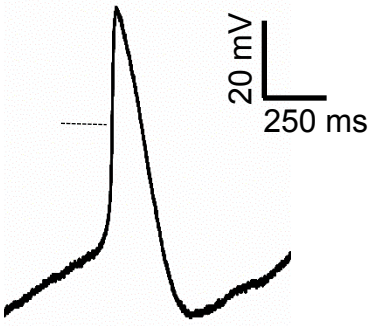




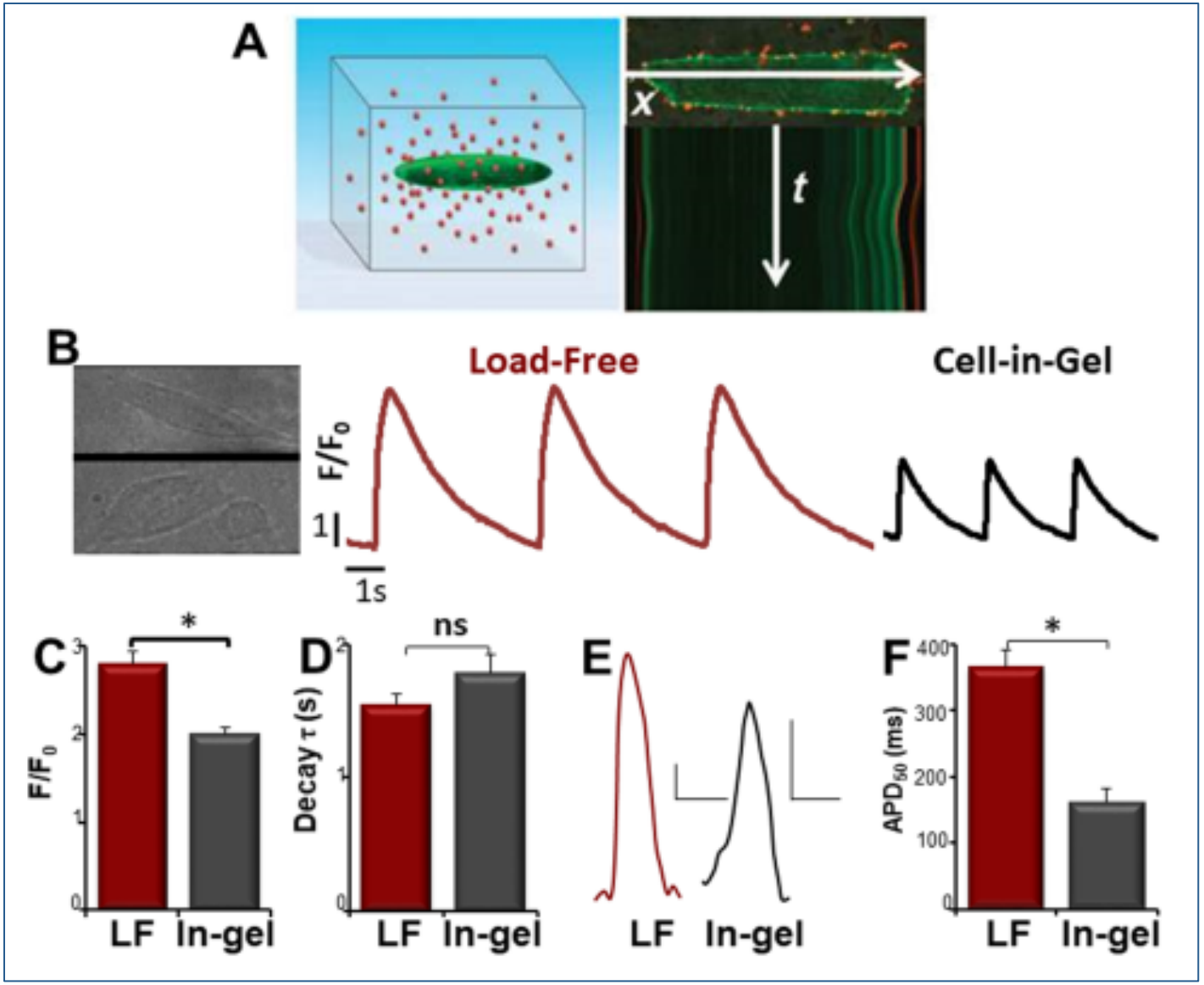
Spontaneous APs



Single APs



Effects of mechanical stress on Ca^{2+} handling



Conclusions

- **Generation of reliable platform for testing the effects of Superfund chemicals on cardiac myocytes and fibroblasts.**
- **Development of bioassays to test the effects of exposure.**

Acknowledgements

- Bruce Hammock
- Aldrin Gomes (Project 4)
- Fawaz G. Haj (Project 5)
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- Padmini Sirish

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