MitoCare 2025

Starting the year with publishing some collaborative projects

PNAS RESEARCH ARTICLE | MICROBIOLOGY

Co-option of mitochondrial nucleic acid–sensing pathways by HSV-1 UL12.5 for reactivation from latent infection

Patryk A. Krakowiak[a,1], Matthew E. Flores[a,1], Sean R. Cuddy[a,b,1], Abigail E. Whitford[a], Sara A. Dochnal[a,c], Aleksandra Babnis[a], Tsuyoshi Miyake[a], Marco Tigano[a], Daniel A. Engel[a], and Anna R. Cliffe[a,2]

Affiliations are included on p. 10

Edited by Thomas Shenk, Princeton University, Princeton, NJ; received July 16, 2024; accepted December 5, 2024

Although viruses subvert innate immune pathways for their replication, there is evidence they can also co-opt antiviral responses for their benefit. The ubiquitous human pathogen, Herpes simplex virus-1 (HSV-1), encodes a protein (UL12.5) that induces the release of mitochondrial nucleic acid into the cytosol, which activates immune-sensing pathways and reduces productive replication in nonneuronal cells. HSV-1 establishes latency in neurons and can reactivate to cause disease. We found that UL12.5 is required for HSV-1 reactivation in neurons and acts to directly promote viral lytic gene expression during initial exit from latency. Further, the direct activation of innate immune-sensing pathways triggered HSV-1 reactivation and compensated for a lack of UL12.5. Finally, we found that the induction of HSV-1 lytic genes during reactivation required intact RNA- and DNA-sensing pathways, demonstrating that HSV-1 can respond to and active antiviral nucleic acid–sensing pathways to reactivate from a latent infection.

herpes simplex virus | reactivation | UL12.5 | mitochondrial DNA | STING

Significance

Herpes simplex virus-1 (HSV-1) persists as a latent infection of neurons and reactivates to cause disease. Understanding host pathways required for reactivation is crucial to developing therapeutics. The HSV-1 protein, UL12.5, activates antiviral pathways, but its function in the viral infection was unknown. We found that UL12.5

CellPress Cell

Resource

Engineering mtDNA deletions by reconstituting end joining in human mitochondria

Yi Fu,[1,7,9] Max Land,[2,8,9] Tamar Kavlashvili,[1,9] Ruobing Cui,[3] Minsoo Kim,[4] Emily DeBitetto,[1] Toby Lieber,[1] Keun Woo Ryu,[3] Elim Choi,[1] Ignas Masilionis,[2] Rahul Saha,[6] Meril Takizawa,[2] Daphne Baker,[3] Marco Tigano,[5] Caleb A. Lareau,[2] Ed Reznik,[6] Roshan Sharma,[2] Ronan Chaligne,[2] Craig B. Thompson,[3] Dana Pe'er,[2,8] and Agnel Sfeir[1,10,*]

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https://doi.org/10.1016/j.cell.2025.02.009

SUMMARY

Recent breakthroughs in the genetic manipulation of mitochondrial DNA (mtDNA) have enabled precise base substitutions and the efficient elimination of genomes carrying pathogenic mutations. However, reconstituting mtDNA deletions linked to mitochondrial myopathies remains challenging. Here, we engineered mtDNA deletions in human cells by co-expressing end-joining (EJ) machinery and targeted endonucleases. Using mitochondrial EJ (mito-EJ) and mito-ScaI, we generated a panel of clonal cell lines harboring a ~3.5 kb mtDNA deletion across the full spectrum of heteroplasmy. Investigating these cells revealed a critical threshold of ~75% deleted genomes, beyond which oxidative phosphorylation (OXPHOS) protein depletion, metabolic disruption, and impaired growth in galactose-containing media were observed. Single-cell multiomic profiling identified two distinct nuclear gene deregulation responses: one triggered at the deletion threshold and another progressively responding to heteroplasmy. Ultimately, we show that our method enables the modeling of disease-associated mtDNA deletions across cell types and could inform the development of targeted therapies.

Original article

MOLECULAR METABOLISM

Mammalian mitochondrial inorganic polyphosphate (polyP) and cell signaling: Crosstalk between polyP and the activity of AMPK

Renata T. Da Costa[1], Anna Nichenko[2], Matheus M. Perez[1], Malgorzata Tokarska-Schlattner[3], Sheida Kavehmoghaddam[1], Vedangi Hambardikar[1], Ernest R. Scoma[1], Erin L. Seifert[1], Uwe Schlattner[3], Joshua C. Drake[2], Maria E. Solesio[1,*]

ABSTRACT

Inorganic polyphosphate (polyP) is an evolutionary and ancient polymer composed by orthophosphate units linked by phosphoanhydride bonds. In mammalian cells, polyP shows a high localization in mammalian mitochondria, and its regulatory role in various aspects of bioenergetics has already been demonstrated, via molecular mechanism(s) yet to be fully elucidated. In recent years, a role for polyP in signal transduction, from brain physiology to the bloodstream, has also emerged.

Objective: In this manuscript, we explored the intriguing possibility that the effects of polyP on signal transduction could be mechanistically linked to those exerted on bioenergetics.

Methods: To conduct our studies, we used a combination of cellular and animal models.

Results: Our findings demonstrate for the first time the intimate crosstalk between the levels of polyP and the activation status of the AMPK signaling pathway, via a mechanism involving free phosphate homeostasis. AMPK is a key player in mammalian cell signaling, and a crucial regulator of cellular and mitochondrial homeostasis. Our results show that the depletion of mitochondrial polyP in mammalian cells downregulates the activity of AMPK. Moreover, increased levels of polyP activate AMPK. Accordingly, the genetic downregulation of AMPKF0611 impairs polyP levels in both SH-SY5Y cells and in the brains of female mice.

Conclusions: This manuscript sheds new light on the regulation of AMPK and positions polyP as a potent regulator of mammalian cell physiology beyond mere bioenergetics, paving the road for using its metabolism as an innovative pharmacological target in pathologies characterized by dysregulated bioenergetics.

Received: 22 July 2024 | Revised: 24 September 2024 | Accepted: 21 October 2024
DOI: 10.1002/alz.14417

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Stabilization of mitochondria-associated endoplasmic reticulum membranes regulates Aβ generation in a three-dimensional neural model of Alzheimer's disease

Jacob C. Zellmer[1] | Marina B. Tarantino[1] | Michelle Kim[1] | Selene Lomoio[2] | Masato Maesako[3] | György Hajnóczky[4] | Raja Bhattacharyya[1]

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Correspondence
Raja Bhattacharyya, Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Henry and Allison McCance Center for Brain Health, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Room 3850, 16th Street, Charlestown, MA 02129, USA

Abstract

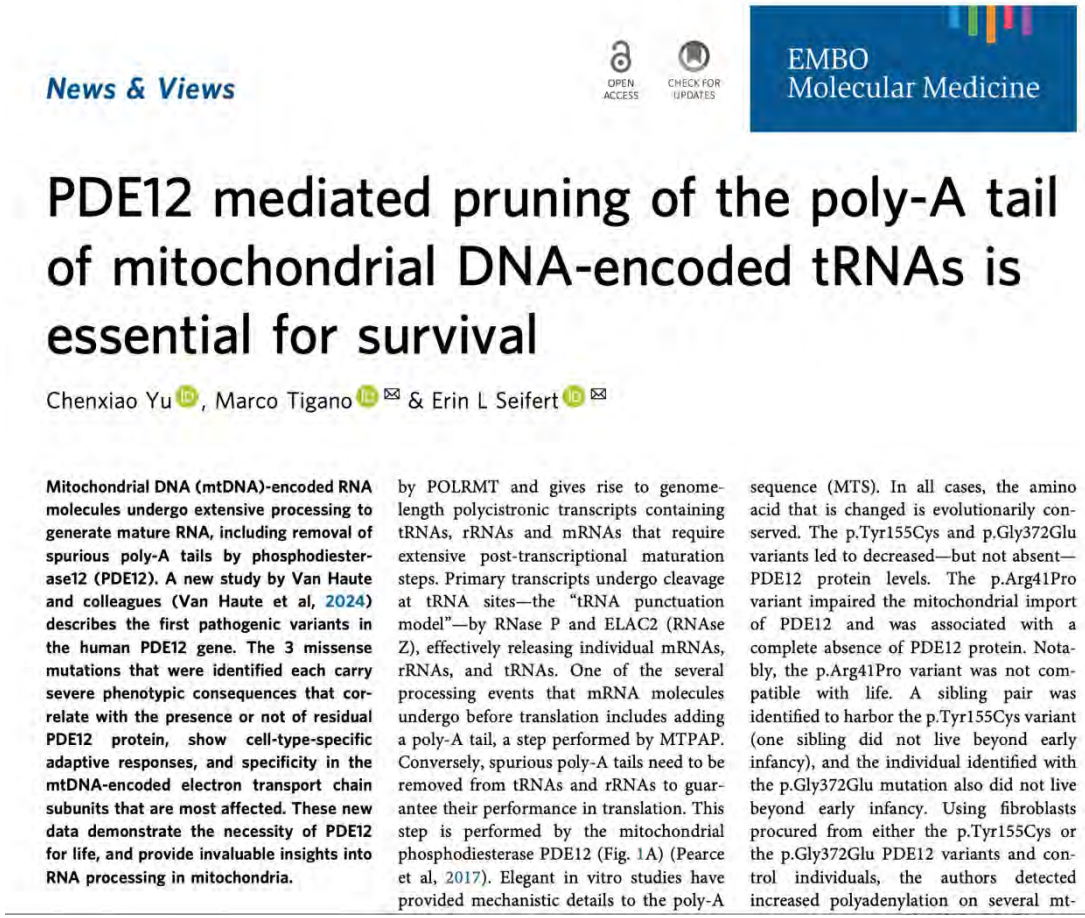
INTRODUCTION: We previously demonstrated that regulating mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs) affects axonal Aβ generation in a well-characterized three-dimensional (3D) neural Alzheimer's disease (AD) model. MAMs vary in thickness and length, impacting their functions. Here, we examined the effect of MAM thickness on Aβ in our 3D neural model of AD.

METHODS: We employed fluorescence resonance energy transfer (FRET) or fluorescence-based MAM stabilizers, electron microscopy, Aβ enzyme-linked immunosorbent assay (ELISA), and live-cell imaging with kymography to assess how stabilizing MAMs of different gap widths influence Aβ production and MAM axonal mobility.

RESULTS: Stabilizing tight MAMs (~6 nm gap width) significantly increased Aβ levels, whereas basal (~25 nm) and loose MAMs (~40 nm) maintained or reduced Aβ levels, respectively. Tight MAMs reduced mitochondrial axonal velocity compared to basal MAMs, while loose MAMs showed severely reduced axonal distribution.

DISCUSSION: Our findings suggest that stabilizing MAMs of specific gap widths, particularly in axons, without complete destabilization could be an effective therapeutic strategy for AD.

and expressing an opinion…



News & Views

OPEN ACCESS CHECK FOR UPDATES

EMBO Molecular Medicine

PDE12 mediated pruning of the poly-A tail of mitochondrial DNA-encoded tRNAs is essential for survival

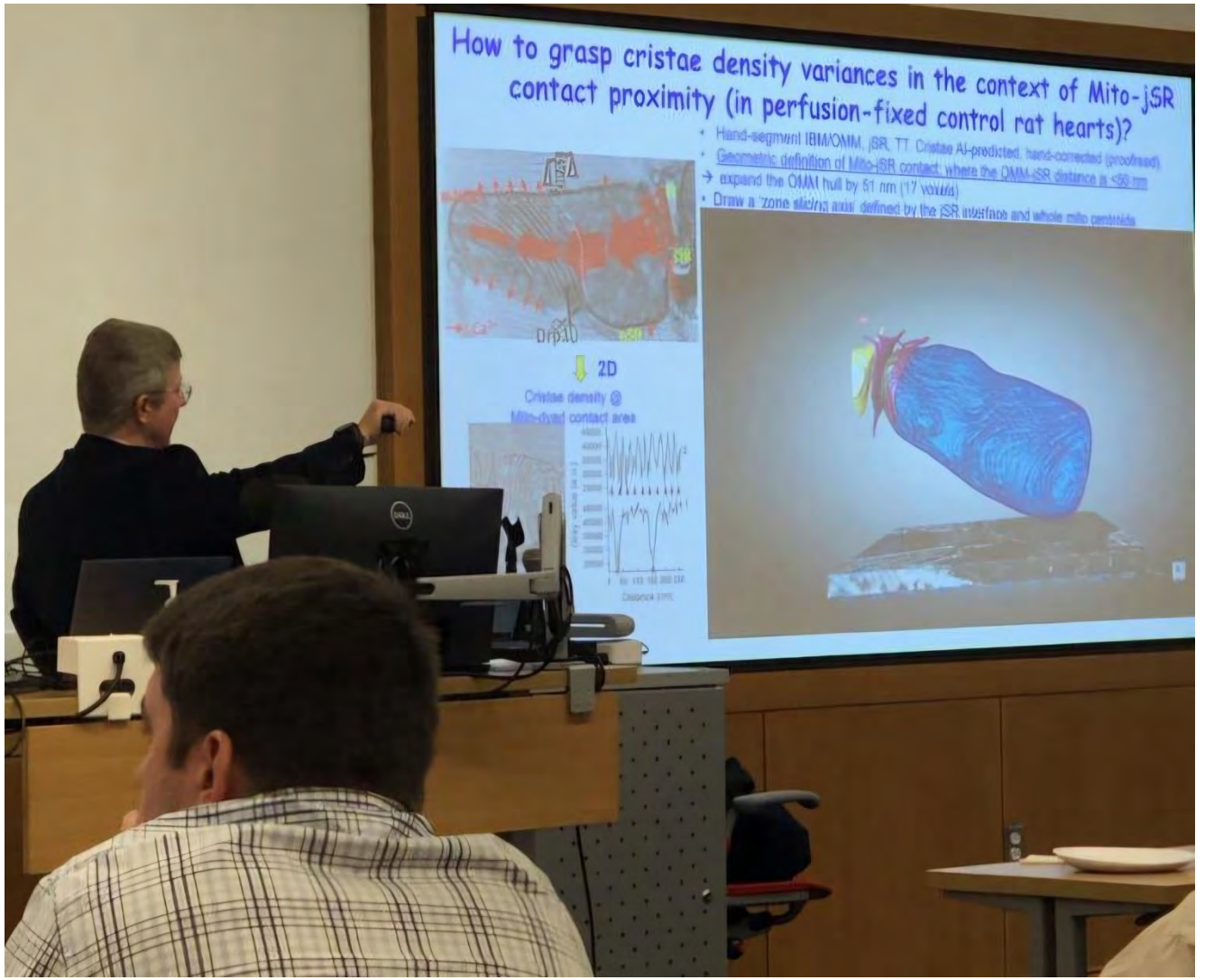
Chenxiao Yu, Marco Tigano ✉ & Erin L Seifert ✉

Mitochondrial DNA (mtDNA)-encoded RNA molecules undergo extensive processing to generate mature RNA, including removal of spurious poly-A tails by phosphodiesterase12 (PDE12). A new study by Van Haute and colleagues (Van Haute et al, 2024) describes the first pathogenic variants in the human PDE12 gene. The 3 missense mutations that were identified each carry severe phenotypic consequences that correlate with the presence or not of residual PDE12 protein, show cell-type-specific adaptive responses, and specificity in the mtDNA-encoded electron transport chain subunits that are most affected. These new data demonstrate the necessity of PDE12 for life, and provide invaluable insights into RNA processing in mitochondria.

by POLRMT and gives rise to genome-length polycistronic transcripts containing tRNAs, rRNAs and mRNAs that require extensive post-transcriptional maturation steps. Primary transcripts undergo cleavage at tRNA sites—the "tRNA punctuation model"—by RNase P and ELAC2 (RNAse Z), effectively releasing individual mRNAs, rRNAs, and tRNAs. One of the several processing events that mRNA molecules undergo before translation includes adding a poly-A tail, a step performed by MTPAP. Conversely, spurious poly-A tails need to be removed from tRNAs and rRNAs to guarantee their performance in translation. This step is performed by the mitochondrial phosphodiesterase PDE12 (Fig. 1A) (Pearce et al, 2017). Elegant in vitro studies have provided mechanistic details to the poly-A sequence (MTS). In all cases, the amino acid that is changed is evolutionarily conserved. The p.Tyr155Cys and p.Gly372Glu variants led to decreased—but not absent—PDE12 protein levels. The p.Arg41Pro variant impaired the mitochondrial import of PDE12 and was associated with a complete absence of PDE12 protein. Notably, the p.Arg41Pro variant was not compatible with life. A sibling pair was identified to harbor the p.Tyr155Cys variant (one sibling did not live beyond early infancy), and the individual identified with the p.Gly372Glu mutation also did not live beyond early infancy. Using fibroblasts procured from either the p.Tyr155Cys or the p.Gly372Glu PDE12 variants and control individuals, the authors detected increased polyadenylation on several mt-

THE only new MC Baby Boy in 2025: Anagh Singh and His proud Father Raghavendra

Gyuri C gives a seminar at Ohio State University with an emphasis on organellar 3D structure in the heart



MitoCare is Present at the March for Science in Philadelphia, 2025

A project that spanned
Generations
…
to identify an
Achilles heel
of liver cancer

nature communications

Article

https://doi.org/10.1038/s41467-025-56898-4

VDAC2 and Bak scarcity in liver mitochondria enables targeting hepatocarcinoma while sparing hepatocytes

Received: 12 November 2023

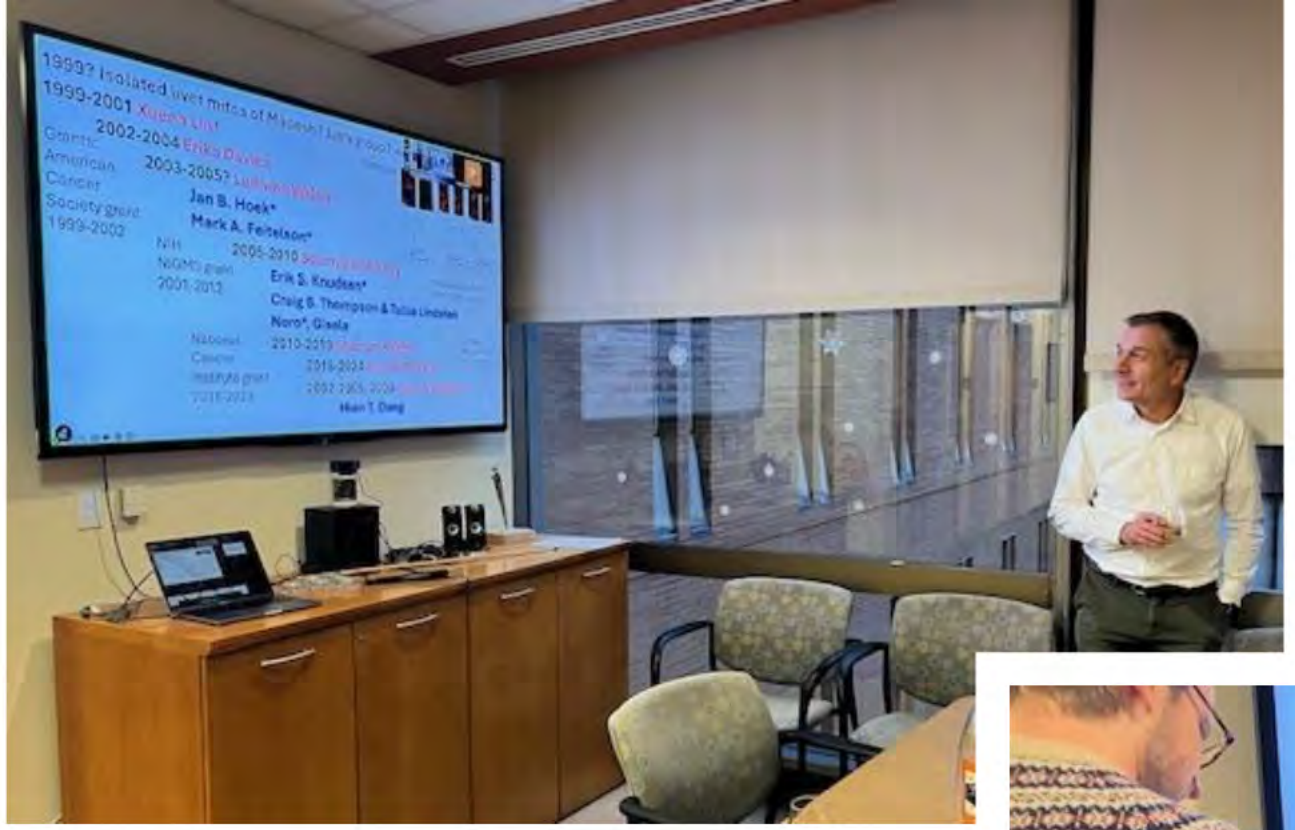
Accepted: 5 February 2025

Published online: 11 March 2025

Check for updates

Shamim Naghdi[1,6], Piyush Mishra[1,6], Soumya Sinha Roy[1,6], David Weaver[1,6], Ludivine Walter[1], Erika Davies[1], Anil Noronha Antony[1], Xuena Lin[1], Gisela Moehren[1], Mark A. Feitelson[1], Christopher A. Reed[2], Tullia Lindsten[3,5], Craig B. Thompson[3,5], Hien T. Dang[4], Jan B. Hoek[1], Erik S. Knudsen[2] & György Hajnóczky[1]

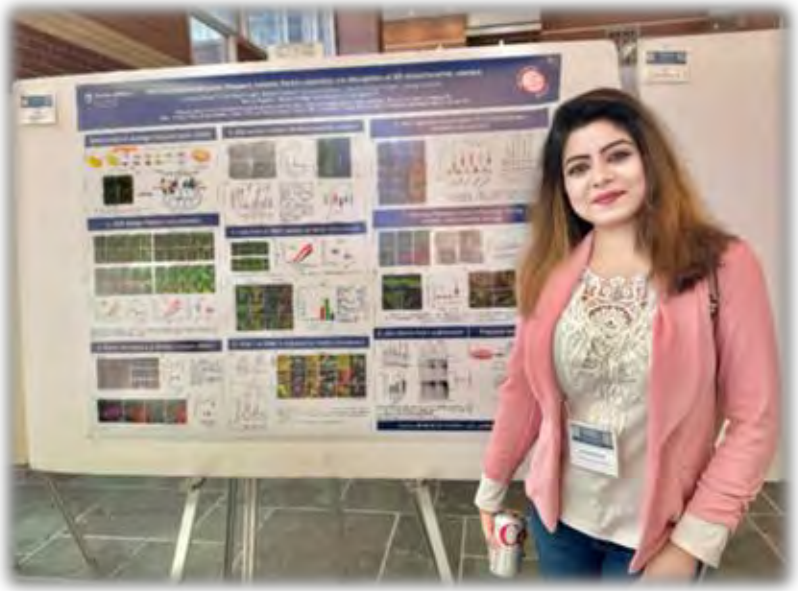
Differences between normal tissues and invading tumors that allow tumor targeting while saving normal tissue are much sought after. Here we show that scarcity of VDAC2, and the consequent lack of Bak recruitment to mitochondria, renders hepatocyte mitochondria resistant to permeabilization by truncated Bid (tBid), a Bcl-2 Homology 3 (BH3)-only, Bcl-2 family protein. Increased VDAC2 and Bak is found in most human liver cancers and mitochondria from tumors and hepatic cancer cell lines exhibit VDAC2- and Bak-dependent tBid sensitivity. Exploring potential therapeutic targeting, we find that combinations of activators of the tBid pathway with inhibitors of the Bcl-2 family proteins that suppress Bak activation enhance VDAC2-dependent death of hepatocarcinoma cells with little effect on normal hepatocytes. Furthermore, in vivo, combination of S63845, a selective Mcl-1 inhibitor, with tumor-nectrosis factor-related, apoptosis-inducing ligand (TRAIL) peptide reduces tumor growth, but only in tumors expressing VDAC2. Thus, we describe mitochondrial molecular fingerprint that discriminates liver from hepatocarcinoma and allows sparing normal tissue while targeting tumors.

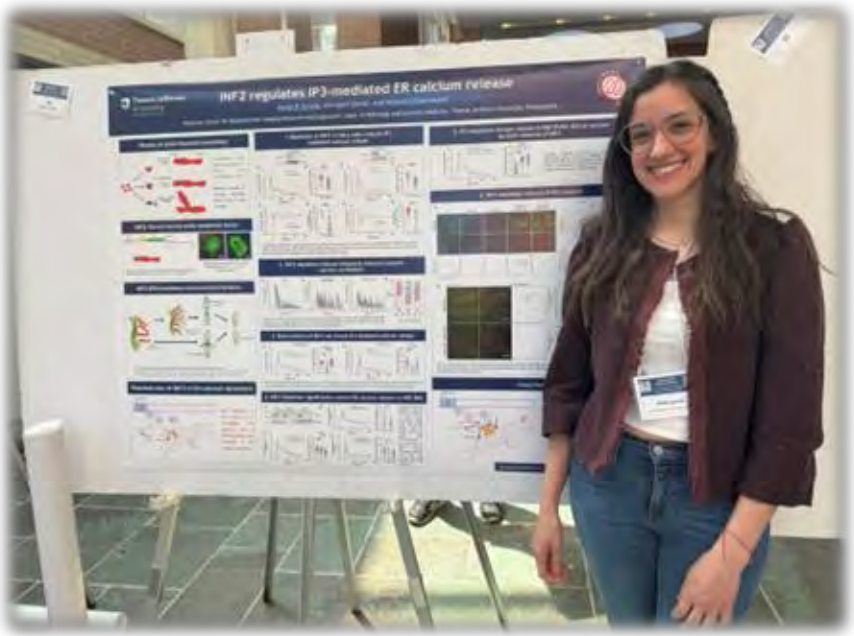


Celebration with the Fellows who contributed at the beginning and finishing

Erika and Adrian Davies on the zoom

Chakrabarti Lab (Amy and Maite) representing MitoCare at the PMI symposium UPENN, March 2025





nature reviews molecular cell biology
https://doi.org/10.1038/s41580-024-00820-1

Review article

Check for updates

The roles of mitochondria in global and local intracellular calcium signalling

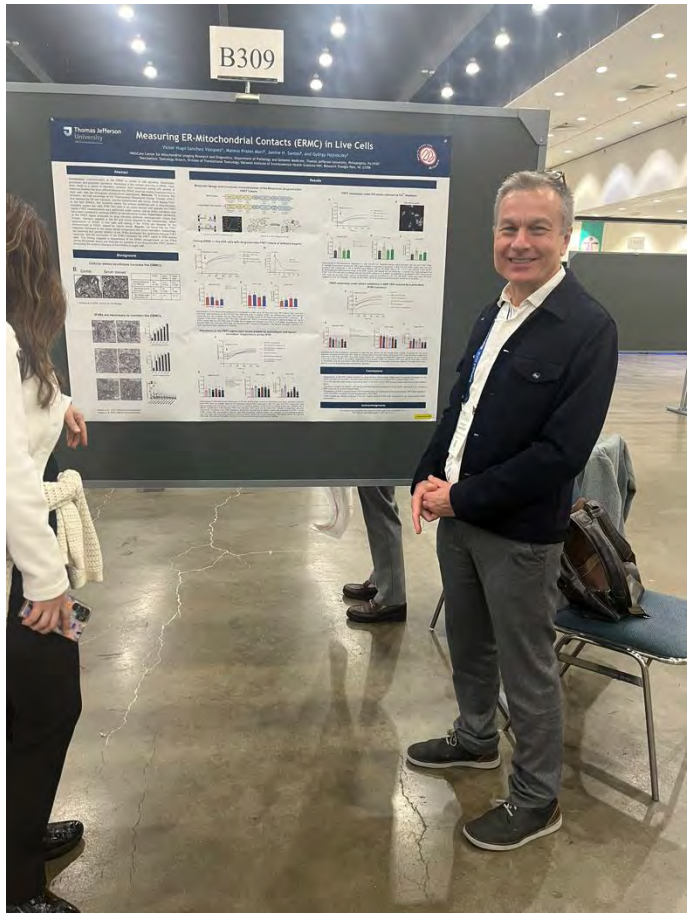
Benjamín Cartes-Saavedra [1,2], Arijita Ghosh [1,2] & György Hajnóczky [1]

Abstract

Activation of Ca^{2+} channels in Ca^{2+} stores in organelles and the plasma membrane generates cytoplasmic calcium ($[Ca^{2+}]_c$) signals that control almost every aspect of cell function, including metabolism, vesicle fusion and contraction. Mitochondria have a high capacity for Ca^{2+} uptake and chelation, alongside efficient Ca^{2+} release mechanisms. Still, mitochondria do not store Ca^{2+} in a prolonged manner under physiological conditions and lack the capacity to generate global $[Ca^{2+}]_c$ signals. However, mitochondria take up Ca^{2+} at high local $[Ca^{2+}]_c$ signals that originate from neighbouring organelles, and also during sustained global elevations of $[Ca^{2+}]_c$. Accumulated Ca^{2+} in the mitochondria stimulates oxidative metabolism and upon return to the cytoplasm, can produce spatially confined rises in $[Ca^{2+}]_c$ to exert control over processes that are sensitive to Ca^{2+}. Thus, the mitochondrial handling of $[Ca^{2+}]_c$ is of physiological relevance. Furthermore, dysregulation of mitochondrial Ca^{2+} handling can contribute to debilitating diseases. We discuss the mechanisms and relevance of mitochondria in local and global calcium signals.

Sections

Erin takes over as Chair of the Bioenergetics Subgroup at the 2025 Biophysical Society Meeting



Presentation of Victor's work at the meeting

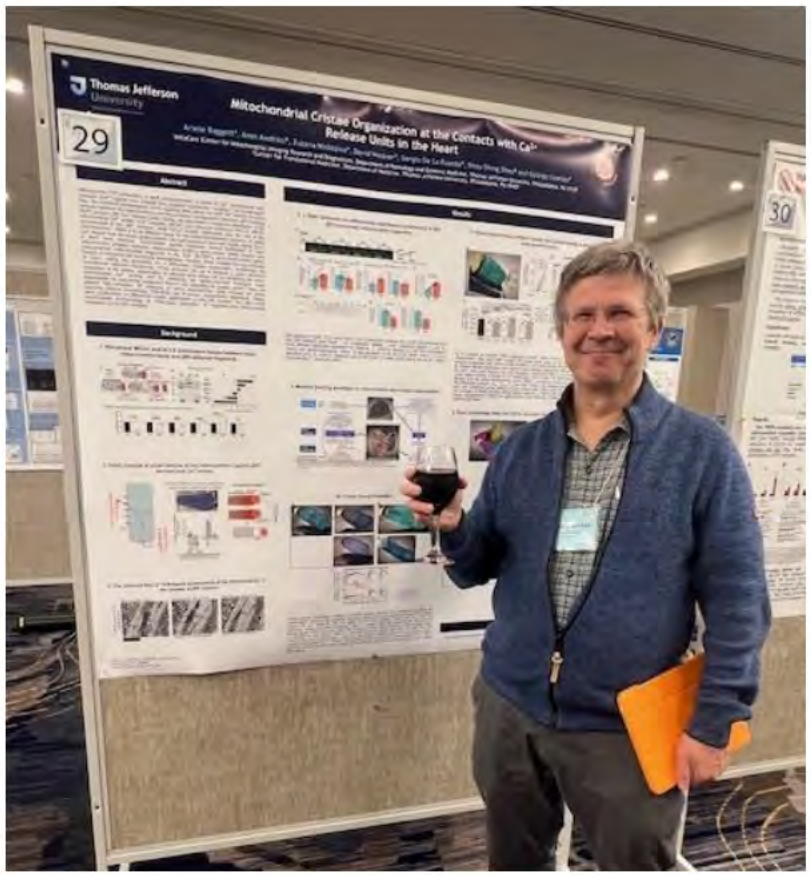
Chenxiao is one of the first MitoTrain test runs.

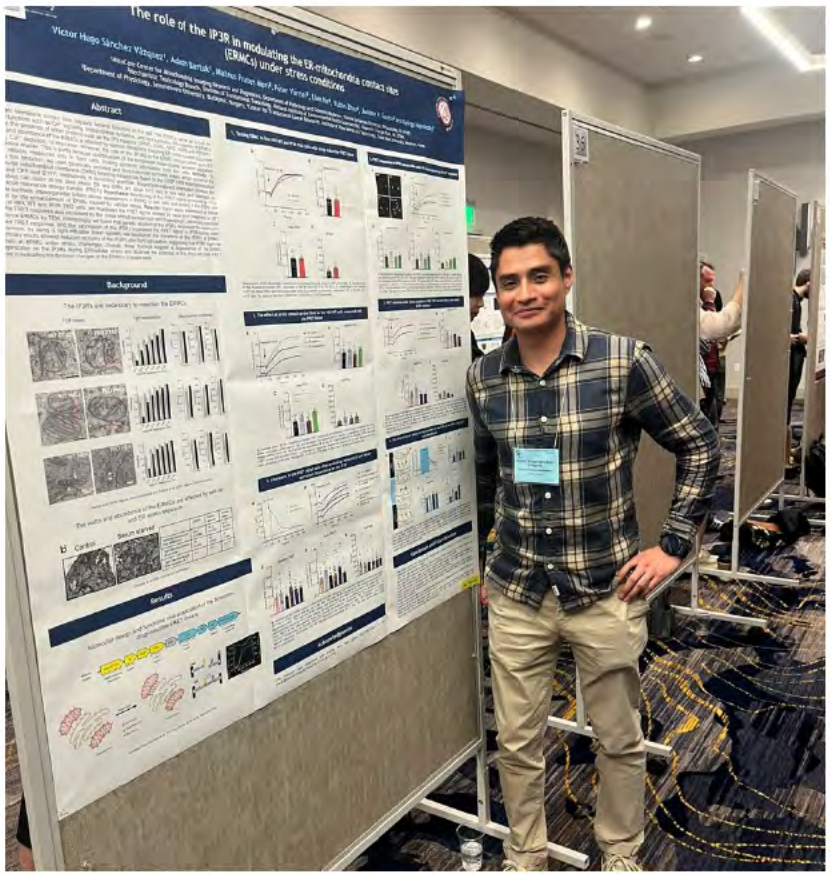
mitoTrain

He seems very excited about it.

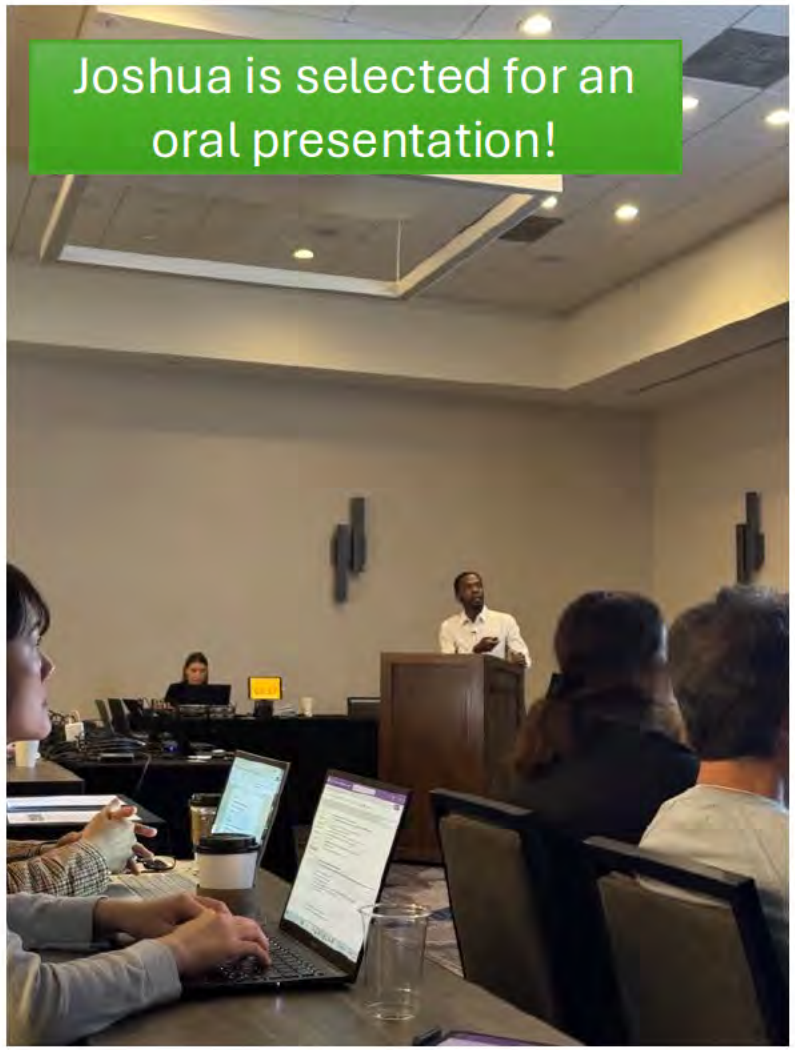
The First Ever MitoTrain Meeting with Joshua's practice presentation for the GRC on Mitochondrial Biology

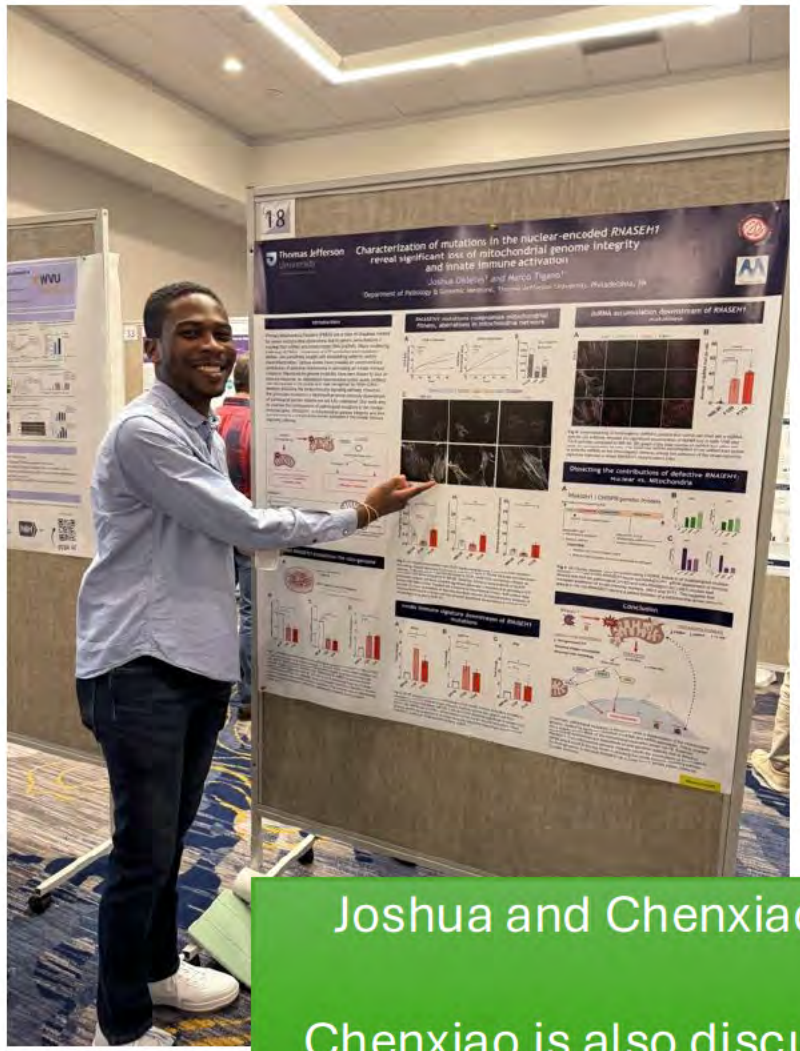
GRC on Mitochondrial Biology #3 - Ventura - March 2025





Tigano Lab's goes to Ventura in March 2025 at the Gordon Research Conference on Mitochondria.





Joshua and Chenxiao present posters.

Chenxiao is also discussion leader at the GRS.

The entire MitoCare Crew of the GRC

Our Parents Poster Award presentation

Accepting the Margaret Reed Lewis Award

Gyuri H Officially Accepts the “Mitolisa”. Dr. Scorrano (in the back) is still holding the prized possession hostage. Ventura, March 2025

Victor and Benjamin are co-leads
of a study
describing an unexpected player
in mitochondrial Calcium,
originally identified by Ryan Cupo,
our new faculty

nature communications

Article

https://doi.org/10.1038/s41467-025-57641-9

Dependence of mitochondrial calcium signalling and dynamics on the disaggregase, CLPB

Received: 15 May 2024

Accepted: 25 February 2025

Published online: 21 March 2025

Check for updates

Donato D'Angelo[1,14], Víctor H. Sánchez-Vázquez[2,14], Benjamín Cartes-Saavedra[2,14], Denis Vecellio Reane[3], Ryan R. Cupo[4,5], Hilda Delgado de la Herran[3], Giorgia Ghirardo[1], James Shorter[4,5,6], Ron A. Wevers[7], Saskia B. Wortmann[8,9], Fabiana Perocchi[3,10,11], Rosario Rizzuto[1,12] ✉, Anna Raffaello[1,13] ✉ & György Hajnóczky[2] ✉

Cells utilize protein disaggregases to avoid abnormal protein aggregation that causes many diseases. Among these, caseinolytic peptidase B protein homolog (CLPB) is localized in the mitochondrial intermembrane space and linked to human disease. Upon CLPB loss, MICU1 and MICU2, regulators of the mitochondrial calcium uniporter complex (mtCU), and OPA1, a main mediator of mitochondrial fusion, become insoluble but the functional outcome remains unclear. In this work we demonstrate that CLPB is required to maintain mitochondrial calcium signalling and fusion dynamics. CLPB loss results in altered mtCU composition, interfering with mitochondrial calcium uptake independently of cytosolic calcium and mitochondrial membrane potential. Additionally, OPA1 decreases, and aggregation occurs, accompanied by mitochondrial fragmentation. Disease-associated mutations in the *CLPB* gene present in skin fibroblasts from patients also display mitochondrial calcium and structural changes. Thus, mtCU and fusion activity are dependent on CLPB, and their impairments might contribute to the disease caused by CLPB variants.

Julius Rönkkö joins and brings iPSC work expertise to MitoCare

Aron leaves MitoCare and returns to Europe

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 07 March 2025
DOI 10.3389/fneur.2025.1493876

The long-waited investiture of Bob Sergott as the Margaret and Richard Hayne Distinguished Professor of Ophthalmology

And the first FLIO publication:

Future applications of fluorescence lifetime imaging ophthalmoscopy in neuro-ophthalmology, neurology, and neurodegenerative conditions

Daniel M. Markowitz[1,2], Elizabeth Affel[2], György Hajnóczky[3] and Robert C. Sergott[2]*

[1]Drexel University College of Medicine, Philadelphia, PA, United States, [2]William H. Annesley, EyeBrain Center, Vicky and Jack Farber Neuroscience Institute, Thomas Jefferson University, Partnered with Wills Eye Hospital, Philadelphia, PA, United States, [3]MitoCare Center, Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, United States

Fluorescence lifetime imaging ophthalmoscopy (FLIO) has emerged as an innovative advancement in retinal imaging, with the potential to provide *in vivo* non-invasive insights into the mitochondrial metabolism of the retina. Traditional retinal imaging, such as optical coherence tomography (OCT) and fundus autofluorescence (FAF) intensity imaging, focus solely on structural changes to the retina. In contrast, FLIO provides data that may reflect retinal fluorophore activity, some of which may indicate mitochondrial metabolism. This review builds upon the existing literature to describe the principles of FLIO and established uses in retinal diseases while introducing the potential for FLIO in neurodegenerative conditions.

Back-to-back talks of mentee and mentor
at the
2025 GRC on Excitation-Contraction Coupling:
Verónica Eisner, currently a Professor
In Santiago, Chile
and Gyuri H

Verónica was not only a postdoctoral fellow at MitoCare, she also served as mentor for the Young Ryan Cupo who is now joining MitoCare as faculty.

Megan and Joshua both pass their Comprehensive Examinations with flying colors and are now Ph.D Candidates.

Tigano Lab celebrate Marco's Birthday

More collaborations involving MitoCare are published:

International Journal of *Molecular Sciences*

MDPI

Article

Rescue of the First Mitochondrial Membrane Carrier, the mPiC, by TAT-Mediated Protein Replacement Treatment

Samar Zabit [1], Orly Melloul [1], Michal Lichtenstein [1], Erin L. Seifert [2] and Haya Lorberboum-Galski [1,*]

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[2] MitoCare Center, Department of Pathology and Genomic Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA; erin.seifert@jefferson.edu

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Abstract: The mitochondrial phosphate carrier (mPiC), encoded by the nuclear gene *SLC25A3*, is synthesized with an N-terminus mitochondrial targeting sequence (MTS), enabling its import into the mitochondria. mPiC imports inorganic phosphate (P_i) into the mitochondrial matrix for ATP production and other matrix phosphorylation reactions, as well as regulates mitochondrial Ca^{2+} uptake and buffering of matrix Ca^{2+}. PiC also imports copper (Cu), crucial to COX subunit holoenzyme assembly. Variants in *SLC25A3* exist and lead to mPiC deficiency (MPCD), cause a rare autosomal recessive disease with no current cure; patients with MPCD usually die within the first year of life. We have developed a novel therapeutic approach using TAT-mPiC fusion protein for cellular delivery since the TAT peptide enables delivery of proteins across biological membranes. We designed, produced, and purified the TAT-mPiC fusion protein. The fusion protein is delivered into the mitochondria and localizes within the mIM, its natural cellular location, as a processed protein. Treatment of mPiC-knockdown cells with TAT-mPiC fusion protein increased cell growth and improved bioenergetic capabilities, as measured by oxygen consumption rate (OCR), ATP production, and reduction in lactate secretion. Most importantly, TAT-mPiC restored P_i and Cu delivery into the mitochondrial matrix. TAT-mPiC fusion protein also restored the mitochondrial activity of cells harboring various mitochondrial defects. This study presents the first successful delivery of a mitochondrial transmembrane carrier using the TAT-fusion system, offering a potential early treatment strategy for newborns with mPiC deficiency.

Academic Editor: Magnus Monné

Received: 25 March 2025

Revised: 1 May 2025

Circulation Research

Volume 137, Issue 3, 18 July 2025; Pages 386-399

https://doi.org/10.1161/CIRCRESAHA.124.325477

American Heart Association

ORIGINAL RESEARCH

Pharmacological Enhancement of Small Conductance Ca^{2+}-Activated K^+ Channels Suppresses Cardiac Arrhythmias in a Mouse Model of Catecholaminergic Polymorphic Ventricular Tachycardia

Meet the First Author, see p 361

Roland Veress, Radmila Terentyeva, Andriy E. Belevych, Fruzsina Perger, Zuzana Nichtova, Anastasia Pokrass, Yujia Cheng, Snizhana Chorna, Isabelle Deschenes, Sandor Gyorke, Bjorn C. Knollmann, Richard T. Clements, Harpreet Singh, Bin Liu, Gyorgy Csordas, Shanna Hamilton, and Dmitry Terentyev

Background: Sarcolemmal small conductance Ca^{2+}-activated K^+ channels have the unique capacity to translate intracellular Ca^{2+} signal into repolarization, while mitochondrial SK channels can link Ca^{2+} cycling to mitochondrial function. We hypothesize that pharmacological enhancement of SK channels can be protective against malignant cardiac arrhythmias associated with disturbances in Ca^{2+} handling machinery.

Methods: A mouse CASQ2 KO (calsequestrin type 2 knockout) model of catecholaminergic polymorphic ventricular tachycardia (CPVT) was used for in vivo ECG recordings and for cell electrophysiology, Ca^{2+}, and reactive oxygen species imaging in isolated ventricular myocytes (VMs).

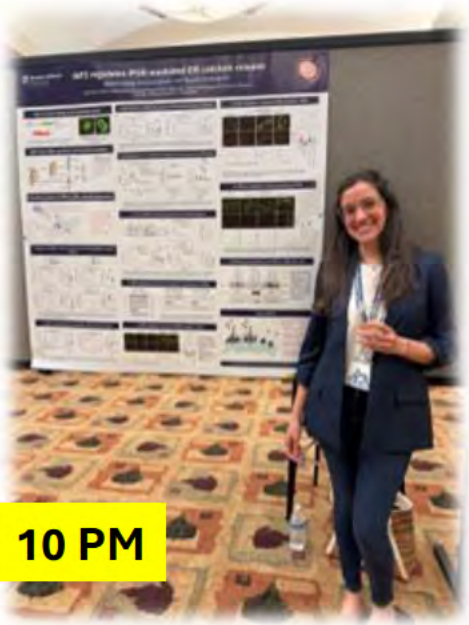
Results: Bidirectional and polymorphic ventricular tachycardias in CASQ2 KO mice induced by stress challenge (epinephrine+caffeine cocktail) were attenuated by injection of NS309, a specific SK channel enhancer. Voltage-clamp experiments in isolated VMs treated with β-adrenergic agonist isoproterenol showed a reduction of sarcolemmal SK channel current (I_{SK}) density in CPVT VMs. Application of NS309 to CPVT VMs increased I_{SK}. Current-clamp experiments demonstrated a significant reduction of arrhythmogenic delayed afterdepolarizations and spontaneous Ca^{2+} waves in isoproterenol-challenged CPVT VMs pretreated with NS309. Importantly, subsequent application of membrane-impermeable SK channel inhibitor apamin did not reverse the protective effects of NS309, suggesting important roles of mitochondrial SK channels in intracellular Ca^{2+} handling rescue. SK channel enhancement reversed the increased rate of reactive oxygen species production by mitochondria in CPVT VMs. It also reversed increased cardiac RyR2 (ryanodine receptor 2) oxidation measured in samples from CPVT hearts of the animals after the stress challenge. Electron microscopy studies showed a significant widening of mitochondria cristae in the ventricular tissue from CPVT mice, which led to a decrease in quaternary supercomplexes of electron transport chain, resulting in impairment of ATP production in VMs under β-adrenergic stimulation. Application of NS309 facilitated cristae flattening in CPVT ventricular tissue and restored supercomplexes and ATP production in VMs from diseased animals.

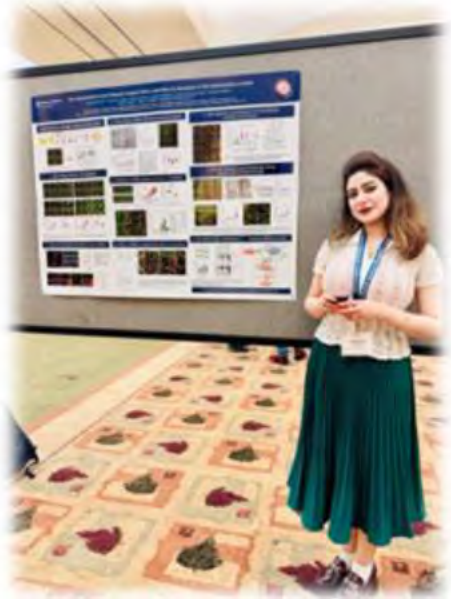
Conclusions: Sarcolemmal SK channel enhancement reduces arrhythmic potential by restoring repolarization force in CPVT VMs. Activation of mitochondrial SK channels attenuates mitochondria structural changes in CPVT, restoring more efficient electron transport chain assembly into supercomplexes and reducing mito-reactive oxygen species production. This decreases RyR2 oxidation and thus channel activity, reducing spontaneous Ca^{2+} waves underlying arrhythmogenic delayed afterdepolarizations.

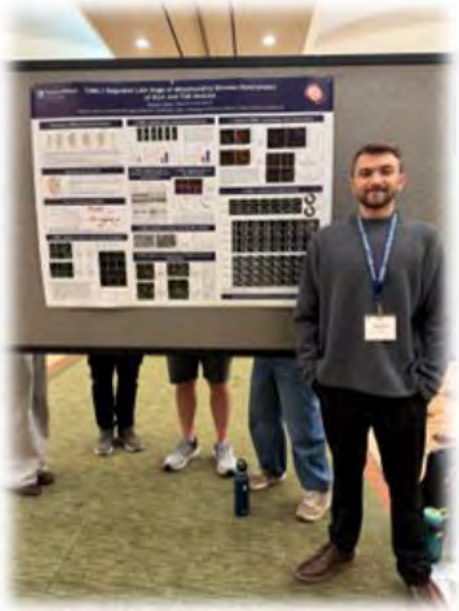
Chakrabarti Lab (Maite, Amy and Brandon) presenting at the FASEB Cytoskeletal meeting, Boston
July 2025

10 AM

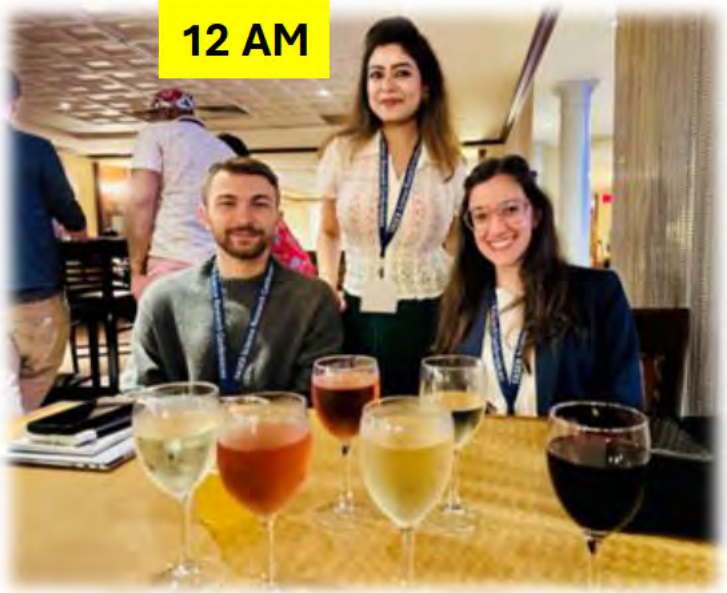
10 PM







12 AM



Chakrabarti Lab “fun activities” at the FASEB Cytoskeletal meeting, Boston July 2025

Studies performed by Kai-Ting Huang and Prottoy Hasan, former MC trainees become part of a paper:

nature communications

Article

https://doi.org/10.1038/s41467-025-59427-5

Mitochondrial membrane hyperpolarization modulates nuclear DNA methylation and gene expression through phospholipid remodeling

Received: 6 June 2024

Accepted: 23 April 2025

Published online: 29 April 2025

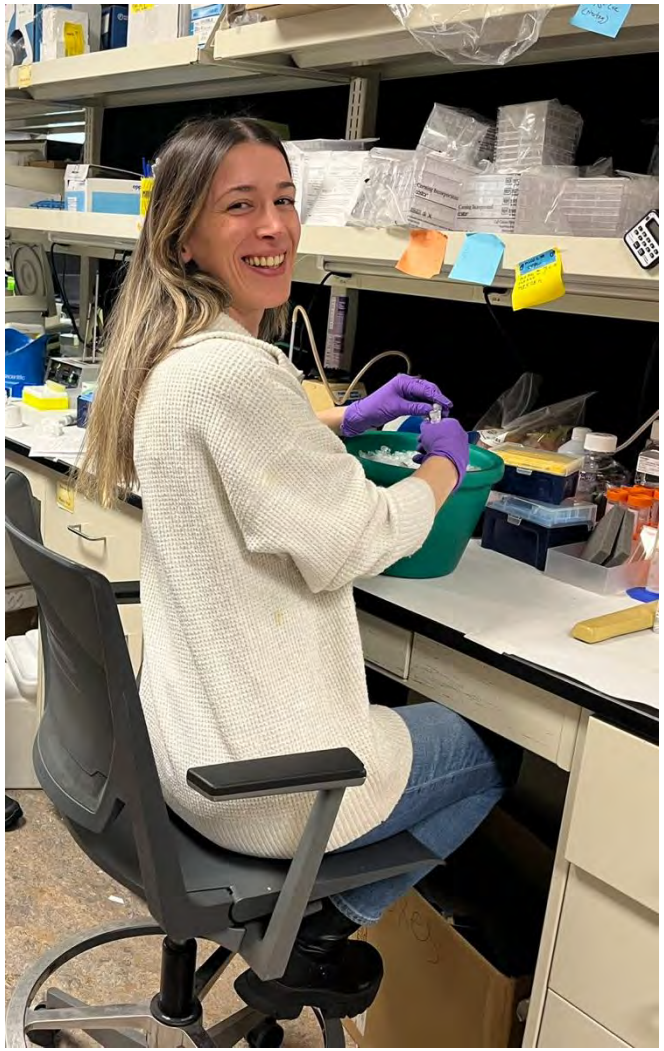
Check for updates

Mateus Prates Mori[1], Oswaldo A. Lozoya[2], Ashley M. Brooks[3], Carl D. Bortner[4], Cristina A. Nadalutti[1], Birgitta Ryback[5], Brittany P. Rickard[6], Marta Overchuk[7], Imran Rizvi[7,8], Tatiana Rogasevskaia[9], Kai Ting Huang[10], Prottoy Hasan[10], György Hajnóczky[10] & Janine H. Santos[1]

Maintenance of the mitochondrial inner membrane potential (ΔΨm) is critical for many aspects of mitochondrial function. While ΔΨm loss and its consequences are well studied, little is known about the effects of mitochondrial hyperpolarization. In this study, we used cells deleted of *ATP5IF1* (IF1), a natural inhibitor of the hydrolytic activity of the ATP synthase, as a genetic model of increased resting ΔΨm. We found that the nuclear DNA hypermethylates when the ΔΨm is chronically high, regulating the transcription of mitochondrial, carbohydrate and lipid genes. These effects can be reversed by decreasing the ΔΨm and recapitulated in wild-type (WT) cells exposed to environmental chemicals that cause hyperpolarization. Surprisingly, phospholipid changes, but not redox or metabolic alterations, linked the ΔΨm to the epigenome. Sorted hyperpolarized WT and ovarian cancer cells naturally depleted of IF1 also showed phospholipid remodeling, indicating this as an adaptation to mitochondrial hyperpolarization. These data provide a new framework for how mitochondria can impact epigenetics and cellular biology to influence health outcomes, including through chemical exposures and in disease states.

The 1st thesis committee meeting of Claire

Selin's hard work paid off
in her Comprehensive Examination,
resulting in a glowing evaluation

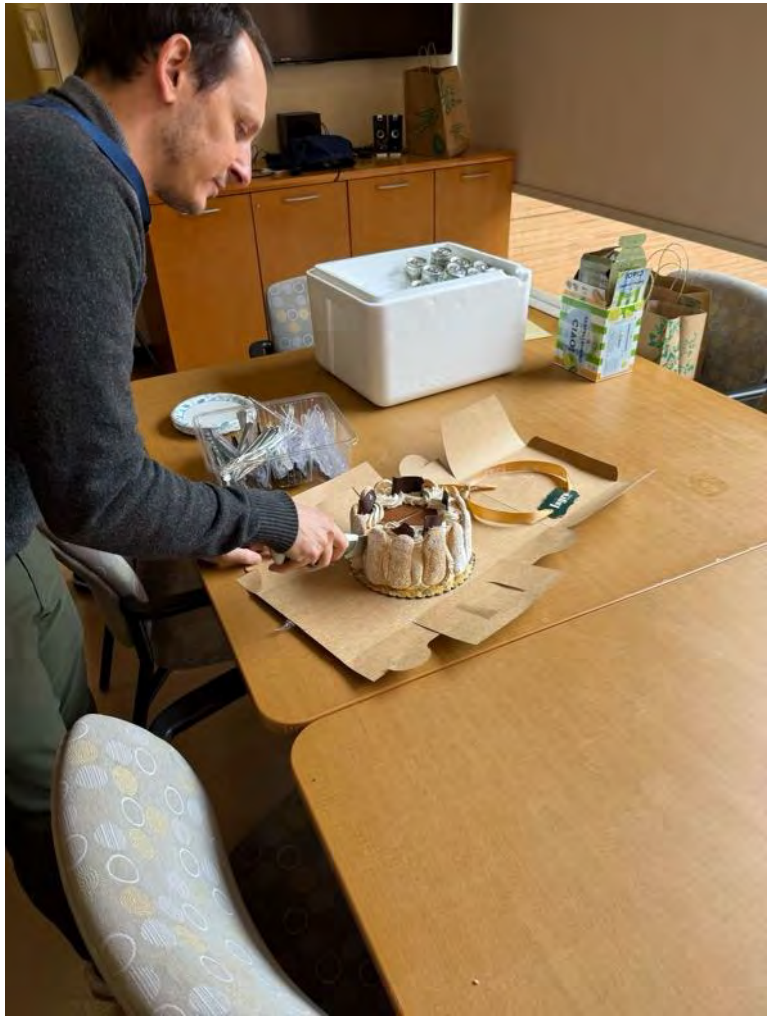


Marite got accepted to the PhD program
and
leaves her technician job at Gyuri's lab

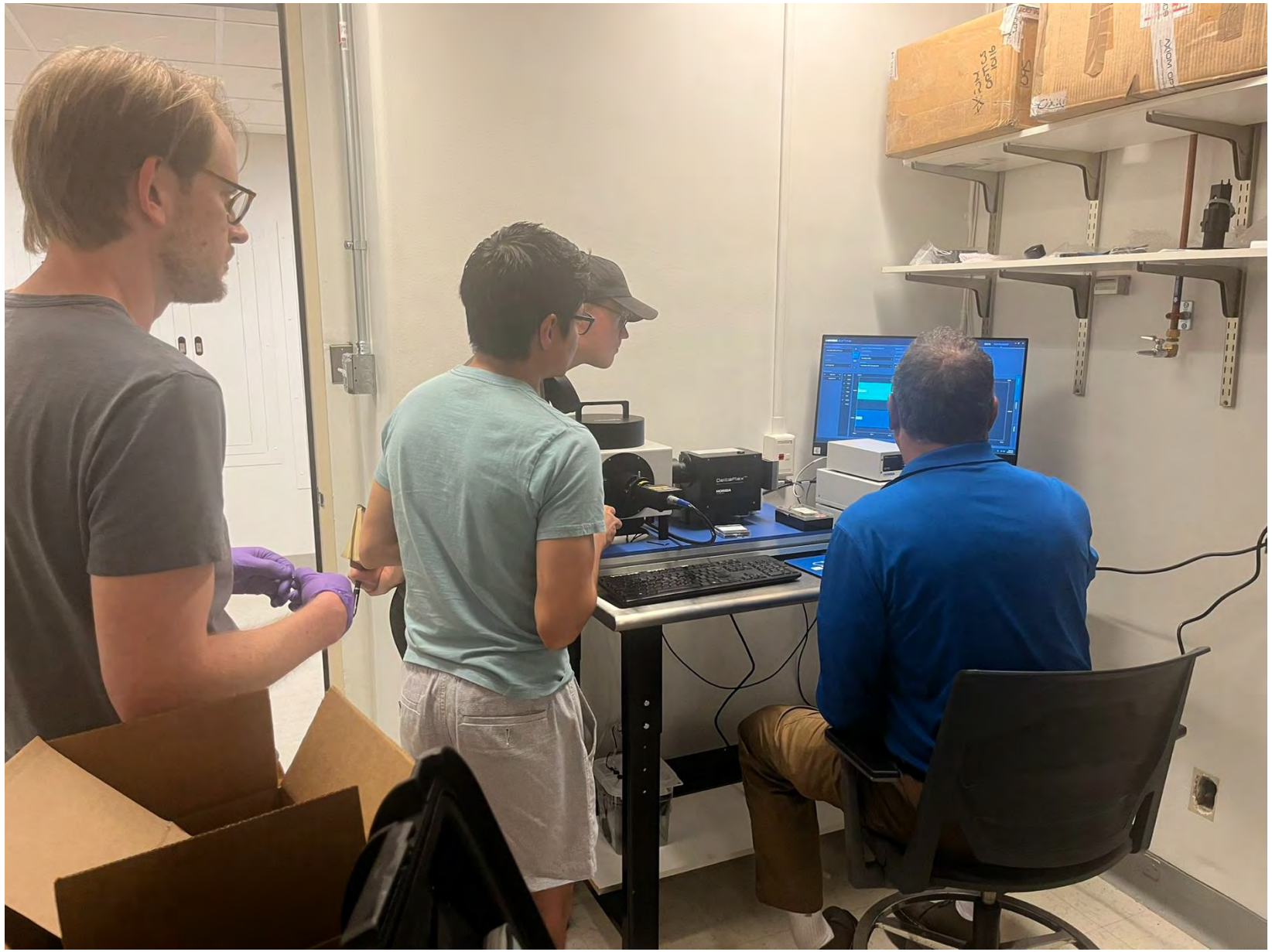
THE only new Baby Girl in 2025:
Rebekka, and her proud Mom: Zuzana

Nina Petrova (center)
Joins the Ultrastructure Team

Of course, Marco’s cake is from a famous Italian bakery in Philadelphia (Isgro’s)



Addition of a fluorometer for Fluorescence Lifetime measurements



Article

EMBO reports

Peri-mitochondrial actin filament inhibits Parkin assembly via disruption of ER-mitochondrial contact

Tak Shun Fung[1,4], Amrapali Ghosh[2,4], Maite R Zavala[2], Zuzana Nichtova[2], Dhavalkumar Shukal[2], Marco Tigano[2], Gyorgy Csordas[2], Henry N Higgs[3] & Rajarshi Chakrabarti[2]✉

Abstract

Mitochondrial damage represents a dramatic change in cellular homeostasis, necessitating metabolic adaptation and clearance of the damaged organelle. One rapid response to mitochondrial damage is peri-mitochondrial actin polymerization within 2 min, which we term ADA (Acute Damage-induced Actin). ADA is vital for a metabolic shift from oxidative phosphorylation to glycolysis upon mitochondrial dysfunction. In the current study, we investigated the effect of ADA on Pink1/Parkin mediated mitochondrial quality control. We show that inhibition of proteins involved in the ADA pathway significantly accelerates Parkin recruitment onto depolarized mitochondria. Addressing the mechanism by which ADA resists Parkin recruitment onto depolarized mitochondria, we found that ADA disrupts ER-mitochondria contacts in an Arp2/3 complex-dependent manner. Interestingly, overexpression of ER-mitochondria tethers overrides the effect of ADA, allowing rapid recruitment of not only Parkin but also LC3 after mitochondrial depolarization. During chronic mitochondrial dysfunction, Parkin and LC3 recruitment are completely blocked, which is reversed rapidly by inhibiting ADA. Taken together we show that ADA acts as a protective mechanism, delaying mitophagy following acute damage, and blocking mitophagy during chronic mitochondrial damage.

Keywords Actin; Arp2/3 Complex; ER; LC3; Parkin
Subject Categories Autophagy & Cell Death; Cell Adhesion, Polarity & Cytoskeleton; Organelles
https://doi.org/10.1038/s44319-025-00561-y
Received 7 May 2024; Revised 12 June 2025; Accepted 6 August 2025
Published online: xx xxx 2025

Introduction

Mitochondria are well known to oxidize organic molecules for ATP production, using the mitochondrial membrane potential (Δψm) generated by the electron transport chain (ETC) across the inner mitochondrial membrane (IMM) to drive ATP synthase (Mitchell, 2011). In addition, mitochondria are important signaling and biosynthetic hubs, participating in calcium signaling (Nicholls, 2005), lipid synthesis (Nowinski et al, 2020), amino acid synthesis (Ahn and Metallo, 2015), iron-sulfur cluster biosynthesis (Braymer and Lill, 2017), apoptosis (Green, 2022) and heat production (Rustin et al, 2025). Mitochondrial dysfunction can lead to unregulated cell death via ferroptosis (Gao et al, 2019) as well as activation of host-pathogen responses and innate immunity (Kim et al, 2023). For these reasons, several pathways exist to mitigate mitochondrial dysfunction, including mitochondrial destruction by mitophagy.

Mammalian mitophagy involves recognition of dysfunctional mitochondrion through specific receptors and/or adaptors, often in a trigger-specific manner. One such trigger is depolarization (the sustained loss of Δψm), a common outcome of mitochondrial dysfunction. Mitochondrial depolarization activates the Pink1/Parkin mitophagy pathway, which in turn stimulates recruitment of LC3 to feed the mitochondrion into the autophagy pathway. In a healthy mitochondrion, the serine-threonine protein kinase Pink1 is continuously degraded through a system that involves its import into the mitochondrial matrix through the Tom and Tim complexes, which requires mitochondrial membrane potential (Deas et al, 2011; Jin et al, 2010; Meissner et al, 2011; Yamano and Youle, 2013). Upon mitochondrial depolarization, Pink1 is stabilized onto the OMM, where it homodimerizes, self-activates, and phosphorylates both ubiquitin and Parkin (a cytoplasmic E3 ubiquitin ligase), leading to Parkin accumulation on OMM (Lazarou et al, 2012; Okatsu et al, 2013). Mitochondrially-recruited Parkin ubiquitinates several substrates, generating an ubiquitinated mask on the OMM which is recognized by a group of adaptors (P62, NBR1, NDP52, TAX1BP1 and Optineurin (OPTN)). These adaptor proteins subsequently recruit LC3.

A growing number of studies have documented several important roles for actin filaments in regulation of mitochondrial homeostasis and dynamics (Basu et al, 2021; Chakrabarti et al, 2018; Coscia et al, 2024; Fung et al, 2019; Korobova et al, 2013; Li et al, 2015; Moore et al, 2021). We and others have shown that acute mitochondrial depolarization using uncouplers like FCCP or CCCP generates a transient cloud of actin filaments, which we term ADA (acute damage-induced actin), around the depolarized

[1]Department of Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [2]Department of Pathology and Genomic Medicine, Thomas Jefferson University, Philadelphia, PA, USA. [3]Department of Biochemistry and Cell Biology, Geisel School of Medicine at Dartmouth College, Hanover, NH, USA. [4]These authors contributed equally: Tak Shun Fung, Amrapali Ghosh. ✉E-mail: Rajarshi.Chakrabarti@jefferson.edu

Chakrabarti Lab's first paper also featured as a cover story !!!
August 2025

MitoCare Visit at the Pennsylvania Ballet thanks to organization by Emma

Amy Ehrlich, a former undergraduate student in Gyuri H's lab, a famous cookie maker, and currently a scientist in Copenhagen recommends some Danish delicacies for MitoCare

60 !

Living in MitoCare
Keeps you young!

Preparing for a bright future for next gen mitochondriacs

T32 for PhD student training in mitochondrial biology
Submitted by Gyuri H, Marco and Erin

SF 424 R&R APPLICATION FOR FEDERAL ASSISTANCE **Page 2**

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Dr.	Gyorgy		Hajnoczky	

Position/Title: Professor
Organization Name: Thomas Jefferson University
Department: Pathology & Genomic Medicine
Division: Pathology
Street1: 1020 Locust St.
Street2:
City: Philadelphia
County/Parish:
State: PA: Pennsylvania
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 19107-6799
Phone Number: 6103892168
Fax Number:
Email: gxh110@jefferson.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested
b. Total Non-Federal Funds
c. Total Federal & Non-Federal Funds
d. Estimated Program Income

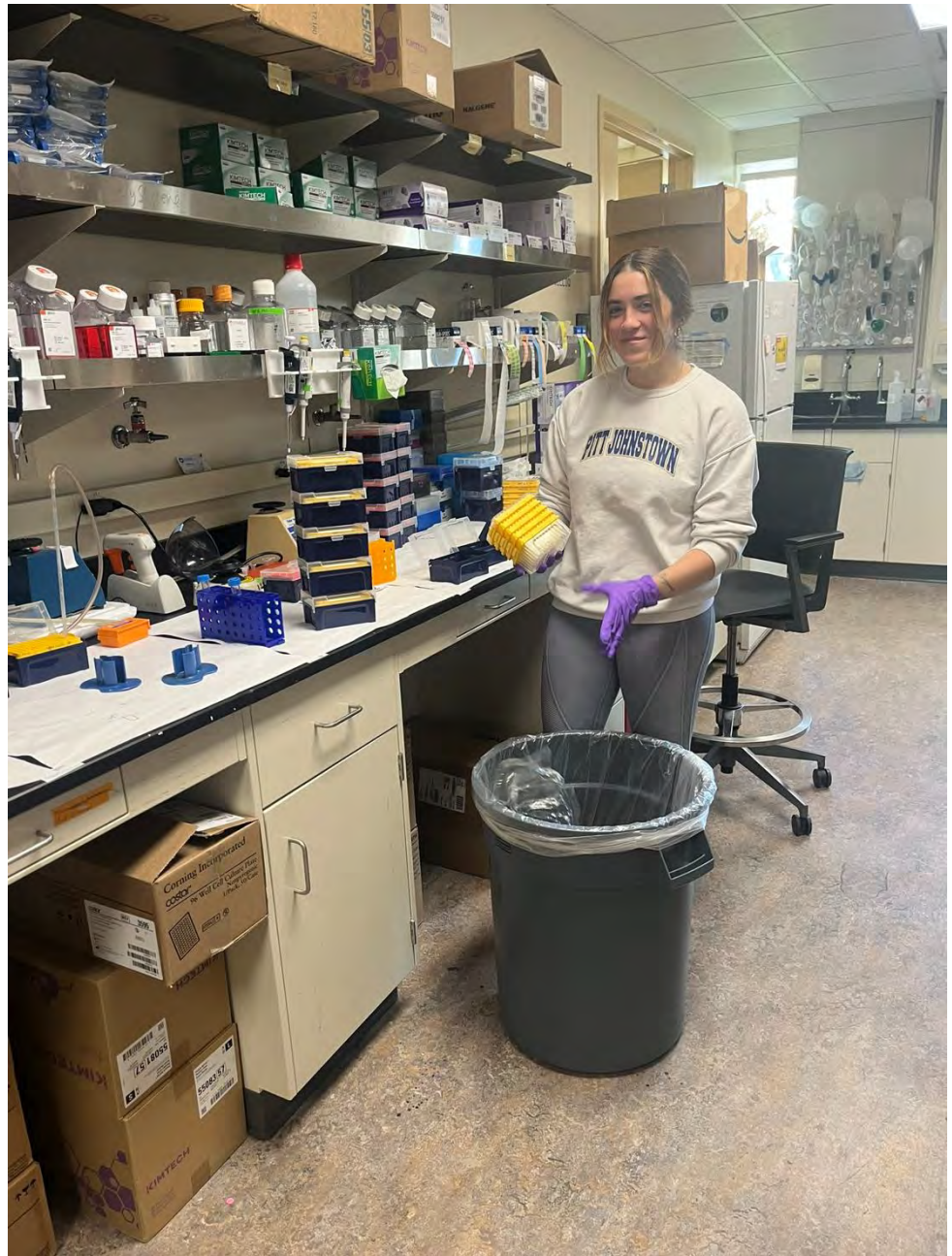
[redacted]

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

We propose a training program in mitochondrial biology based on exponentially increasing interest in the role of mitochondria in many areas of biology, including physiology, and the minimal training available, combined with frequent lack of understanding of basic concepts about measuring mitochondria. We build on the prosperity of the MitoCare mitochondrial research center and its educational programs, and a large number of faculty with mitochondrial research interests at Jefferson. We expect to help PhD students to rigorously and creatively undertake the mitochondria-focused part of their project, to expose them to the excitement of new concepts in mitochondrial biology and to provide them with a template for approaching other subject areas.

Claire doesn't excel only in 3D ultrastructure image analysis and labchores but she also masters baking



Raji, Rajeswari Krishnamurthy
a former postdoctoral fellow,
and Venka, her husband
return another time to see
MitoCare's Evolution

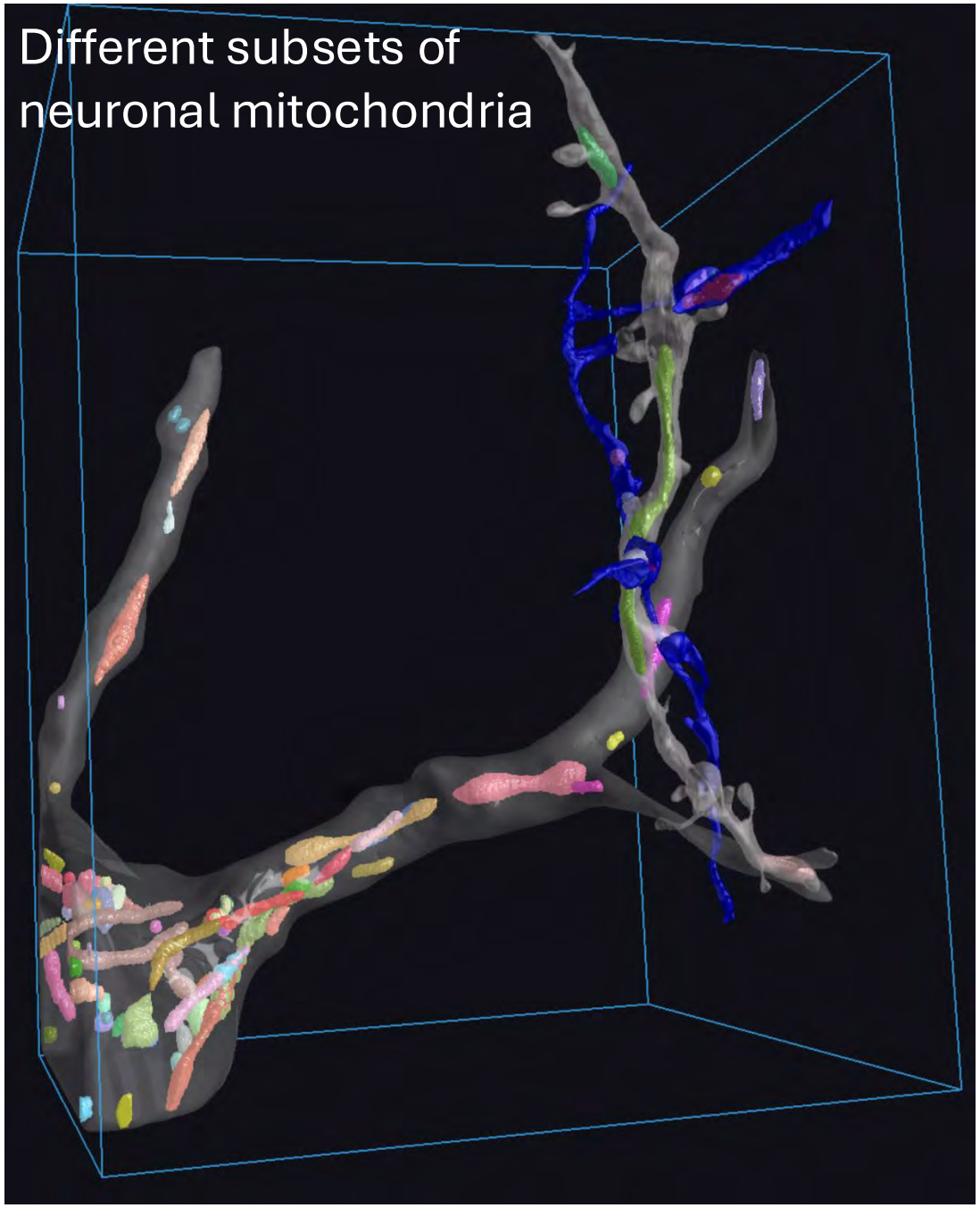
BTW We can be super proud of
Raji, who established and has
been growing Bioklone,
one of the top antibody
Producing companies of India

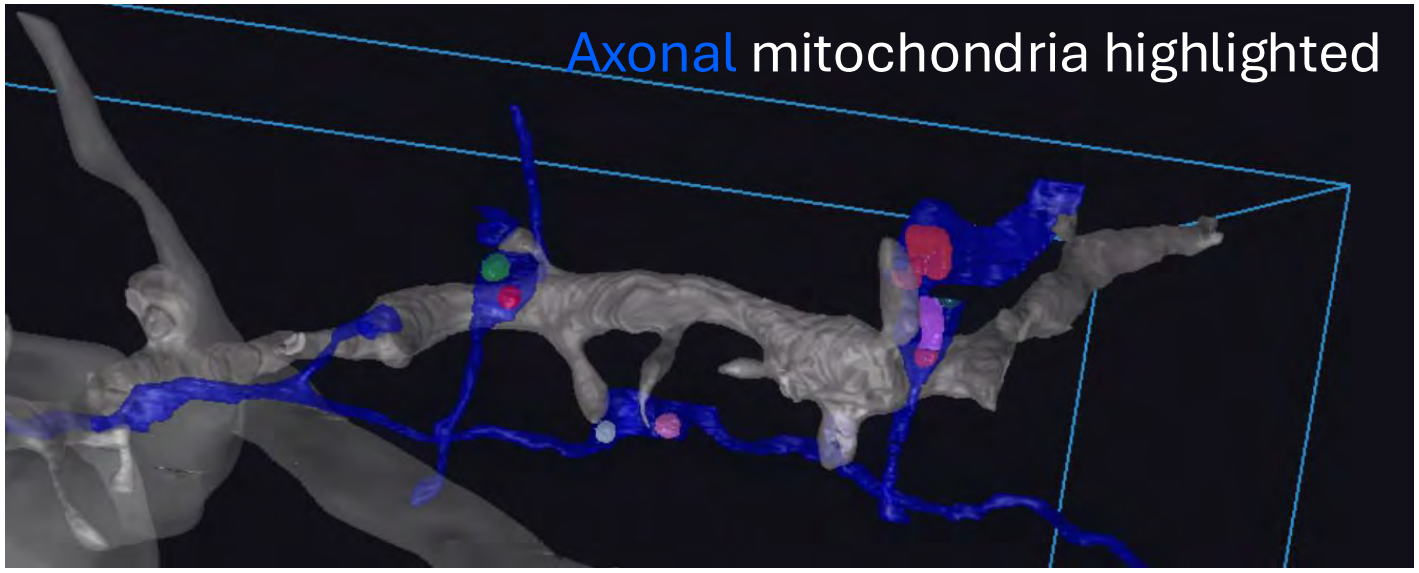
Saluting the retiring Grace by the MitoCare faculty

Saying Goodbye to Dave

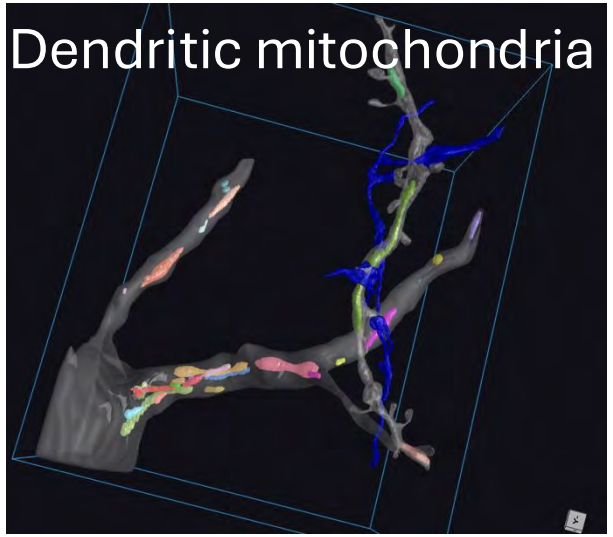

FIRE EXTINGUISHER
FIRE EXTINGUISHER
FIRE EXTINGUISHER
Offices
CAUTION
WET

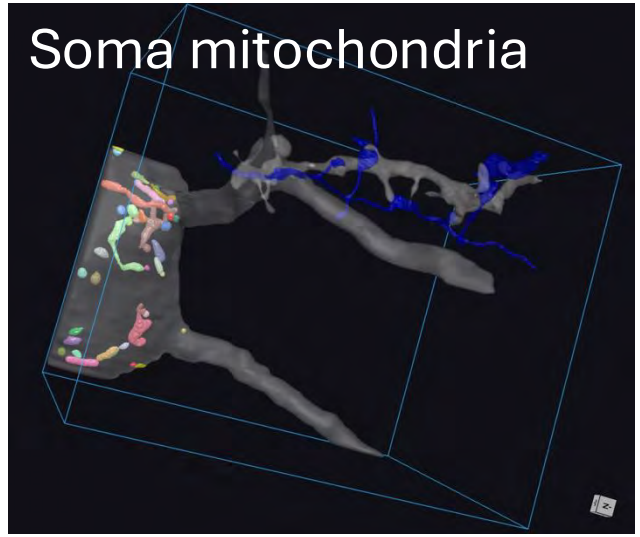
Still unpublished 3D brain ultrastructure



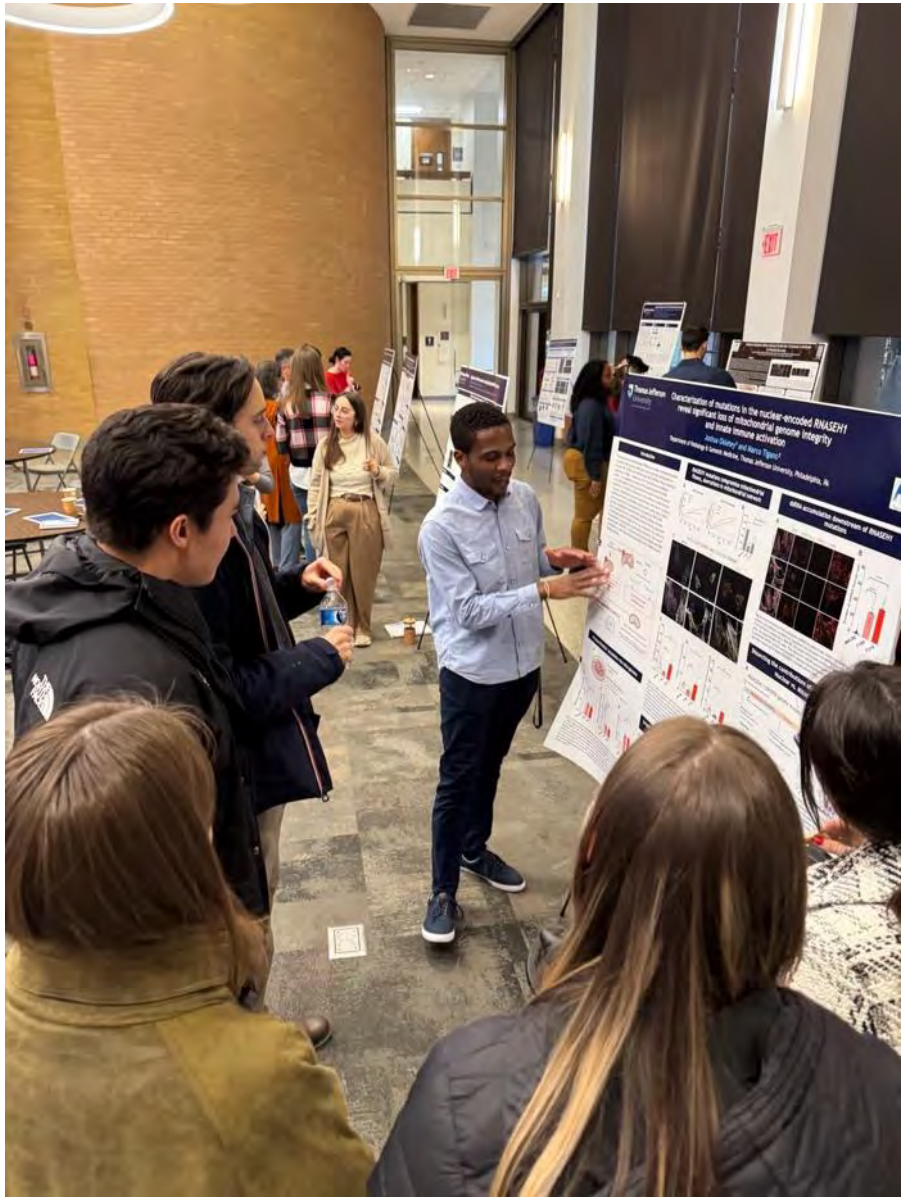


Mitochondrial architecture in the brain cortex during normal aging and neurodegeneration
Dave, Raghavendra, Claire, Zuzana, Prashant, Gyuri C et al





Joshua entertains an audience at the T32 Annual Retreat



Marco is ready to chair at FASEB Research meeting on MtDNA in true Nashville style.

Academic Ambassadorship Honor at the University of Urbino

Tigano Lab's first Corresponding Author Manuscript is Accepted (from Dr. Emanuele Vitale's visit in 2022).

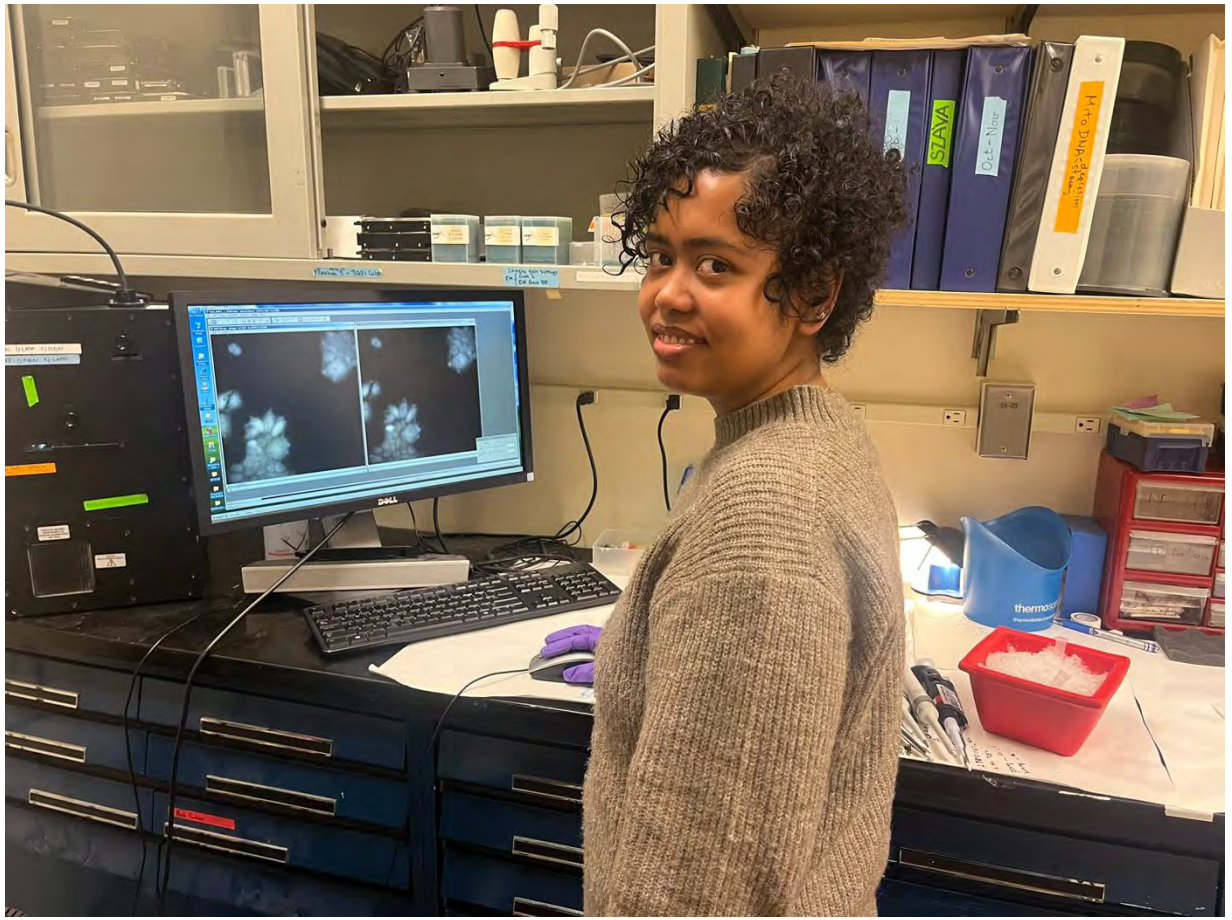
RUNX2 cooperates with SREBP1 to rewire cancer metabolism and promote aggressiveness

Research | Open access | Published: 31 October 2025

Volume 44, article number 298, (2025) Cite this article

Emanuele Vitale, Mila Gugnoni, Veronica Manicardi, Silvia Muccioli, Federica Torricelli, Benedetta Donati, Simonetta Piana, Gloria Manzotti, Elisa Salviato, Francesca Reggiani, Cristian Ascione, Rebecca Vezzani, Moira Ragazzi, Mattia Forcato, Oriana Romano, Silvio Bicciato, Aaron R. Goldman, Marco Tigano & Alessia Ciarrocchi

Priyanka Bose is gaining expertise in live cell imaging



The joint MitoCare – Jefferson Weinberg ALS Center team (Drs Tigano, Trotti and Pasinelli) meet with their international partners from Gemelli Hospital (Dr. Primiano, Italy) and Shiba Hospital (Dr. Dori, Israel)

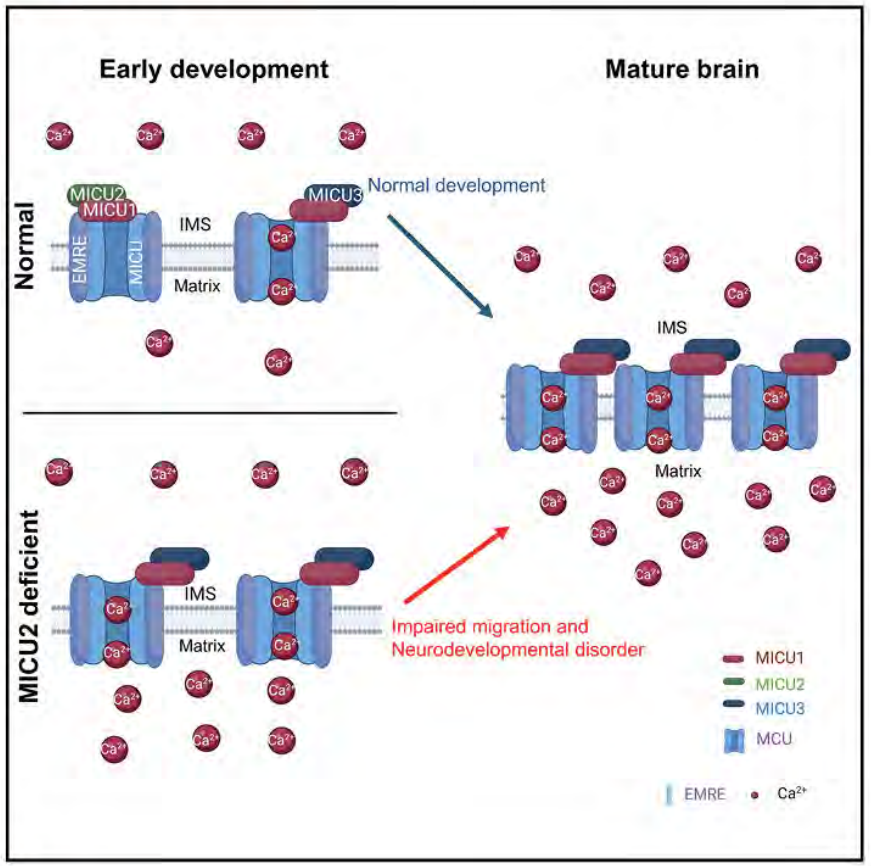
Elena helped finalizing several studies,
finally, her main project is also published

Report

Cell Reports

MICU2 controls mitochondrial calcium signaling and migration in neurons during development

Graphical abstract



Authors

Elena Berezhnaya,
Benjamín Cartes-Saavedra,
Raghavendra Singh,
Macarena Rodríguez-Prados, Orly Reiner,
Fowzan S. Alkuraya, György Hajnóczky

Correspondence

gyorgy.hajnoczky@jefferson.edu

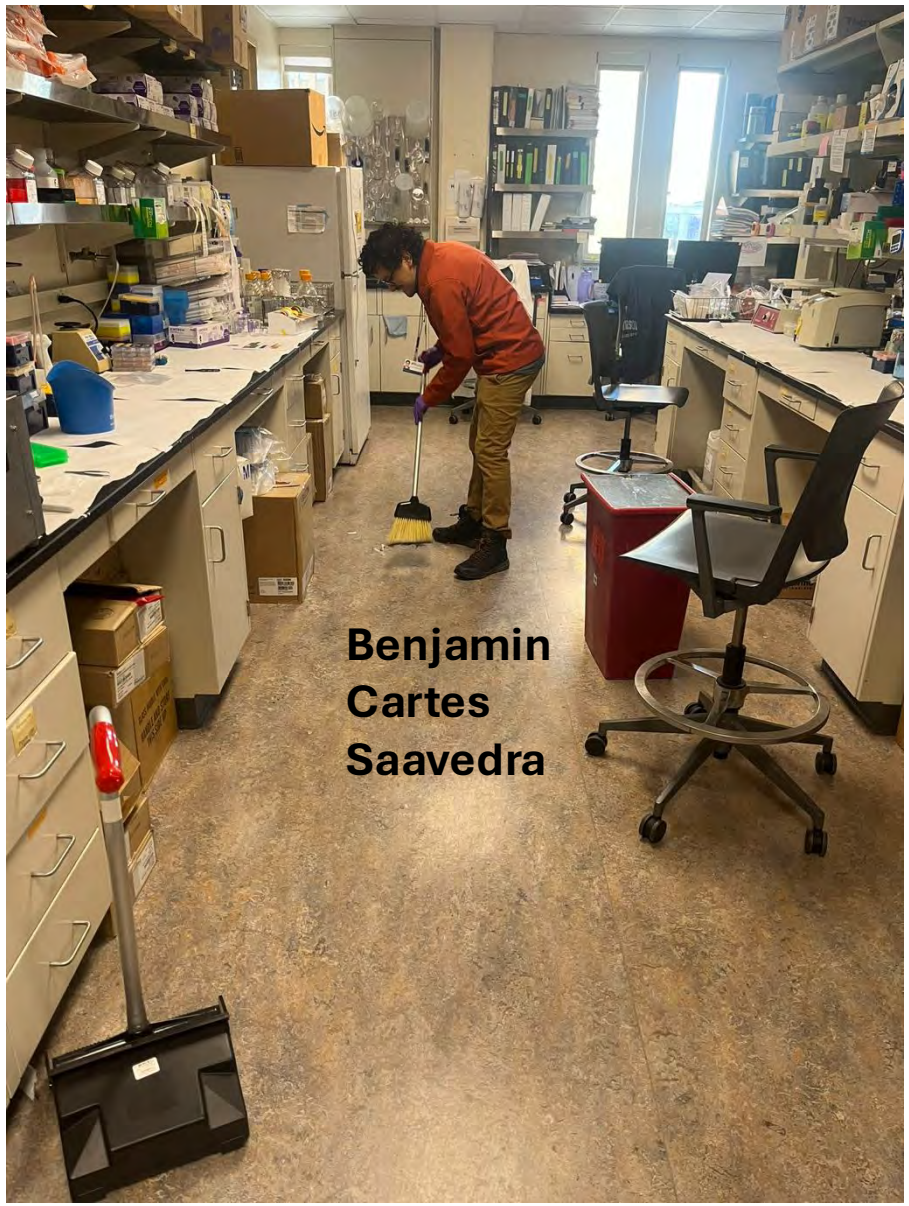
In brief

Berezhnaya et al. showed that MICU2 is present in the brain during development but is replaced during maturation by MICU3. MICU2 loss during development results in neuronal overmigration in the cortex and anxiety-like behavior in mice that may contribute to the neurodevelopmental disorder observed in patients with the MICU2 null mutationreported previously.

Highlights

Time to change the location of Ryan Cupo's photo

Paying attention to our environment paves the way to greatness



MDA Muscular Dystrophy Association

November 13, 2025

Benjamin Cartes Saavedra, PhD
Postdoctoral Fellow
Thomas Jefferson University
1020 Locust Street
Philadelphia, PA 19103

Dear Dr. Cartes Saavedra,

On behalf of the Muscular Dystrophy Association Board of Directors, staff, and millions of people touched by neuromuscular disease, we are pleased to inform you that your project, titled "**MICU1 loss-related myopathy: Role of mitochondrial fusion (MDA 1457676)**," has been approved for funding.

Your research progress is very important to MDA, to those we serve, and to the donors who keep the research pipeline flowing. Therefore, as reiterated in the attached policy manual, it is crucial that MDA receive all manuscripts resulting from this research project immediately upon their acceptance for publication so that we can communicate the results to our community. MDA adheres strictly to all journal embargos. Please send your publications and news of other research advances, accolades, or items of interest to your MDA Scientific Portfolio Director, Brian Lin, at blin@mdausa.org.

Congratulations and thank you for turning to MDA to support your work and for joining in our mission to save lives. We look forward to working with you and celebrating your successes, and we hope to have the opportunity to further support your research in the future.

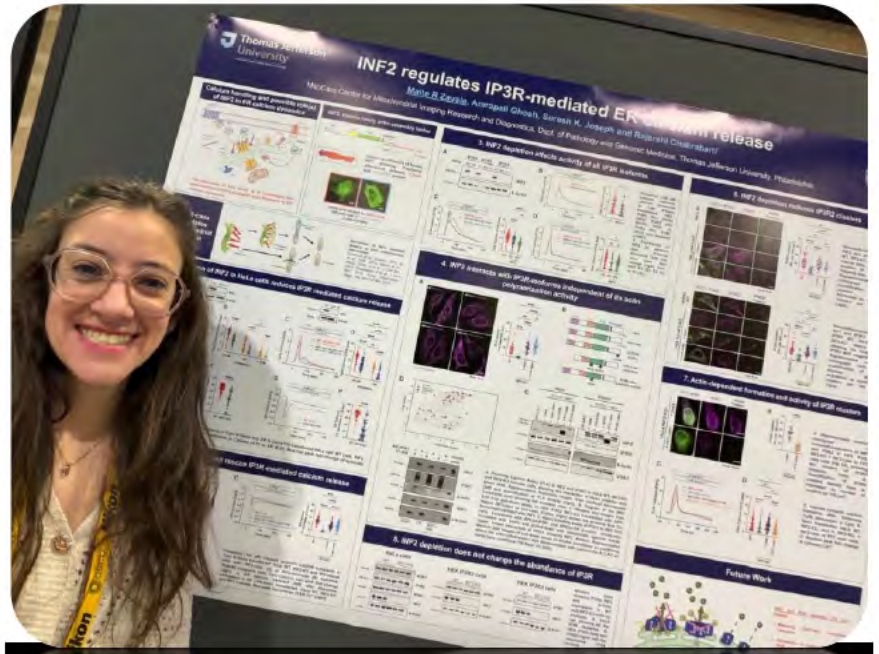
Please call on me or my colleagues if we can be of assistance to you as a research partner!

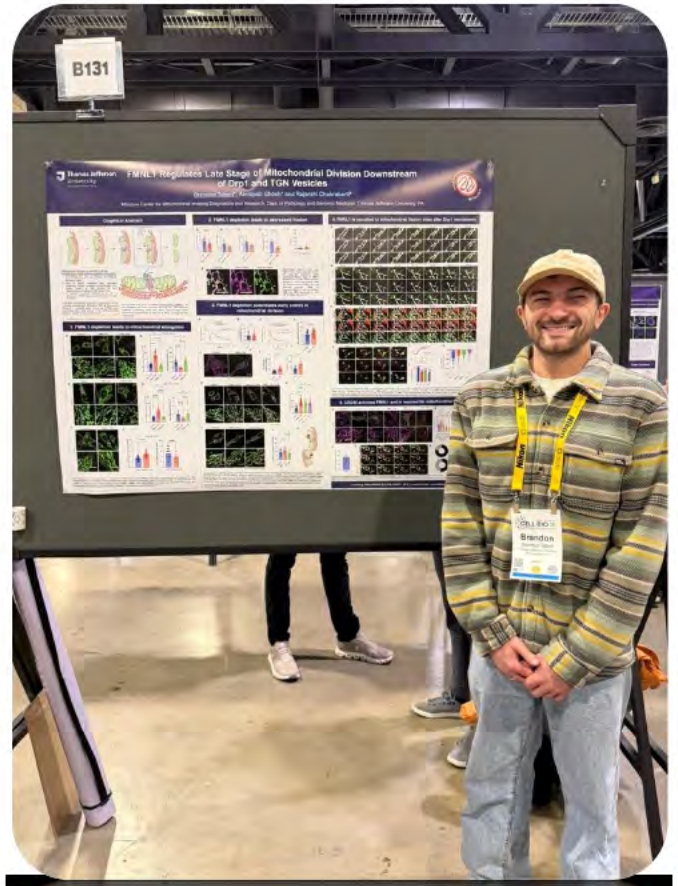
Sincerely,

Elizabeth Habeeb-Louks
Grants Manager

CC: Brad Henry, Chairman of the Board of Directors, MDA
Angela Lek, Ph.D., Chief Research Officer, MDA

Maite and Brandon presents at ASCB, December 2025





Collaborative projects published in the end of the year

Circulation Research
Volume 137, Issue 12, 5 December 2025; Pages 1385-1403
https://doi.org/10.1161/CIRCRESAHA.125.326841

ORIGINAL RESEARCH

Increased Intermembrane Space [Ca^{2+}] Drives Mitochondrial Structural Damage in CPVT

Editorial, see p 1404

Shanna Hamilton, Radmila Terentyeva, Roland Veress, Fruzsina Perger, Zuzana Nichtova, Mark Bannister, Jinxi Wang, Sage Quiggle, Rachel Battershell, Matthew W. Gorr, Sandor Györke, Bum-Rak Choi, Christopher H. George, Andriy E. Belevych, György Csordás, and Dmitry Terentyev

Background: Mitochondrial dysfunction caused by abnormally high RyR2 (ryanodine receptor) activity is a common finding in cardiovascular diseases. Mechanisms linking RyR2 gain of function with mitochondrial remodeling remain elusive. We hypothesized that RyR2 hyperactivity in cardiac disease increases [Ca^{2+}] in the mitochondrial intermembrane space (IMS) and activates the Ca^{2+}-sensitive protease calpain, driving remodeling of mitochondrial cristae architecture through cleavage of structural protein OPA1 (optic atrophy protein 1).

Methods: We generated a highly arrhythmogenic rat model of catecholaminergic polymorphic ventricular tachycardia, induced by RyR2 gain-of-function mutation S2236L(Ser2336Leu)$^{(+/-)}$. We created a new biosensor to measure IMS-[Ca^{2+}] in adult cardiomyocytes with intact Ca^{2+} cycling. We used ex vivo whole heart optical mapping, confocal and electron microscopy, as well as in vivo/in vitro gene editing techniques to test the effects of calpain in the IMS.

Results: We found altered mitochondrial cristae structure, increased IMS-[Ca^{2+}], reduced OPA1 expression, and augmented mito-reactive oxygen species emission in catecholaminergic polymorphic ventricular tachycardia myocytes. We show that calpain-mediated OPA1 cleavage led to disrupted cristae organization and, thereby, decreased electron transport chain supercomplex assembly, resulting in accelerated reactive oxygen species production. Genetic inhibition of calpain activity in IMS reversed mitochondria structural defects in catecholaminergic polymorphic ventricular tachycardia myocytes and reduced arrhythmic burden in ex vivo optically mapped hearts.

Conclusions: Our data suggest that RyR2 hyperactivity contributes to mitochondrial structural damage by promoting an increase in IMS-[Ca^{2+}], sufficient to activate IMS-residing calpain. Calpain activation leads to proteolysis of OPA1 and cristae widening, thereby decreasing assembly of electron transport chain components into supercomplexes. Consequently, excessive mito-reactive oxygen species release critically contributes to RyR2 hyperactivation and ventricular tachyarrhythmia. Our new findings suggest that targeting IMS calpain may be beneficial in patients at risk for sudden cardiac death.

Circulation Research
Volume 137, Issue 10, 24 October 2025; Pages e197-e217
https://doi.org/10.1161/CIRCRESAHA.125.326221

ORIGINAL RESEARCH

Adaptation to Elevated Mitochondrial Calcium Is Distinct in the Left and Right Ventricles

Shanmugasundaram Pakkiriswami*, Jae Hwi Sung*, Kshama R. Shah, Ulaş Özkurede, Megan K. Sumera, Feng Feng, Héctor Chapoy Villanueva, Eun Suh Cho, Andrea A. Torniainen, Jop H. van Berlo, György Hajnóczky, Kurt W. Prins, and Julia C. Liu

Background: Mitochondrial ATP production, essential for cardiomyocyte function, is regulated by mitochondrial Ca^{2+} (mtCa^{2+}). The primary route for mtCa^{2+} influx is the mitochondrial calcium uniporter complex. The mitochondrial calcium uniporter complex subunit MICU (mitochondrial calcium uptake) 1 limits mtCa^{2+} uptake, preventing mtCa^{2+} overload. Although elevated mtCa^{2+} has been observed in multiple diseases including heart failure, its effects on heart function remain elusive.

Methods: To investigate the impact of elevated mtCa^{2+} in adult hearts, we generated a mouse model with cardiomyocyte-specific tamoxifen-inducible *Micu1* deletion (*Micu1*^{cKO}). Cardiac function was assessed through echocardiography. Mitochondria, adult cardiomyocytes, and tissue extracts were isolated from the left ventricle (LV) and right ventricle (RV) for comprehensive analysis at multiple time points ranging from 1 to 9 weeks post-tamoxifen injection.

Results: Acute MICU1 deficiency resulted in increased mtCa^{2+} accompanied by reduced mitochondrial respiration in both the RV and LV. Contractile function, which was diminished in both ventricles initially, remained reduced in the RV upon prolonged MICU1 deficiency. In contrast, the LV exhibited signs of recovery over time, including restored ejection fraction concurrent with normalization of mtCa^{2+} levels. This pattern was mirrored in cardiomyocyte contractility. In *Micu1*^{cKO} RV, mtCa^{2+} remained elevated, likely contributing to oxidative stress. As a potential mechanism underlying LV-specific recovery, EMRE (essential MCU [mitochondrial calcium uniporter] regulator), an mitochondrial calcium uniporter complex subunit that promotes mtCa^{2+} uptake, was found to be downregulated only in the LV. This suggested that the LV initiated a compensatory response to elevated mtCa^{2+}, while the RV remained impacted. Supporting this, proteomics analysis indicated a divergent proteomic signature in *Micu1*^{cKO} RV. Follow-up experiments suggested enhanced EMRE degradation in *Micu1*^{cKO} LV mediated by m-AAA proteases through a PKA (protein kinase A)–regulated mechanism. In MICU1-deficient neonatal cardiomyocytes, pharmacological PKA inhibition was sufficient to decrease EMRE levels. Analysis of LV tissues from patients with dilated cardiomyopathy suggested that this pathway may be relevant in human DCM.

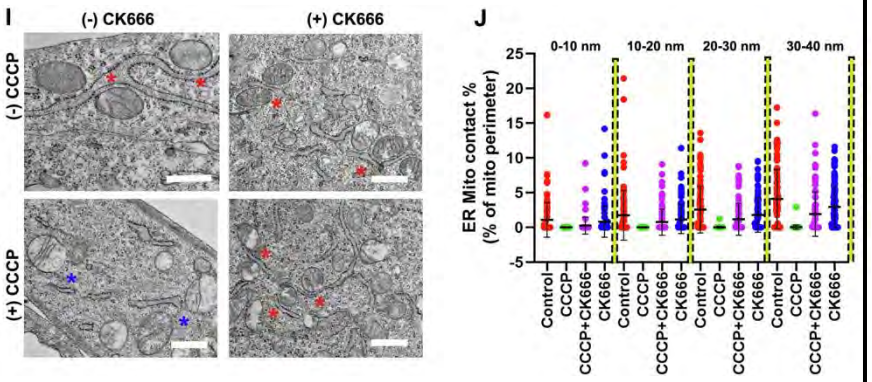
Conclusions: While elevated mtCa^{2+} disrupted cardiac function in both ventricles, it induced an LV-specific adaptive response that suppressed mtCa^{2+} intake, contributing to the recovery of mitochondrial and cardiac function. The absence of this pathway in the RV has implications for therapeutics targeting RV dysfunction, a key determinant of mortality in heart failure.

Publication contributions by the 2D & 3D EM Service Center - 2025

Peri-mitochondrial actin filaments inhibit Parkin assembly by disrupting ER-mitochondria contacts

EMBO Reports 2025 Oct;26(20):4977-5008.

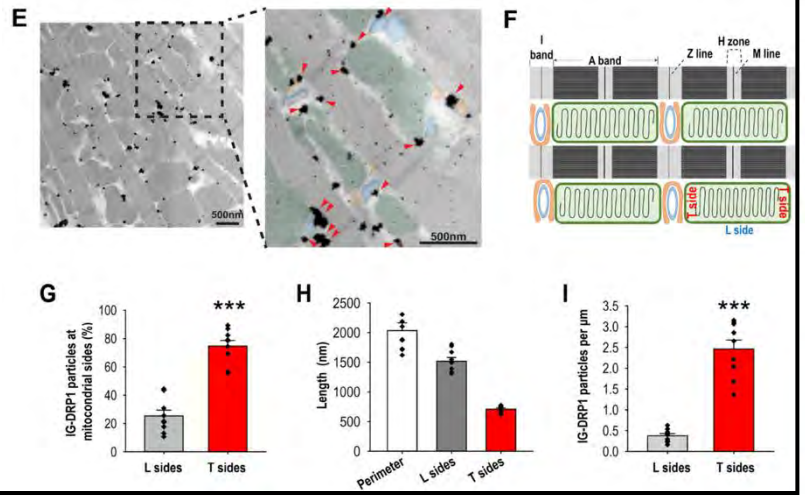
Tak Shun Fung # 1, Amrapali Ghosh # 2, Maite R Zavala 2, **Zuzana Nichtova** 2, Dhavalkumar Shukal 2, Marco Tigano 2, **Gyorgy Csordas** 2, Henry N Higgs 3, Rajarshi Chakrabarti 4



Highly Oligomeric DRP1 Strategic Positioning at Mitochondria–Sarcoplasmic Reticulum Contacts in Adult Murine Heart Through ACTIN Anchoring

Cells. 2025 Aug 14;14(16):1259.

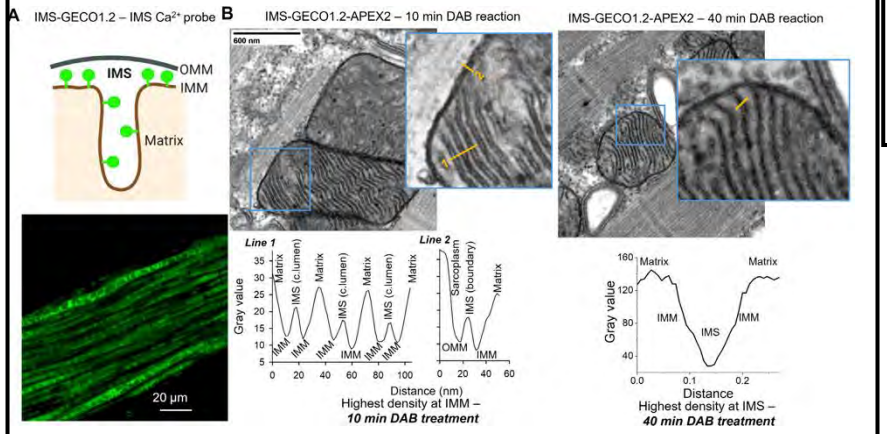
Celia Fernandez-Sanz 1 2, Sergio De la Fuente 1 3, **Zuzana Nichtova** 4, Marilen Federico 1, Stephane Duvezin-Caubet 2, Sebastian Lanvermann 1, Hui-Ying Tsai 1, Yanguo Xin 5, **Gyorgy Csordas** 4, Wang Wang 5, Arnaud Mourier 2, Shey-Shing Sheu 1



Increased Intermembrane Space [Ca2+] Drives Mitochondrial Structural Damage in CPVT

Circulation Research 2025 Dec 5;137(12):1385-1403

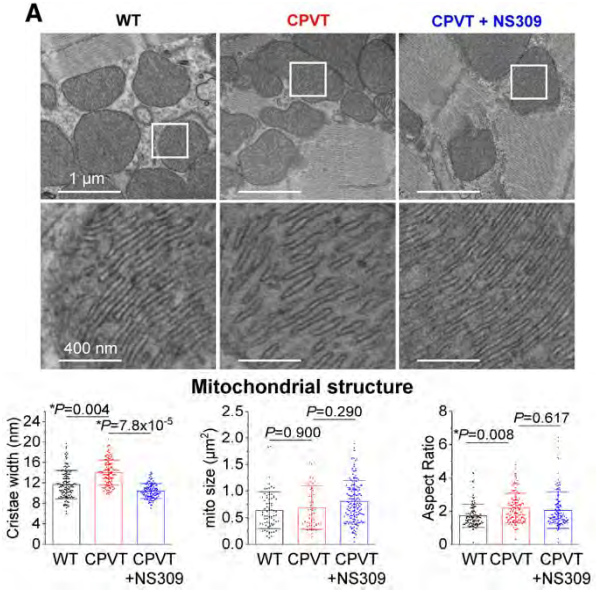
Shanna Hamilton 1 2 3, Radmila Terentyeva 1 2, Roland Veress 1 2, Fruzsina Perger 1 2, **Zuzana Nichtova** 4, Mark Bannister 5, Jinxi Wang 6, Sage Quiggle 1 3, Rachel Battershell 3, Matthew W Gorr 7 2, Sandor Györke 2, Bum-Rak Choi 8, Christopher H George 5, Andriy E Belevych 1 2, **György Csordás** 4, Dmitry Terentyev 1 2



Pharmacological Enhancement of Small Conductance Ca2+-Activated K+ Channels Suppresses Cardiac Arrhythmias in a Mouse Model of Catecholaminergic Polymorphic Ventricular Tachycardia

Circulation Research 2025 Jul 18;137(3):386-399.

Roland Veress 1 2, Radmila Terentyeva 1 2, Andriy E Belevych 1 2, Fruzsina Perger 1 2, **Zuzana Nichtova** 3, Anastasia Pokrass 1 2, Yujia Cheng 4, Snizhana Chorna 1 2, Isabelle Deschenes 1 2, Sandor Gyorke 1 2, Bjorn C Knollmann 5, Richard T Clements 6 7, Harpreet Singh 1 2, Bin Liu 4, **Gyorgy Csordas** 3, Shanna Hamilton 8, Dmitry Terentyev 1 2



Tigano Lab at the Gordon Research Conference, Ventura, March 2025

Tigano Lab Holiday Greetings 2025

MitoCircle: the 2025 edition

Raja Bhattacharrya, PhD – Massachusetts General Hospital and Harvard Medical School
Targeting MAM Stability and Endosomal Abnormalities in Neurons to Prevent Early-Stage Alzheimer's Disease (AD) Pathogenesis April 22nd, 11AM *Co-hosted with Dept of Biochemistry (Phil Wedegaertner PhD)

Dmitry Terentyev, PhD – Department of Physiology and Cell Biology, Ohio State College of Medicine
The roles and mechanisms of mitochondrial small conductance Ca2+-activated K+ channels in cardioprotection May 27th, 11AM

Atan Gross, PhD – Department of Immunology and Regenerative Biology, Weizmann Institute
The love story of my life: BID, MTCH2 and alpha-synuclein June 16th, 11AM

Katy Wellen, PhD – Perelman School of Medicine, University of Pennsylvania
Metabolic signaling in pancreatic cancer June 24th, Noon

John Elrod, PhD - Aging + Cardiovascular Discovery Center, Lewis Katz School of Medicine at Temple University
New Discoveries in mitochondrial metabolism – Ca2+-dependent metabolon formation Sept 9th, 11AM

Luca Pellegrini, PhD - Department of Biochem, Microbio, Immuno, University of Ottawa, Canada
Mitochondria Wars, Episode VII: The Intermembrane Zone Awakens Nov 14th, 11AM

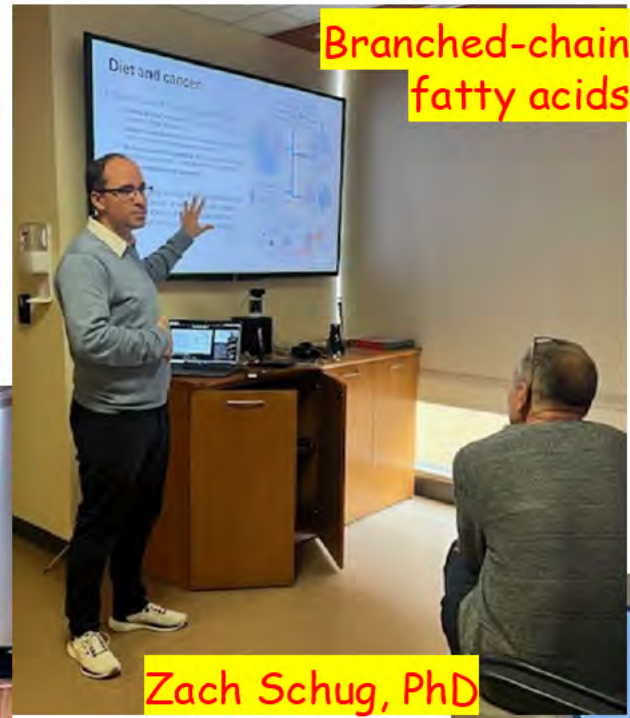
Zach Schug, PhD - Department of Pharmacology, Physiology, and Cancer Biology, TJU
Branched-chain fatty acid metabolism in health and disease Nov 25th, 11AM

Arup Das, PhD - Indiana School of Medicine
Pharmacologic Reprogramming of Mitochondrial Quality Control Mechanisms Promotes Retinal Ganglion Cell Differentiation and Neuroprotection Dec 11th, 11AM

Views of MitoCircle 2025


Atan Gross, PhD

BID, MTCH2 and alpha-synuclein



Branched-chain fatty acids

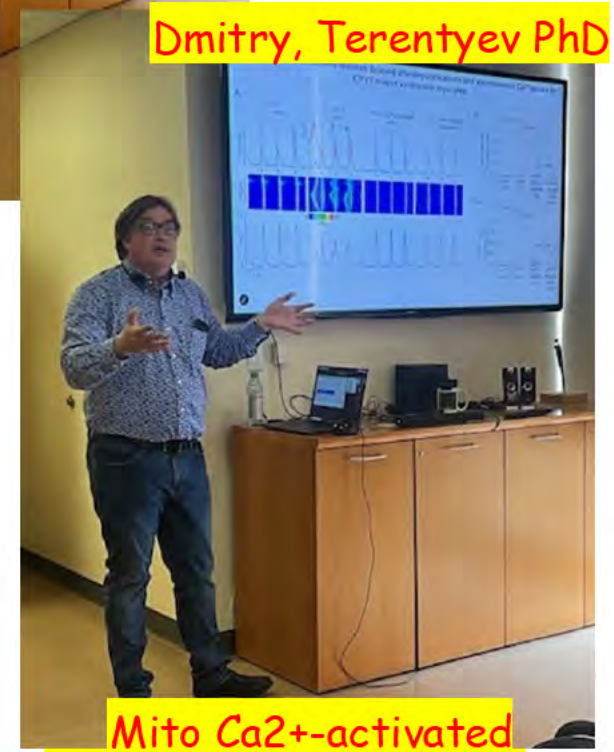
Zach Schug, PhD

Arup Das, PhD

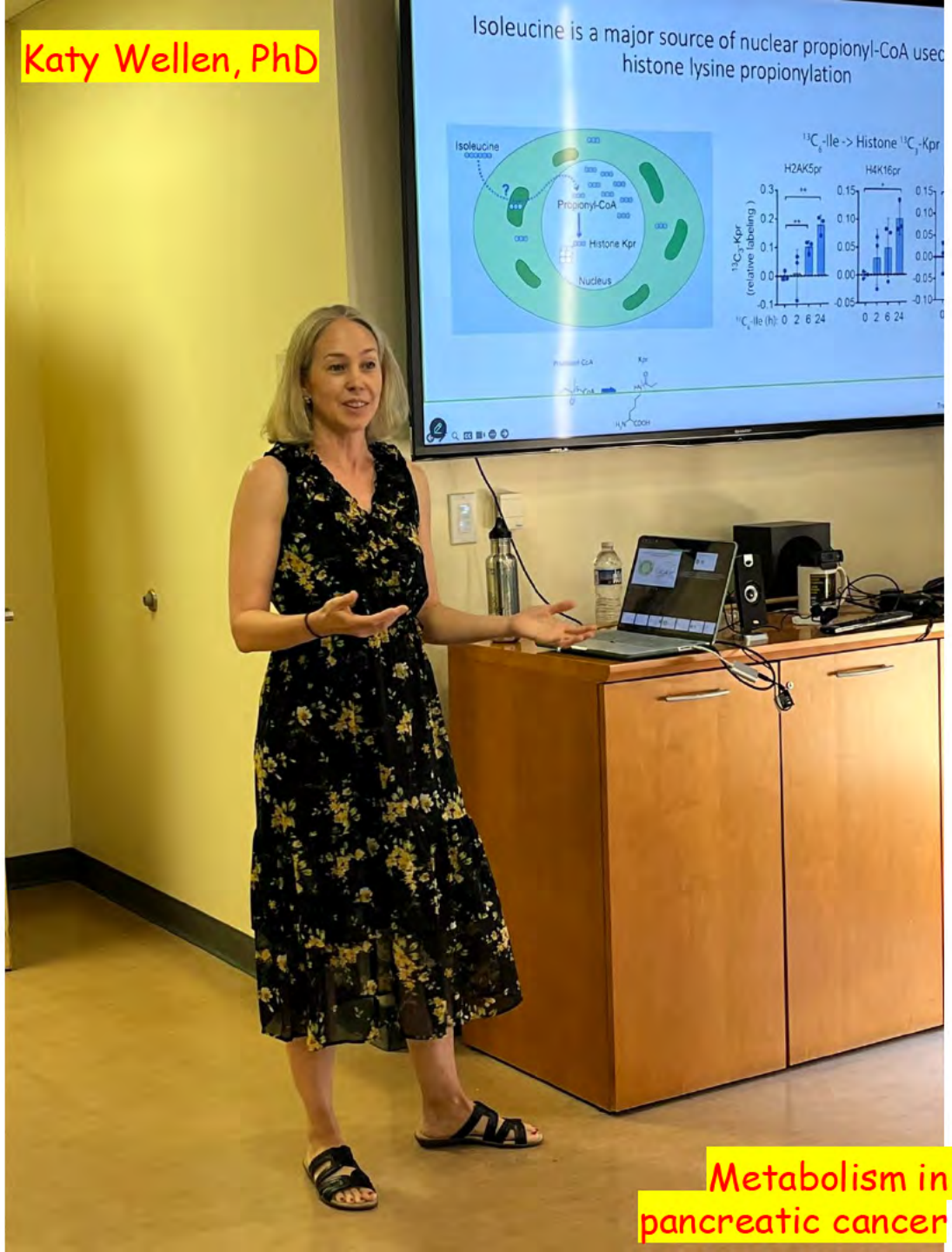
Protecting Retinal Ganglion Cells


Luca Pellegrini, PhD

The Intermembrane Zone Awakens


Dmitry, Terentyev PhD

Mito Ca2+-activated K+ channels in the heart


Katy Wellen, PhD
Isoleucine is a major source of nuclear propionyl-CoA used
histone lysine propionylation
Isoleucine
Propionyl-CoA
Histone Kpr
Nucleus
H2AK5pr
H4K16pr
Metabolism in
pancreatic cancer


John Elrod, PhD
Phosphate as the
energetic currency of life
Mito Ca2+ metabolon

Seifert Lab @ MitoCar 2025 highlights

Big efforts for the revision of the PiC Ca^{2+} study

Finishing up a large study on FA

PiC ER stress-ISR MSc poster

Saying goodbye to Victoria

Birthday goodies

Some highlights:

Welcome to Sruthi!

Lots of learning about Ca2+ by Brittney, Mehak, Zach, Sruthi, and great collab with Victor and Gyuri H! Revision soon to be submitted

Ongoing FRDA collab with clinical partners at UPenn and Australia: stayed tuned for an exciting study - Brittney's first 1st au and Sourav first pub in the lab!
Also: Collab with UPenn clinicians: revised ms at The Lancet

Diving deeper into stress responses – ms in prep, Amanda's first 1st au study

Goodbye to Victoria and Amanda – wishing all the best! Victoria works in a Vet clinic and Amanda is applying to vet school

Erin was promoted to Professor and voted to be co-chair of the 2029 Mito Gordon Conference

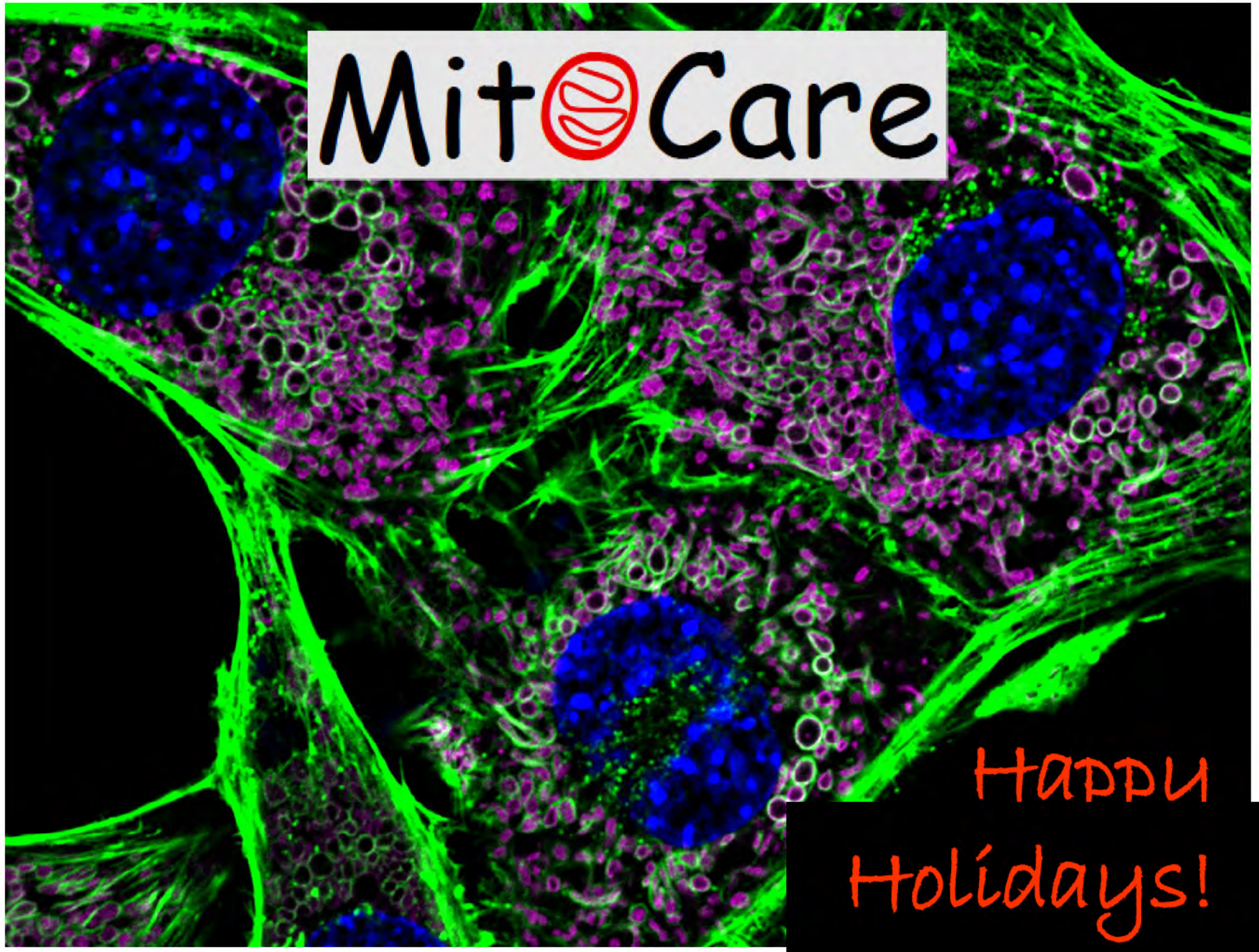
Speaker opportunities at Mito GRC, Houston Muscle Meeting, IUPS Muscle Satellite Meeting in Frankfurt, FRDA @ Broad Inst

Publications: PMID 39567836, 39617267, 40362619

Mito Circle Journal Club 2025 Summary

Date	Name	Paper
January 27	Gyuri Hajnoczky	**Periodic ER-plasma membrane junctions support long-range Ca^{2+} signal integration in dendrites.** Benedetti et al. (Lippincott-Schwartz lab) 2025 *Cell*
February 10	Marco Tigano	**Cyclophilin D plays a critical role in the survival of senescent cells.** Protasoni et al. (Serrano lab) 2024 *EMBO J*
February 24	Dave Booth, Erin, Gyuri H, Shey	**Biophysical Society Meting -- briefings**
March 10	Samieh Asadian	**Mitochondrial DNA replication stress triggers a pro-inflammatory endosomal pathway of nucleoid disposal.** Newman et al. (Manor/Shadel labs) 2024 *Nat Cell Biol*
March 31	Many People	**Gordon Research Conference on Mitochondria in Health and Disease – Briefings, Pt1**
April 21	Many People	**Gordon Research Conference on Mitochondria in Health and Disease – Briefings, Pt2**
April 28	Erin Seifert	**-Preserved respiratory chain capacity and physiology in mice with profoundly reduced levels of mitochondrial respirasomes** Milenkovic et al. (N-G Larsson lab) 2023 *Cell Metab* **-Two independent respiratory chains adapt OXPHOS performance to glycolytic switch** Fernández-Vizarra et al. (Ugalde lab) 2022 *Cell Metab*
June 2	Arijita Ghosh	**ER-mitochondria contacts mediate lipid radical transfer via RMDN3/PTPIP51 phosphorylation to reduce mitochondrial oxidative stress.** Shiiba et al. (Yanagi lab) 2025 *Nat Commun*
June 23	Chenxiao Yu	**Spatial analysis of mitochondrial gene expression reveals dynamic translation hubs and remodeling in stress.** Begeman et al. (S Lewis lab) 2025 *Sci Adv*
September 8	Davide Pantaleoni	**Mutant p53 affects the mitochondrial proteome, promoting mitochondrial fragmentation and OXPHOS in pancreatic ductal adenocarcinoma cells.** Poles et al. 2025 *FEBS J*
September 22	Ben Cartes S	**Pearling Drives Mitochondrial DNA Nucleoid Distribution.** Landoni et al. (S Manley lab) 2024 *BioRxiv*
October 6	Victor Hugo SV	**Structure and mechanism of the mitochondrial calcium transporter NCLX.** Fan et al. (Tsai/Feng labs) 2025 *Nature.*
November 3	Maite Zavala	**PERK-ATAD3A interaction provides a subcellular safe haven for protein synthesis during ER stress.** Brar et al. (Malucci lab) 2024 *Science*
December 22	Gyuri Csordas	**Mitochondria-derived nuclear ATP surge protects against confinement-induced proliferation defects.** Ghose et al. (V Ruprecht lab) 2025. *Nat Commun*
	STATS	**Faculty – 4; Senior Postdoc/Res.Associates – 3; Junior Postdoc (<2 years) – 3; TJU Student – 0 ☹; Visiting student – 1**

MitoCare Crew in Late 2025


MitoCare
Happy
Holidays!