# Mit@Care

# 2022

We are grateful for all the help we got to expand our faculty team, to establish our data science operation, and to initiate exciting new adventures in mitochondrial biology and medicine in 2022.

#### Mito Circle Journal Club 2022 Summary

Date	Name	1st au_last au: title_yr_journal
Jan 10	Steve Hurst	MICU1 occludes MCU in the mitochondrial calcium uniporter complexTsai C-W et al. 2021 bioRxiv
Jan 24	Erin	1. Combinatorial G x G x E CRISPR screening and functional analysis highlights SLC25A39 in mitochondrial GSH transport. Shi X et al. 2021 BioRxiv; 2. SLC25A39 is necessary for mitochondrial glutathione import in mammalian cells. Wang Y et al. 2021 Nature
Feb 7	Gyuri C	Metabolic design in a mammalian model of extreme metabolism, the North American least shrew (Cryptotis parva). Chung DJ et al 2022 J Physiol
March 14	Dave Booth	1. Ultrasensitive Genetically Encoded Indicator for Hydrogen Peroxide Identifies Roles for the Oxidant in Cell Migration and Mitochondrial Function. Pak et al. 2020 Cell Metab. 2. Spatial and temporal control of mitochondrial H2O2 release in intact human cells. Hoehne et al. 2022 EMBO J.
Mar 28	Tom Neil	Mosaic dysfunction of mitophagy in mitochondrial muscle disease. Mito et al 2022 Cell Metab
Apr 11	Ben	A comprehensive approach to artifact-free sample preparation and the assessment of mitochondrial morphology in tissue and cultured cells. Hinton et al. 2021. BioRxiv
Apr 25	Marco	The interplay between BAX and BAK tunes apoptotic pore growth to control mitochondrial-DNA-mediated inflammation. Cosentino et al. 2022. Mol. Cell.
June 6	Elena	A Ca21-Dependent Mechanism Boosting Glycolysis and OXPHOS by Activating Aralar-Malate-Aspartate Shuttle, upon Neuronal Stimulation. Pérez-Liébana et al. 2022 J Neurosci.
Aug 29	Gyuri H	Regulation of mitochondrial proteostasis by the proton gradient. Patron et al. 2022. EMBO J
Sep 12	Steve Hurst	The mitochondrial calcium uniporter engages UCP1 to form a thermoporter that promotes thermogenesis. Xue K et al. 2022. Cell Metab.
Sep26	Marilen	Enhanced NCLX-dependent mitochondrial Ca2+ efflux attenuates pathological remodeling in heart failure. Garbincius et al. 2022 JMCC
Oct 10	Piyush	Mitochondrial dynamics regulate genome stability via control of caspase-dependent DNA damage. Cao K et al. 2022 Dev Cell
Oct 24	Arijita	A three-organelle complex made by wrappER contacts with peroxisomes and mitochondria responds to liver lipid flux changes. Ilacqua et al. 2022 J Cell Sci.
Nov 7	RVS	Synaptic vesicle pools are a major hidden resting metabolic burden of nerve terminals. Pulido and Ryan 2021 Sci Adv
Nov 21	Elena (2 <sup>nd</sup> )	Ca2+ channels couple spiking to mitochondrial metabolism in substantia nigra dopaminergic neurons.  Zampese et al. 2022. Sci. Adv.
Dec 5	Shey	Magnetic sensitivity of cryptochrome 4 from a migratory songbird. Xu J et al. 2021. Nature
Dec 19	Caitlyn	Mitochondrial functional resilience after TFAM ablation in the adult heart. Ghazal et al. 2021 AJP Cell

#### MitoCircle 2022

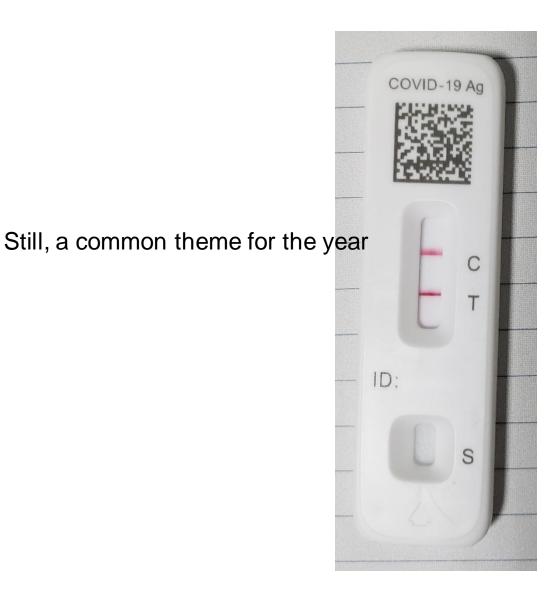
An-Chi Wei, Ph.D. Jan 31 MitoTox: a mitochondrial toxicity database and screening platform

Geert Bultynck, Ph.D. Feb 14 The Bcl-2 family and Ca2+ signaling in health & disease

Evgeny Pavlov, Ph.D. Mar 1 Novel holographic imaging assay of the permeability transition pore in living cells: dissecting specific contributions of the ANT and ATP synthase

Suliana Manley & Tatjana Kleele, Ph.D. May 3 Distinct fission signatures predict mitochondrial degradation or biogenesis

Julia Liu, Ph.D. Sept 12 Mitochondrial calcium regulation in cardiac function



#### In January Zuzana departed from Csordas lab for an indefinite period



#### **JBC** RESEARCH ARTICLE



# Metabolic adaptation to the chronic loss of Ca<sup>2+</sup> signaling induced by KO of IP<sub>3</sub> receptors or the mitochondrial Ca<sup>2+</sup> uniporter

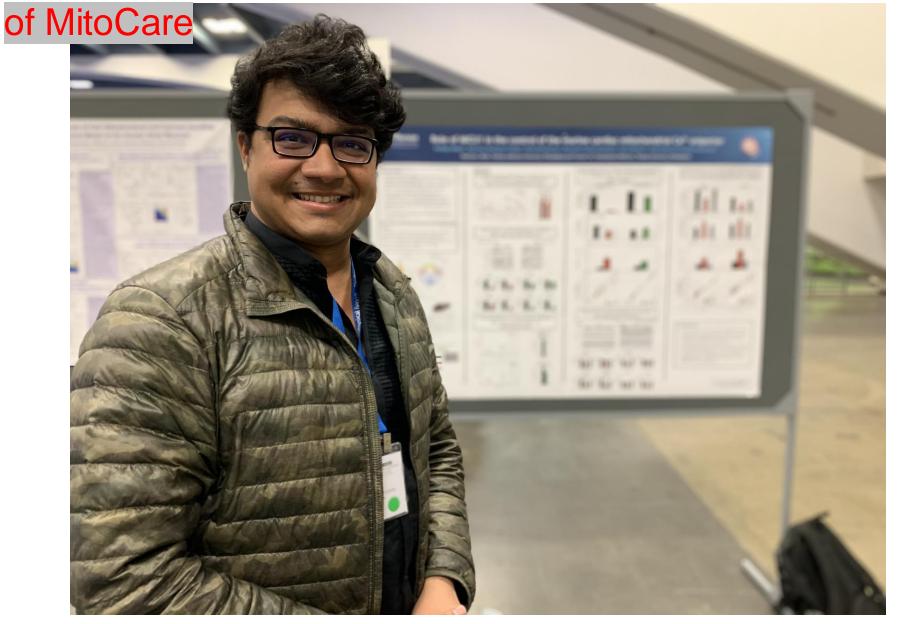
Received for publication, April 18, 2021, and in revised form, October 4, 2021 Published, Papers in Press, November 19, 2021, https://doi.org/10.1016/j.jbc.2021.101436

Michael P. Young<sup>1</sup>, Zachary T. Schug<sup>2</sup>, David M. Booth<sup>1</sup>, David I. Yule<sup>3</sup>, Katsuhiko Mikoshiba<sup>4,5</sup>, György Hajnóczky<sup>1</sup>, and Suresh K. Joseph<sup>1,\*</sup>

From the <sup>1</sup>Department of Pathology, MitoCare Center, Anatomy, and Cell Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; <sup>2</sup>Molecular and Cellular Oncogenesis, The Wistar Institute, Philadelphia, Pennsylvania, USA; <sup>3</sup>Department of Pharmacology & Physiology, University of Rochester, Rochester, New York, USA; <sup>4</sup>Shanghai Institute of Advanced Immunochemical Studies (SIAIS), Shanghai Tech University, Shanghai, China; <sup>5</sup>Department of Biomolecular Science, Faculty of Science, Toho University, Funabashi, Japan



### Biophysics at SF; Prottoy was the ONLY poster presenter

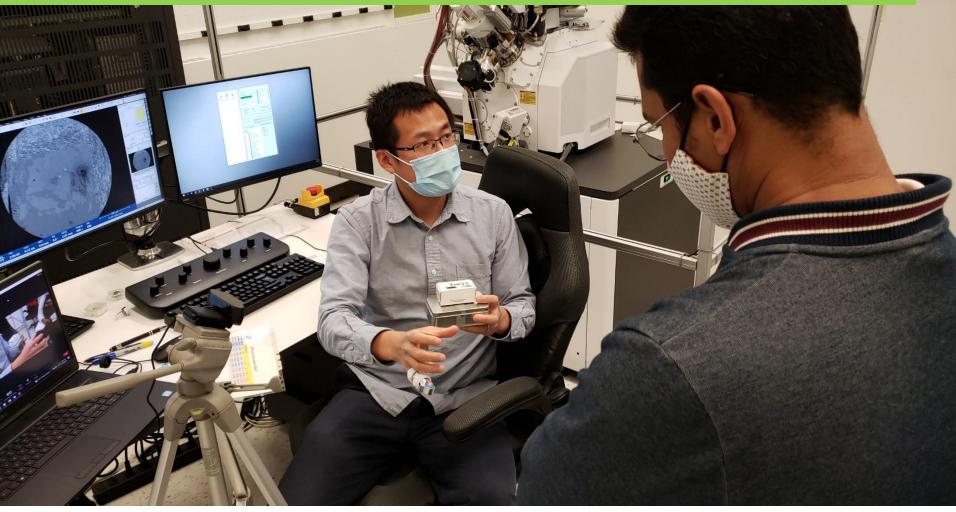


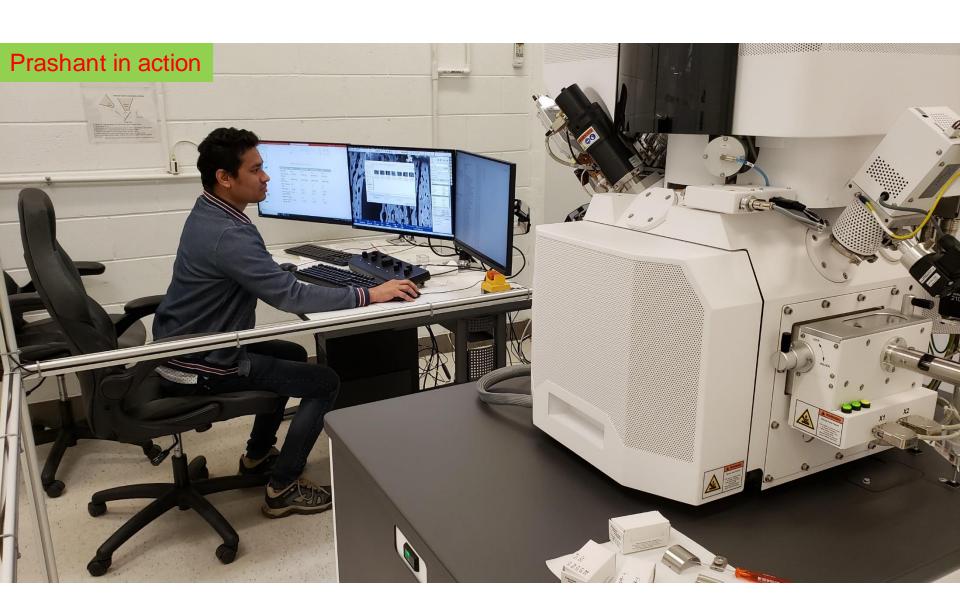




But Adam and Veronica, two MC Alumni gave talks







#### Kata says goodbye



Mid-March
Catching up with
Zuzana in
Bratislava

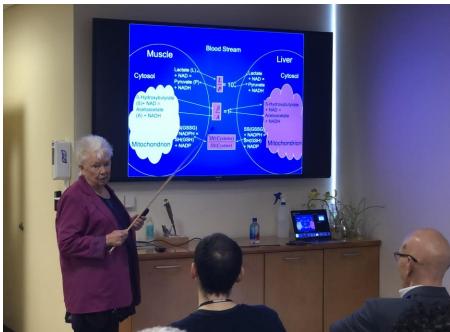






# Celebrating Jan's 80<sup>th</sup> at MitoCare



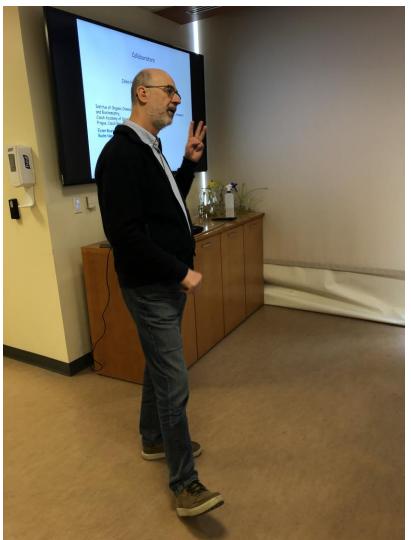


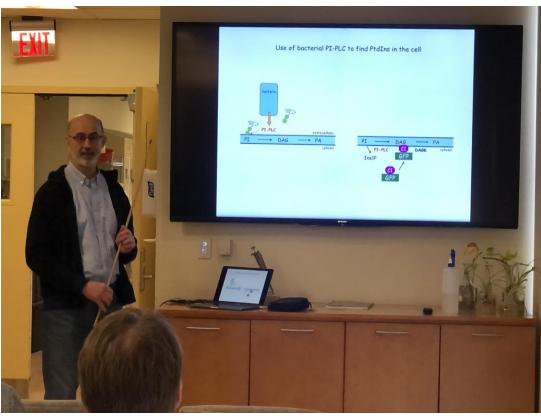






# Tamas Balla (NIH) on Mitochondria & Lipid





#### Macarena's Farewell



#### End of April – Hitachi HT7800 120kV TEM Demo in Clarksburg, MD



#### Early May – JEOL JEM1400 Flash 120kV TEM Demo at Eurofins, in Lancaster PA





# Mid May – ThermoScientific Talos L120C 120kV TEM Demo at the 'Nanoport', in Hillboro OR





# Frataxin deficiency lowers lean mass and triggers the integrated stress response in skeletal muscle

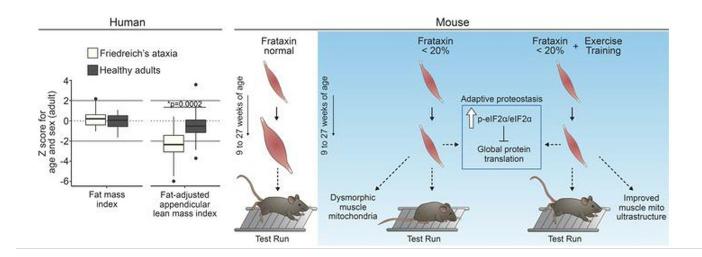
César Vásquez-Trincado, ..., Shana E. McCormack, Erin L. Seifert

JCI Insight. 2022;7(9):e155201. https://doi.org/10.1172/jci.insight.155201.

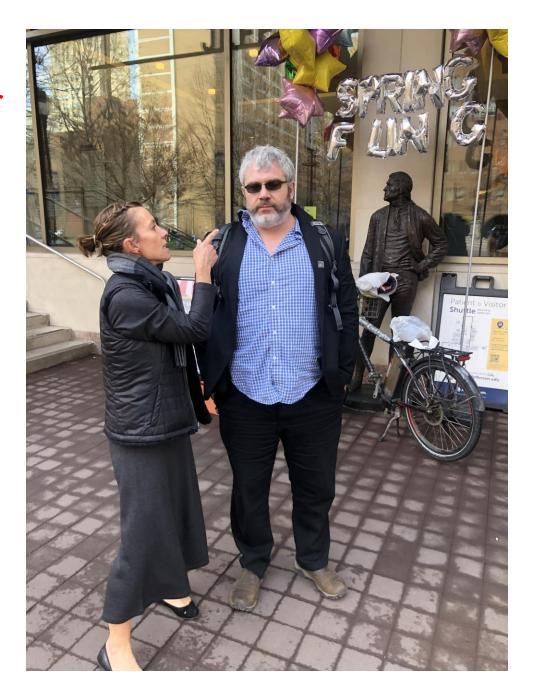
Research Article

Muscle biology

#### **Graphical abstract**

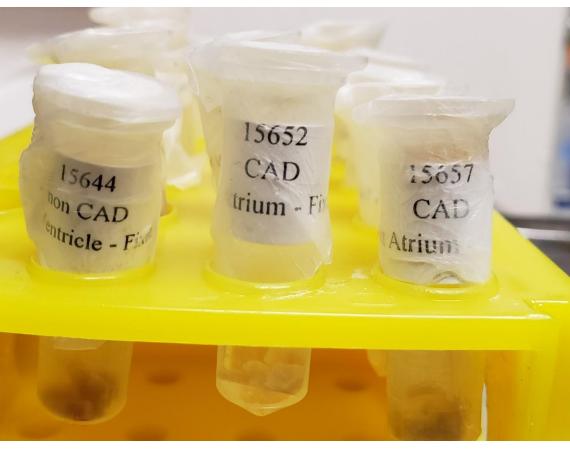


Andreas Bayer (MCW), our Newest Collaborator In the Human Heart Studies with TJ & JHS



# The 'Human heart connection' Donor heart samples from MCW for FIB-SEM and TEM analysis



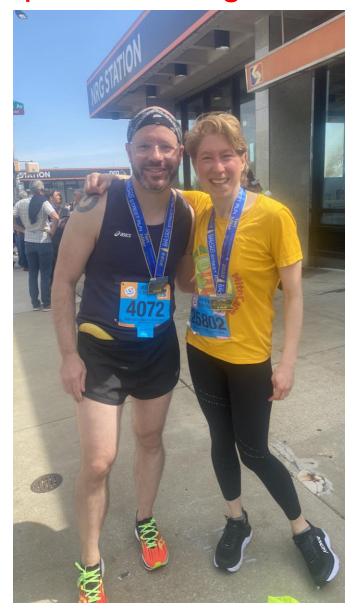




#### **Broad Street 10M:**

Our troopers + George + Masha





#### Combination of Human and Robot Forces in the Tigano Lab





MitoCare kids do not stop growing and being adorable





#### Marco's FIRST NIH Grant!



#### Department of Health and Human Services

National Institutes of Health
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Notice of Award FAIN# R35GM147191 Federal Award Date 06/21/2022

#### **Recipient Information**

1. Recipient Name

THOMAS JEFFERSON UNIVERSITY 1020 WALNUT ST STE 1

PHILADELPHIA, 19107

- 2. Congressional District of Recipient 03
- 3. Payment System Identifier (ID) 1231352651A1
- 4. Employer Identification Number (EIN) 231352651
- 5. Data Universal Numbering System (DUNS) 053284659
- 6. Recipient's Unique Entity Identifier R8JEVL4ULGB7
- 7. Project Director or Principal Investigator Marco Tigano, PHD

mxt422@jefferson.edu 215-503-8558

8. Authorized Official

Burwell, Margaret resadmin@jefferson.edu 215-503-6976

#### Federal Agency Information

9. Awarding Agency Contact Information
Kaui MacDonald Porche
Grants Management Specialist
NATIONAL INSTITUTE OF GENERAL
MEDICAL SCIENCES
kaui.macdonaldporche@nih.gov

#### Federal Award Information

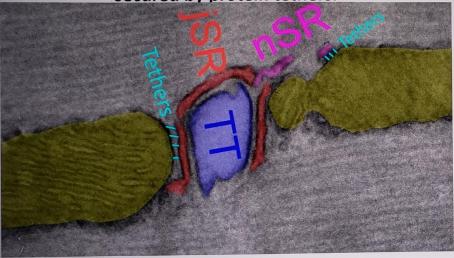
- 11. Award Number 1R35GM147191-01
- 12. Unique Federal Award Identification Number (FAIN) R35GM147191
- 13. Statutory Authority 42 USC 241 42 CFR 52
- 14. Federal Award Project Title
  From mtDNA stress to cellular immunity: Triggers, Mechanisms and Effectors
- 15. Assistance Listing Number 93,859
- 16. Assistance Listing Program Title
  Biomedical Research and Research Training
- 17. Award Action Type
  New Competing
- 18. Is the Award R&D?

Yes

Summary Federal Award Financial Information			
19. Budget Period Start Date 07/01/2022 – End Date 04/30/2023			
20. Total Amount of Federal Funds Obligated by this Action	\$390,000		
20 a. Direct Cost Amount	\$250,000		
20 b. Indirect Cost Amount	\$140,000		
21. Authorized Carryover			
22. Offset			
23. Total Amount of Federal Funds Obligated this budget period	\$390,000		
24. Total Approved Cost Sharing or Matching, where applicable	\$0		
25. Total Federal and Non-Federal Approved this Budget Period	\$390,000		
26. Project Period Start Date 07/01/2022 - End Date 04/30/2027			
27. Total Amount of the Federal Award including Approved Cost	\$390,000		
Sharing or Matching this Project Period			

# End of June GC Flash Talk at the Cardiac Regulatory Mechanisms Gordon Conference (Colby College, NH)

Mitochondria and SR form close contacts, which are secured by protein tethers.



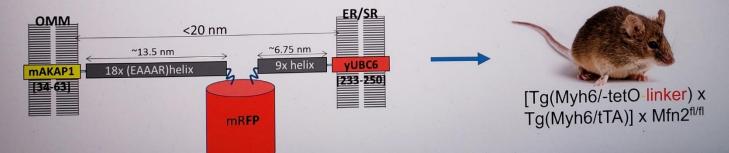
#### GENETICALLY ENGINEERED SR-MITOCHONDRIA LINKER IN THE MOUSE HEART

Zuzana Nichtova, (+10 others), <u>Gyorgy Csordas</u>
Thomas Jefferson University



- Benefit: Excitation-Energetics coupling
   RyR2→Ca<sup>2+</sup>→(MCUc)→matrix dehydrogenases↑→ATP↑
- Risk: mitochondrial Ca<sup>2+</sup> overload, Ca<sup>2+</sup>/ROS vicious cycles, mPTP activation→→myocyte loss
- Dilemma: most endogenous tethers are multifunctional.
   How can one test selectively tethering function?

We developed a dedicated tether transgene expressed under the Myh6 promoter in mouse

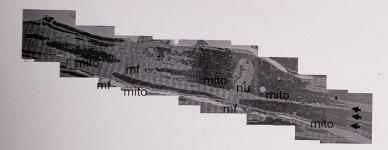


# End of June GC Flash Talk at the Cardiac Regulatory Mechanisms Gordon Conference ] (Colby College, NH)

#### P #22

#### **Outcomes**

 Overt cardiomyocyte remodeling with dense mitochondrial clusters



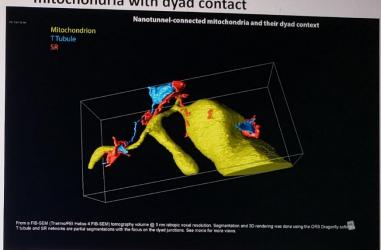
 Dense clusters excluded dyads. There are fewer but individually enhanced mitochondria-dyad contacts.







Increased nanotunnel communication by the mitochondria with dyad contact



- Mice are healthy, active/hyperactive
- · Improved excitation-energetics coupling
- Increased tolerance to acute adrenergic stress
- Milder ex vivo I/R injury
- Thus, the remodeling is adaptive, not maladaptive. Increased nanotunnel communication likely helps to redistribute the individually increased Ca<sup>2+</sup> load.

End of June GC and Marilen at the Cardiac Regulatory Mechanisms Gordon Conference Lobster Dinner (She didn't like the arthropod)



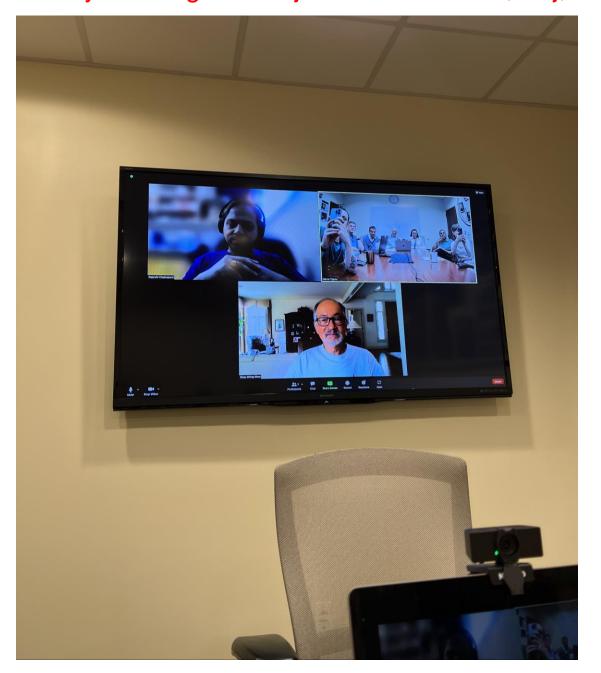
#### End of June Cardiac Regulatory Mechanisms Gordon Conference (Colby College, NH)

A take-home wisdom from Colby College (NH)





First MitoCare Faculty Meeting with Rajarshi Chakrabarti, Raj, our new faculty











## Summer of Scott

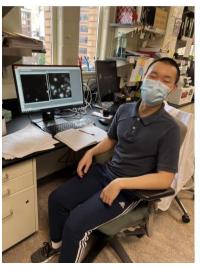




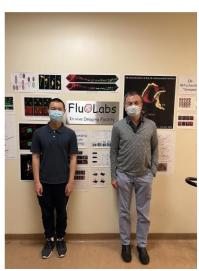




### MitoCare 2022







Scott Gu, a rising Senior

at Abington Sr. High School, showed remarkable work ethic and development in 8 wks



Life before and after the arrival of Raj ..how many differences you can count in the 2 photos



Farewell Sadness for Briyanna

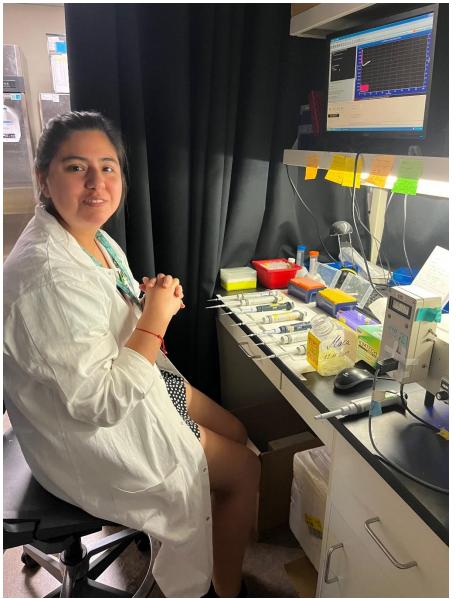






# Marite's preparation for a perfect calcium imaging/PTI day





### Arijita at the 16th International Meeting of the European Calcium Society:

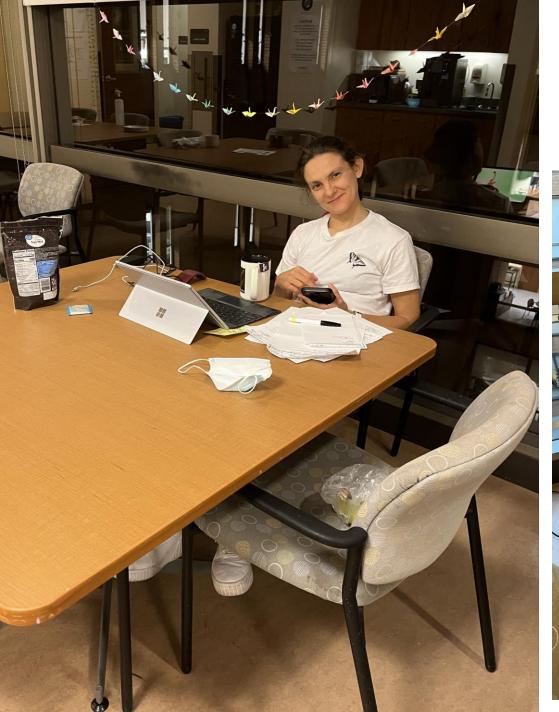
- -selected for oral presentation
- -supported by 2 travel awards





# Jefferson Postdoctoral Symposium 2022:





# Elena's manuscript writing station



## Marco's Jefferson-wide impact

# Invigorate your connection to literature with these Al-driven tools

Academic Commons Training Session

Instructors: Marco Tigano, PhD and Gary Kaplan, MSLIS

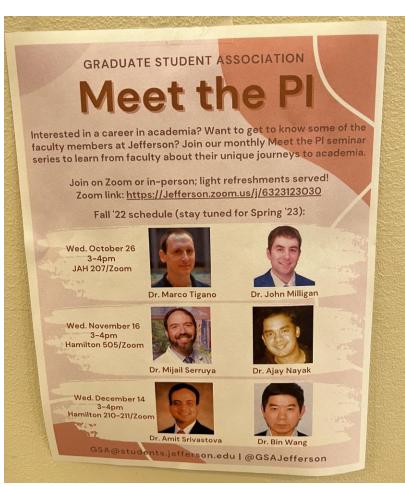
Date: Thursday, September 22, 2022

Time: 12 p.m.-1 p.m.

Location: Hybrid – 200A Scott Memorial Library, Center City Campus or Virtual (a link to the Zoom session will be provided approximately 24-48 hours before the workshop begins).

Educator Domains: Learning Environment Management, Innovation and Professional Vitality

Link to register: http://library.jefferson.edu/tech/workshops/register.cfm?WorkshopID=3963



### Erin continues her success streak with DoD grants

RE: PR220761 - "Inhibiting Mitochondrial Permeability Transition Pore Opening to Treat Mitochondrial Myopathy"

STATUS: RECOMMENDED FOR FUNDING

# New Team Science Award in the area of Cancer Featuring Piyush, Mizue Terai and Phil Wedegartner

Dr. Gyorgy Hajnoczky,

Thank you for your submission of "Development of Novel Therapeutics for Uveal Melanoma" to the Team Award Program of the Melanoma Research Institute of Excellence (MRIE). We are pleased to inform you that your application for an award has been reviewed and will be receiving funding.

Funding will be for up to \$100,000 per year for up to a total of two years. Please be advised that second year funding is contingent on your team showing progress during the first 12 months of the project. Accounts will be created and funds will be dispersed in the near future.

At the end of the two years, the project should have shown significant achievements that would support the application for extramural programmatic funding such as P01 and multi-PI RO1-type grants.

Please be aware of the following tentative submission dates for progress reports:

- 6-Month report; April 1, 2023
- Year 1 Progress Report: October 1, 2023
- Year 2 Progress Report: October 1, 2024

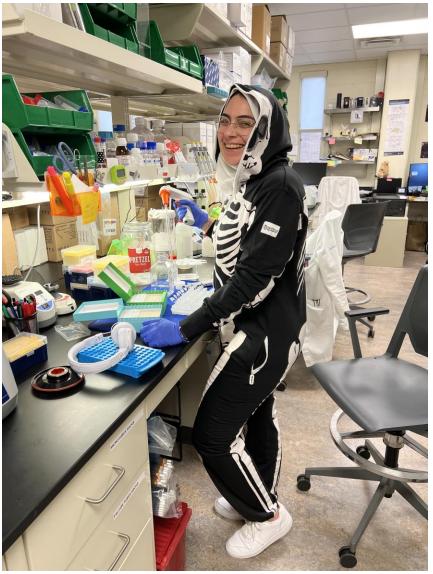
Reminders will be sent out approximately 1 month prior to the due date. **Failure to submit progress reports could result in loss of funding.** 

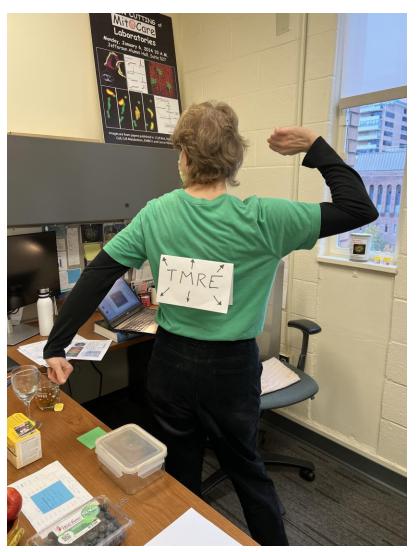
Finally, please ensure to cite the **Melanoma Research Institute of Excellence** as a source of funding in all future presentations or publications relating to your project.

Please direct questions to: Mitch Berkowitz (Program Manager)

# Halloween 2022









### First attempt with a Neuroscience NIH Grant with unexpected success

#### SUMMARY STATEMENT

PROGRAM CONTACT:

( Privileged Communication )

Release Date: Revised Date: 11/29/2022

**Jill Morris** 301-496-5745

morrisja2@mail.nih.gov

Application Number: 1 R01 NS132056-01

**Principal Investigator** 

HAJNOCZKY, GYORGY

Applicant Organization: THOMAS JEFFERSON UNIVERSITY

Review Group: **NOMD** 

**Neural Oxidative Metabolism and Death Study Section** 

Meeting Date: 11/03/2022 RFA/PA: PA20-185 **MORRIJNG** 

Council: **JAN 2023** 

Requested Start: 04/01/2023

Project Title: Mitochondrial Calcium and Neuronal Health

SRG Action: Impact Score:20 Percentile:1

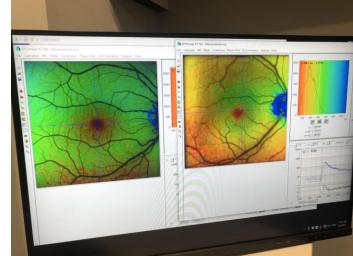
Next Steps: Visit https://grants.nih.gov/grants/next\_steps.htm

Human Subjects: 10-No human subjects involved

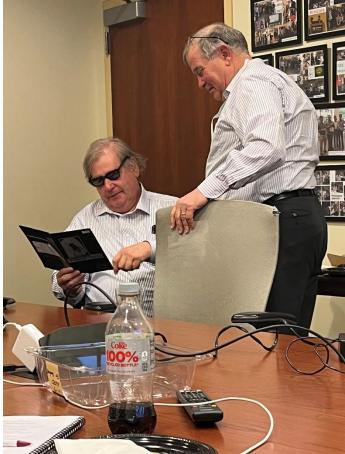
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

Project	Direct Costs	Estimated
Year	Requested	Total Cost
1	479,035	747,295
2	479,035	747,295
3	493,613	770,036
4	493,613	770,036
5	493,613	770,036
TOTAL	2,438,909	3,804,698

NeuroMito presentation to the Gates Foundation with Bob Sergott, President Tykocinski, Thomas Leist, Libba Affel & Molly Gerber













### Seifert Lab 2022







### Seifert Lab News 2022

Goodbye to Cesar, Briyanna and Carmen: we wish everyone all the best in the next steps!!

**Welcome to** Brittney Blackburne, Shannon Lynch and Matt Dina, and Lauren Israel (PhD rotation student)! **Publications** 

### More news on Frataxin: a collaboration with the Csordás lab, and with UPenn

### clinicians that allowed data sets from FRDA patients to be included:

Frataxin deficiency lowers lean mass and triggers the integrated stress response in skeletal muscle

Cesar Vasquez-Trincado<sup>1</sup>, Julia Dunn<sup>2</sup>, Ji In Han<sup>1</sup>, Briyanna Hymms<sup>1</sup>, Jaclyn Tamaroff<sup>2</sup>, Monika Patel<sup>1</sup>, Sara Nguyen<sup>2</sup>,

Anna Dedio<sup>2</sup>, Kristin Wade<sup>2</sup>, Chinazo Enigwe<sup>2</sup>, Zuzana Nichtova<sup>1</sup>, David R. Lynch<sup>3,4</sup>, Gyorgy Csordas<sup>1</sup>, Shana E.

McCormack<sup>2,5</sup>, Erin L. Seifert<sup>1\*</sup>. JCI Insight PMID 35531957

#### Co-author publications:

Dylgieri et al Clin Cancer Res PMID 35078861 (Knudsen group)

Han et al Oncogene PMID 35046531 (Aplin group)

Zhi et al J Vis Exp PMID 35758711 (Zhang group)

Monteith et al Infect Immun PMID 34871043 (Skaar group, Vanderbilt)

#### **Grants**

Awarded a Department of Defense Discovery Award!

Submitted: 2 R01s, to NIGMS (with Gyuri C as Co-I) and MPI NIGMS (with Nate Snyder at Temple), an MPI R21 (with Janice Walker), and a CURE grant MitoCare effort (with Gyuri H, Gyuri C, Marco and Raj)

### Meetings: Acot2 and Frataxin projects on the road (and the zoom)

FASEB Molecular Metabolism, Oak Island, Nova Scotia, Canada Aug 7-11

Mitochondria 2022, Ein Gedi, Israel, Nov 13-16

Invited talks at West Virginia University (host Roberta Leonardi), ECU (host Darrell Neufer), FARA (host Liz Soragni)

# Carmen's farewell











# Cupcake Collection 2022





# Cupcake Collection 2022







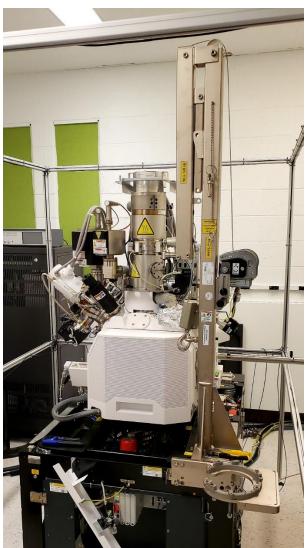
# **Cupcake Collection 2022**

Someone gets a Poppyseed Muffin Cupcake with melted candle in the middle



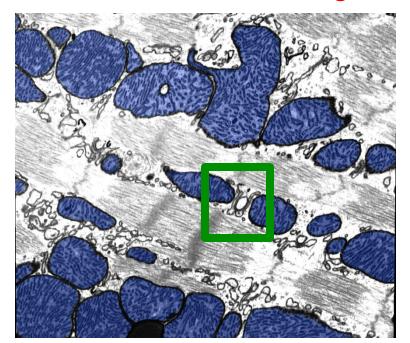


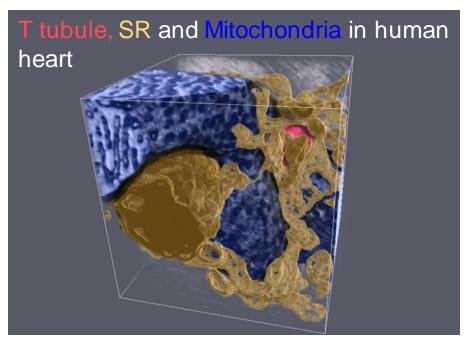


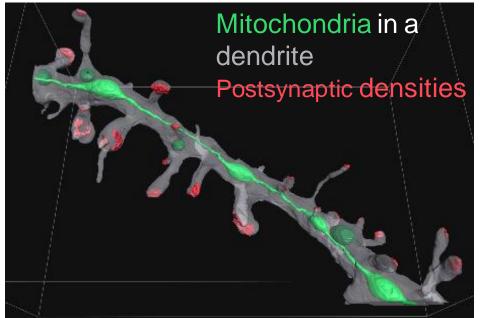


FIB-SEM had a bad year in terms of downtimes. At least, we could get some literal insights, what's under the hood....

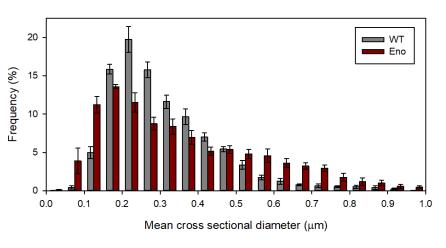
### Still the flow of astonishing structures and quantification has started







### Dendrite mito transverse sections



And the Data Science Infrastructure for FIB-SEM analysis has been established under Dave's lead

Our Team: Diverse Backgrounds and Expertise

### **MitoCare Director**

Gyorgy Hajnoczky

### **Analysis Team**

David Weaver – MitoCare Bioinformatician (Director of Technology Development 2014-2022)

### **Operational Arm**

Prahlad Menon – Jefferson Data Science

Engineer

Aron Andresi – MitoCare Data Scientist

(starting 2023)

### **Experimental Arm**

Vijay Rajagopal – Univ. of Melbourne,

Biomedical Engineering

U. Melbourne Ph.D. student, starting

sometime in 2023?

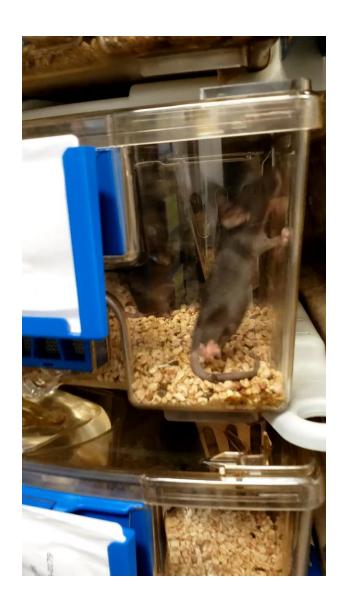
### **FIB-SEM Operations Team**

Gyorgy Csordas, PI and Director of Electron Microscopy

Prashant Badjugar, FIB-SEM operator

Biologists: Pls, Post-Docs, Grad Students

Linker mouse agility and tail-strength demo



### Enhanced mitochondria-SR tethering triggers adaptive cardiac muscle remodeling.

Zuzana Nichtová PhD¹, Celia Fernandez-Sanz PhD², Sergio De La Fuente PhD², Yuexing Yuan PhD², Stephen Hurst PhD¹, Sebastian Lanvermann PhD², Hui-Ying Tsai MS², David Weaver MS¹, Ariele Baggett MS¹, Christopher Thompson³, Cedric Bouchet-Marquis PhD³, Péter Várnai MD,PhD⁴, Erin L Seifert PhD¹, Gerald W Dorn II MD⁵, Shey-Shing Sheu PhD², György Csordás MD¹



Revision submitted to Circulation Research



### Publications of the year from the Hajnoczky lab

Katona M, Bartók Á, Nichtova Z, Csordás G, Berezhnaya E, Weaver D, Ghosh A, Várnai P, Yule DI, Hajnóczky G. Capture at the ER-mitochondrial contacts licenses IP3 receptors to stimulate local Ca2+ transfer and oxidative metabolism. **Nat Commun**. 2022 Nov 9;13(1):6779. PMID: 36351901; PMCID: PMC9646835.

Paillard M, Huang KT, Weaver D, Lambert JP, Elrod JW, Hajnóczky G. Altered composition of the mitochondrial Ca2+ uniporter in the failing human heart. **Cell Calcium**. 2022 Jul;105:102618. doi:10.1016/j.ceca.2022.102618. PMID: 35779476.

Singh R, Bartok A, Paillard M, Tyburski A, Elliott M, Hajnóczky G. Uncontrolled mitochondrial calcium uptake underlies the pathogenesis of neurodegeneration in MICU1-deficient mice and patients. **Sci Adv**. 2022 Mar 18;8(11):eabj4716. PMID: 35302860; PMCID: PMC8932652.

Çoku J, Booth DM, Skoda J, Pedrotty MC, Vogel J, Liu K, Vu A, Carpenter EL, Ye JC, Chen MA, Dunbar P, Scadden E, Yun TD, Nakamaru-Ogiso E, Area-Gomez E, Li Y, Goldsmith KC, Reynolds CP, Hajnoczky G, Hogarty MD. Reduced ER-mitochondria connectivity promotes neuroblastoma multidrug resistance. **EMBO J**. 2022 Apr 19;41(8):e108272. PMID: 35211994; PMCID: PMC9016347.

Márta K, Booth D, Csordás G, Hajnóczky G. Fluorescent protein transgenic mice for the study of Ca2+ and redox signaling. **Free Radic Biol Med**. 2022 Mar;181:241-250. PMID: 35158029; PMCID: PMC8988923.

Booth DM, Várnai P, Joseph SK, Hajnóczky G. Fluorescence imaging detection of nanodomain redox signaling events at organellar contacts. **STAR Protoc**. 2022 Jan 20;3(1):101119. PMID: 35098166; PMCID: PMC8783204.

Cartes-Saavedra B, Macuada J, Lagos D, Arancibia D, Andrés ME, Yu-Wai-Man P, Hajnóczky G, Eisner V. OPA1 Modulates Mitochondrial Ca2+ Uptake Through ER-Mitochondria Coupling. **Front Cell Dev Biol**. 2022 Jan 3;9:774108. PMID: 35047497; PMCID: PMC8762365.

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## Holiday Party 2022 with Trivia and Ugly Sweater competition





# The Ugly Sweater Competitors



The 2022 Trivia Champions with the Golden Pipette and Dave and Bradley, the Masters of the Ceremony



