Peering into the mitochondria to reveal cellular stress and disease

Danielle Grotjahn
Assistant Professor

Scripps Research
Integrative Structural
and Computational Biology

Photo Credit: Michael Jach

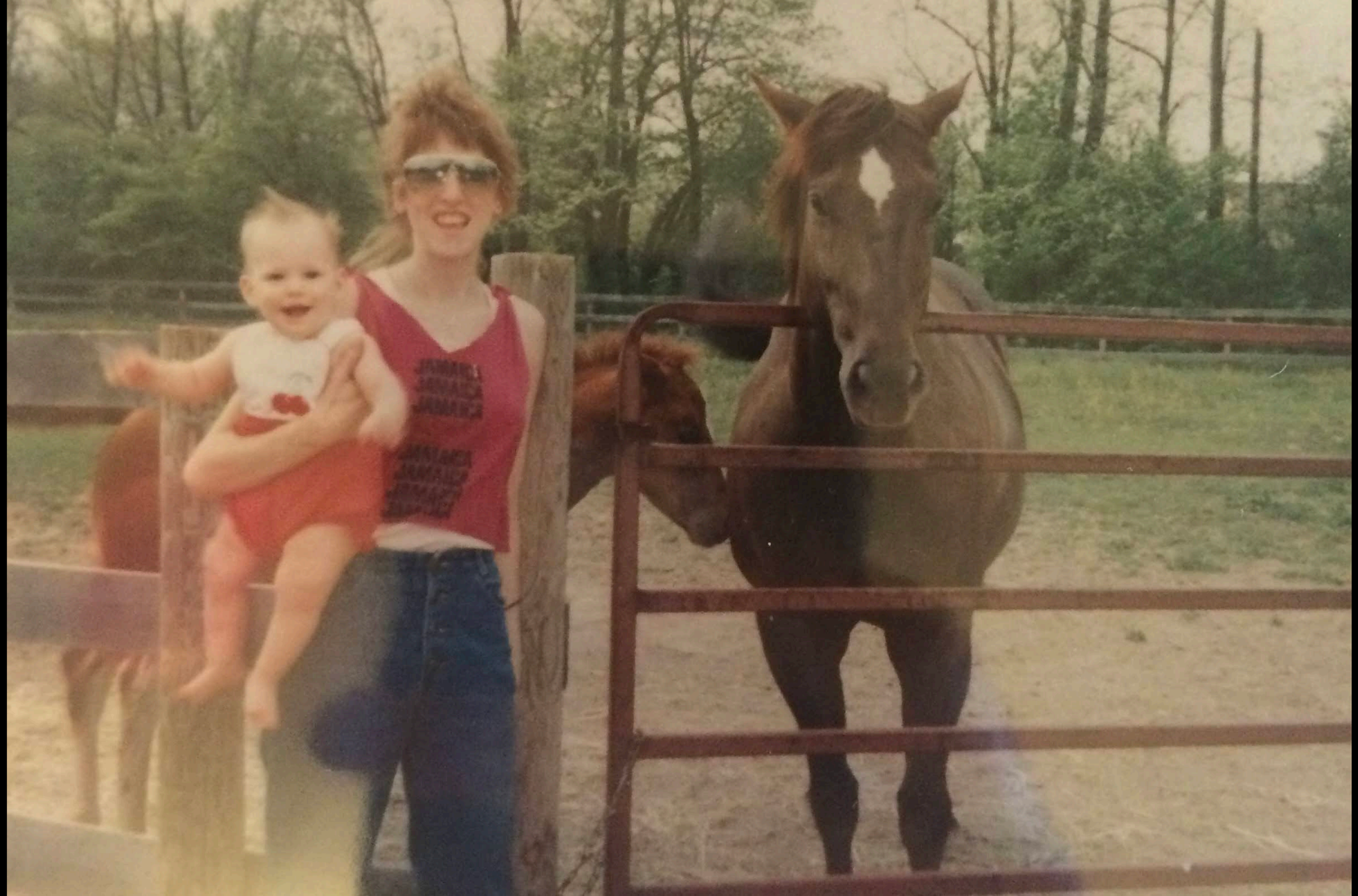

Photo Credit: Michael Jach

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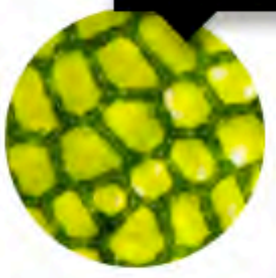
Omano JuniorScope

Complete Kit

6 years +

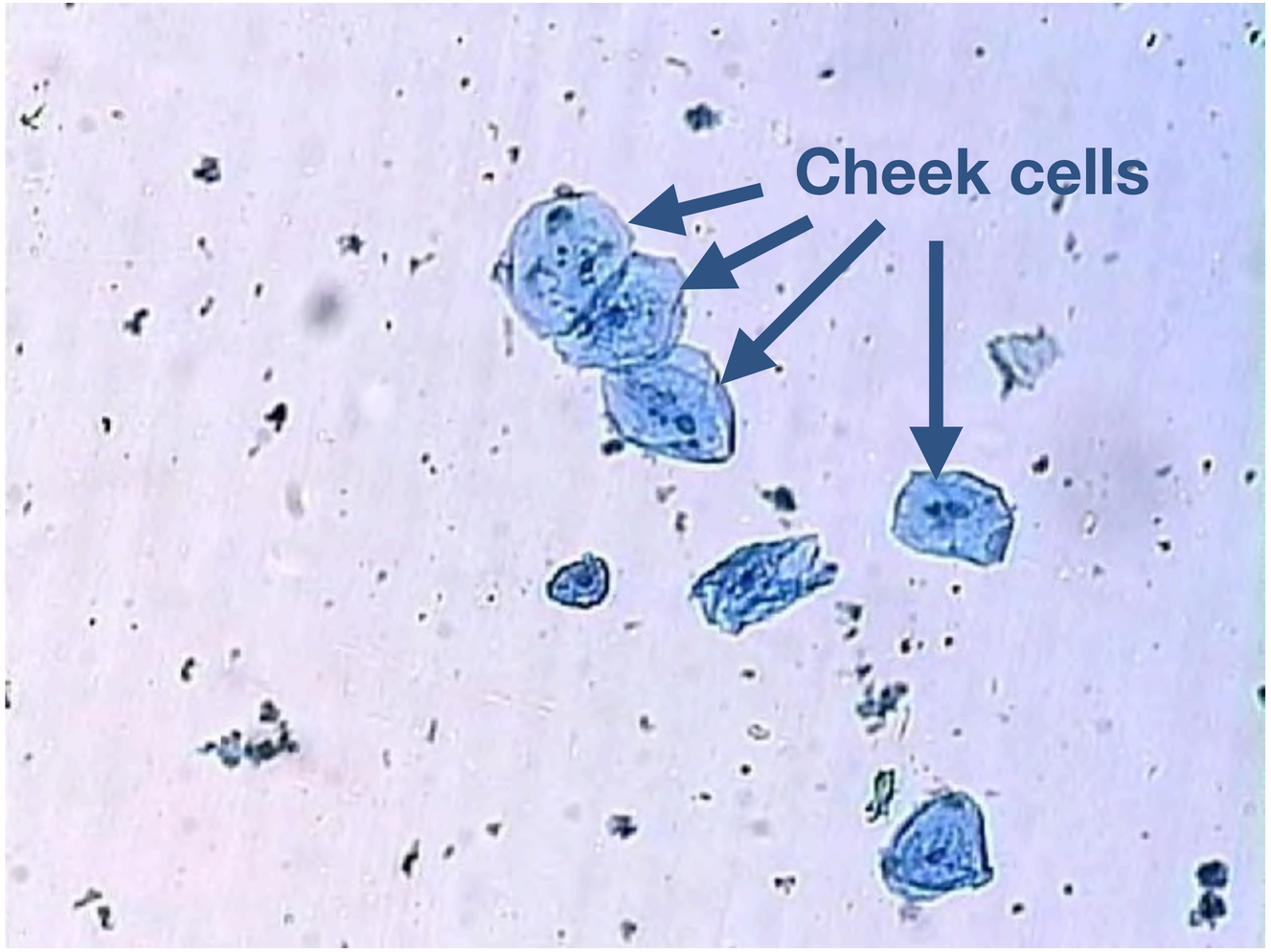
Low Power



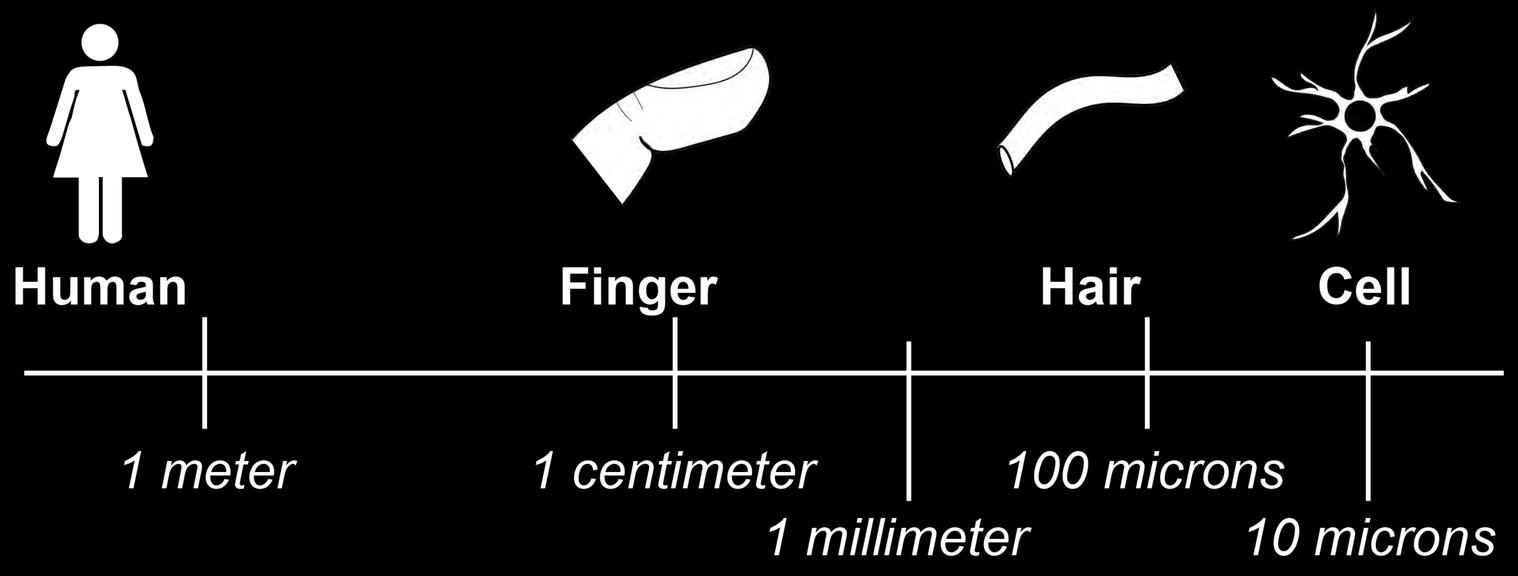
High Power

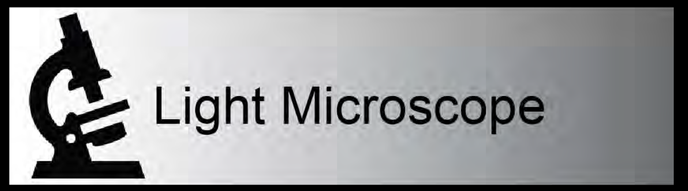
View plants, insects, blood, DNA, germs, and more


Omano JuniorScope
Complete Kit
6 years +
Low Power
High Power
View plants, insects, blood, DNA, germs, and more
1. Microscope Basics
2. Crime Scene Investigation
3. Plants
4. The Human Body
5. Insects
JUNIOR SCOPE
omano
THE ULTIMATE MICROSCOPE
FOR KIDS


Cheek cells

Visualizing Life Across Scales





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Growing the future

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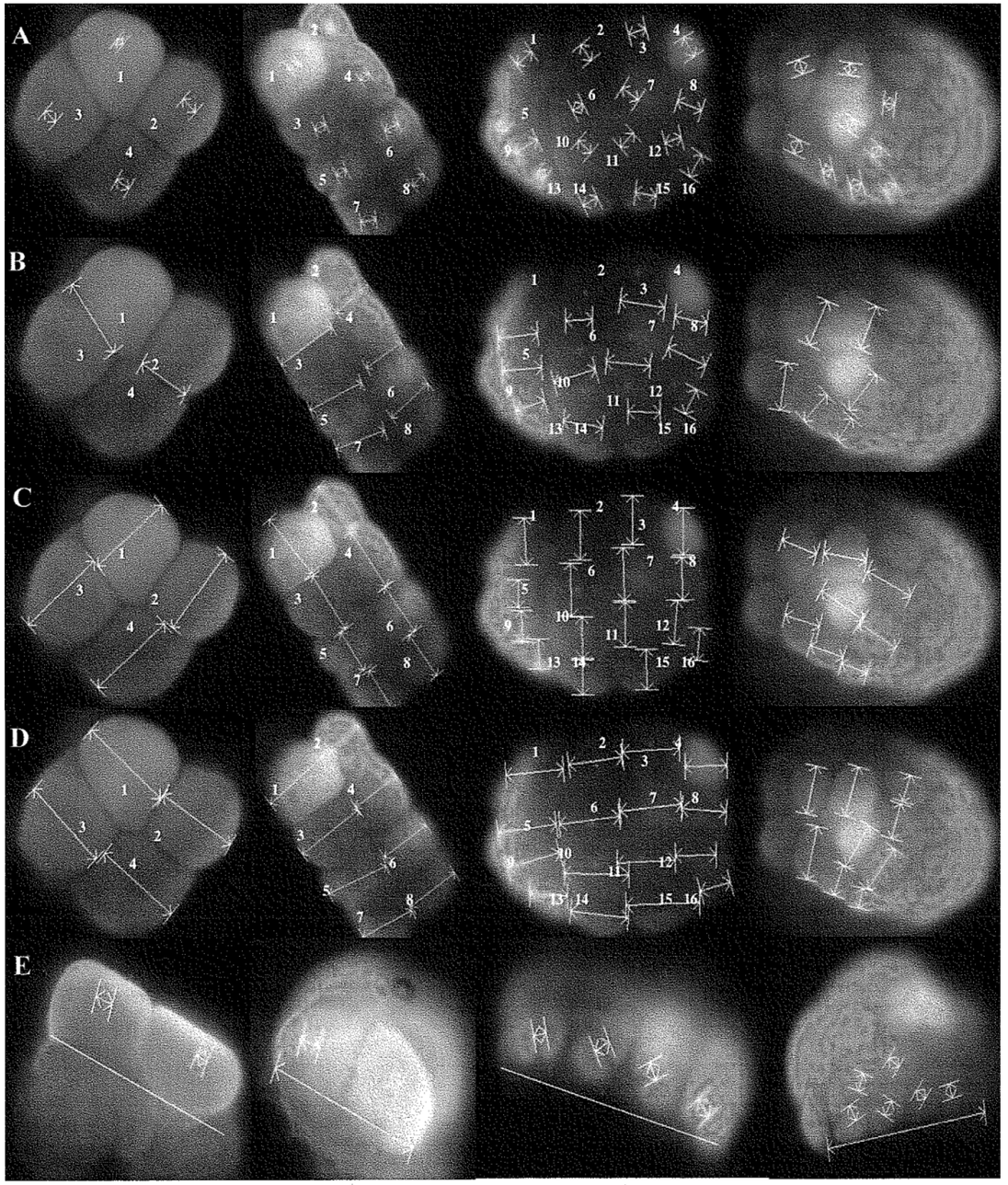

Figure 1 Images of measurements taken of 4, 8, 16 and 32-cell embryos using OpenLab measurement tool. Measurements are organized by: A) spindle axis angle B) furrow axis angle C) short axis length, D) long axis length and E) basal plane angle and spindle axis angle.

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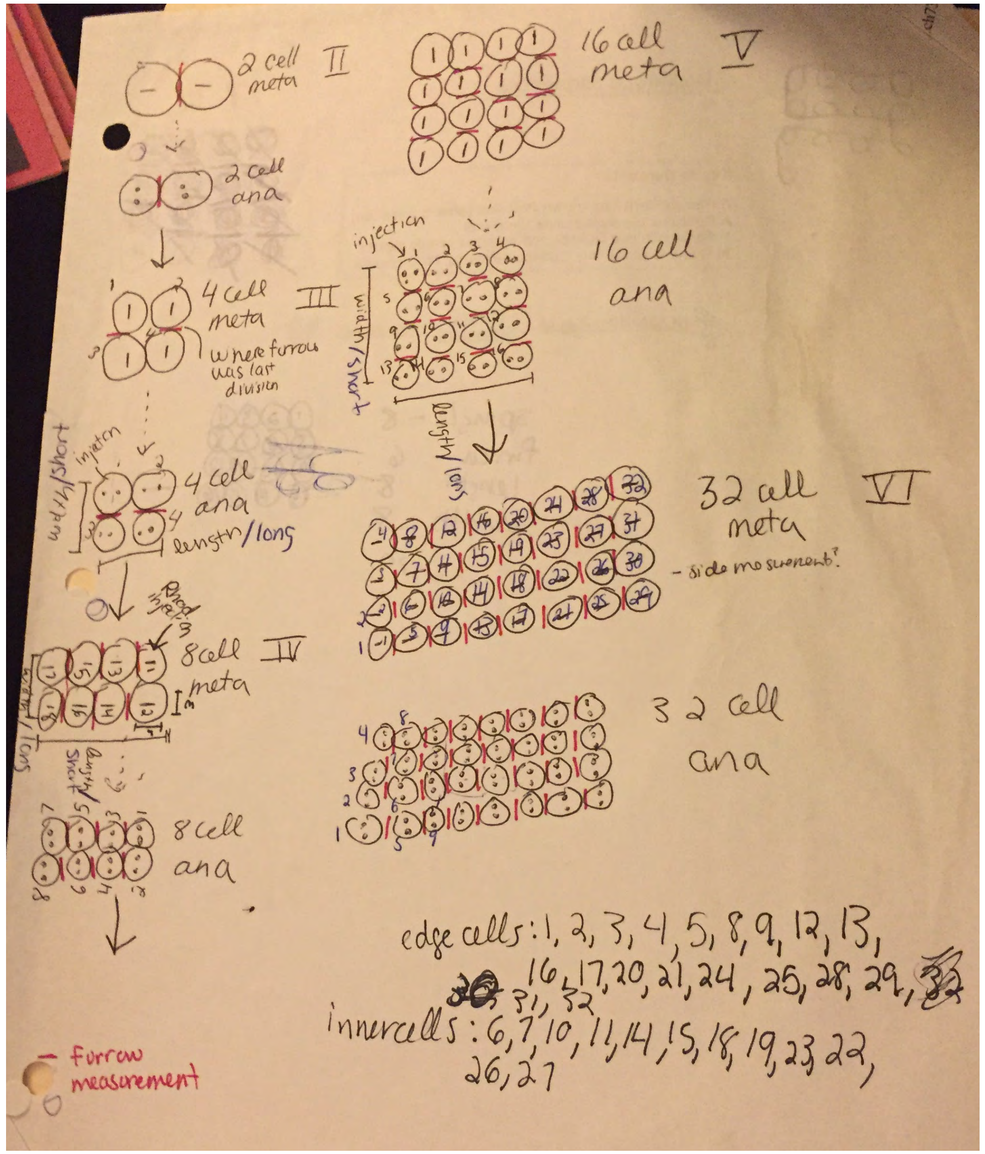

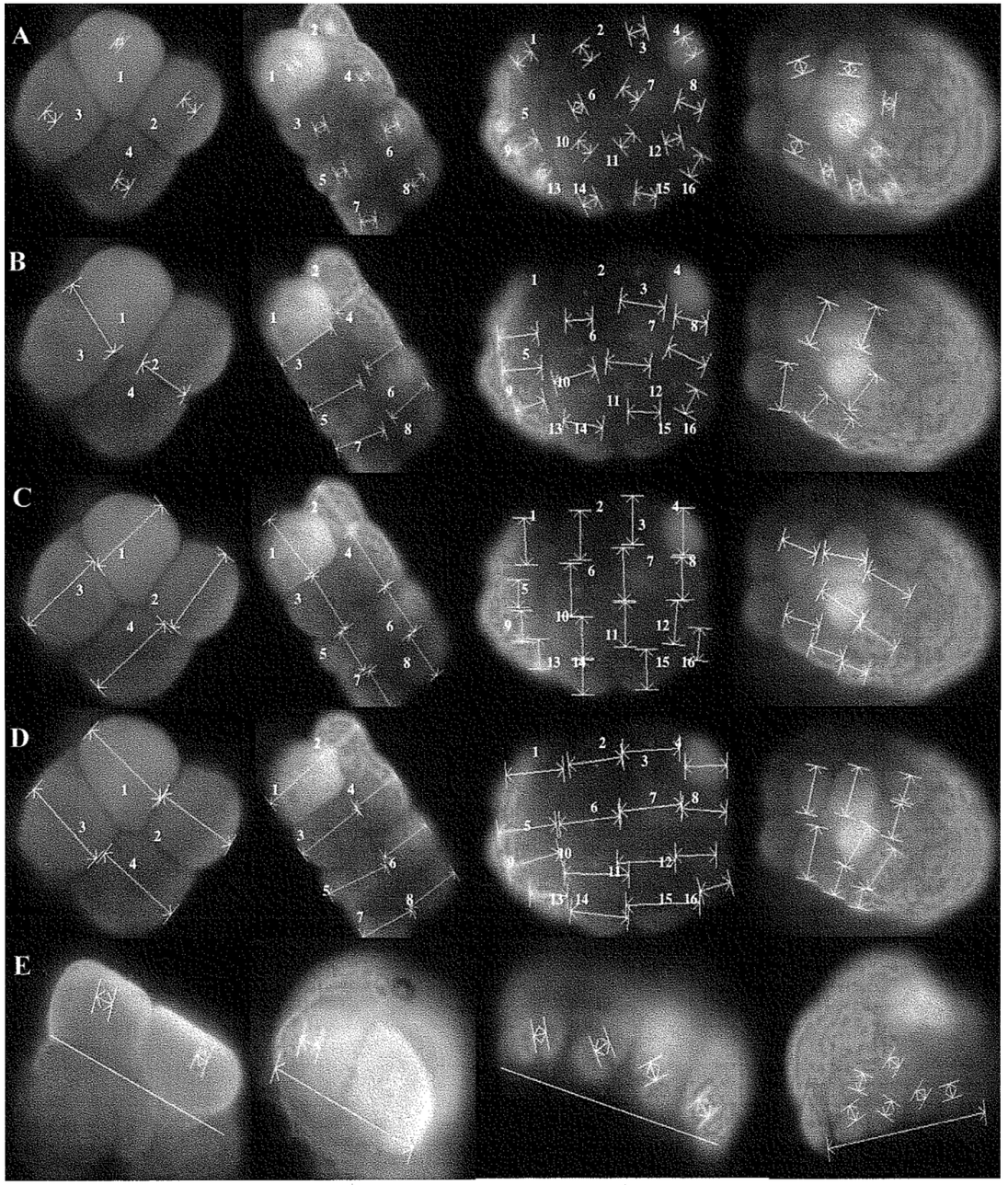

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Growing the future

Examining cell shape as the mechanism for furrow positioning in the early Zebrafish (*Danio rerio*) embryo

Through previous studies, it has been found that Zebrafish embryos show a predictable pattern of cell division consisting of the spindle apparatus always aligning perpendicular to its orientation in the previous cell stage. Although a predictable pattern for cell division has been determined, the exact mechanisms for the spindle positioning are unknown. One proposed determinant of spindle alignment is cell shape. This study aims to quantitatively analyze certain inherit characteristics of cells in early Zebrafish embryos to observe any relationships or trends that may occur. Patterns observed in these quantitative measurements may eventually help to formulate a model that predicts this pattern of cell division. The data shows a relationship between cell geometry and the orientation of the spindle axis by demonstrating that a greater difference between the long and short axis lengths and a ratio of these lengths further from 1.0 corresponds to a smaller angle difference between the spindle and furrow axis.

Danielle Grotjahn / Biology ? Spanish
Author Name/Major

Author Signature

Francisco Pelegri / Genetics
Mentor Name/Department

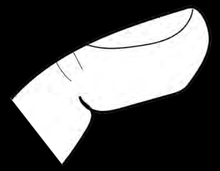
Mentor Signature

12/17/10
Date

Visualizing Life Across Scales

Human

1 meter



Finger

1 centimeter

1 millimeter

Hair

100 microns

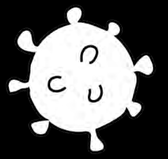
Cell

10 microns

Mitochondria

1 micron

100 nanometers



Virus

Protein

10 nanometers

DNA

1 nanometer

Eye

Light Microscope

Electron Microscope

“The Scripps Research Institute Hosts Burgeoning Electron Microscopy Workshop”

December 10, 2012

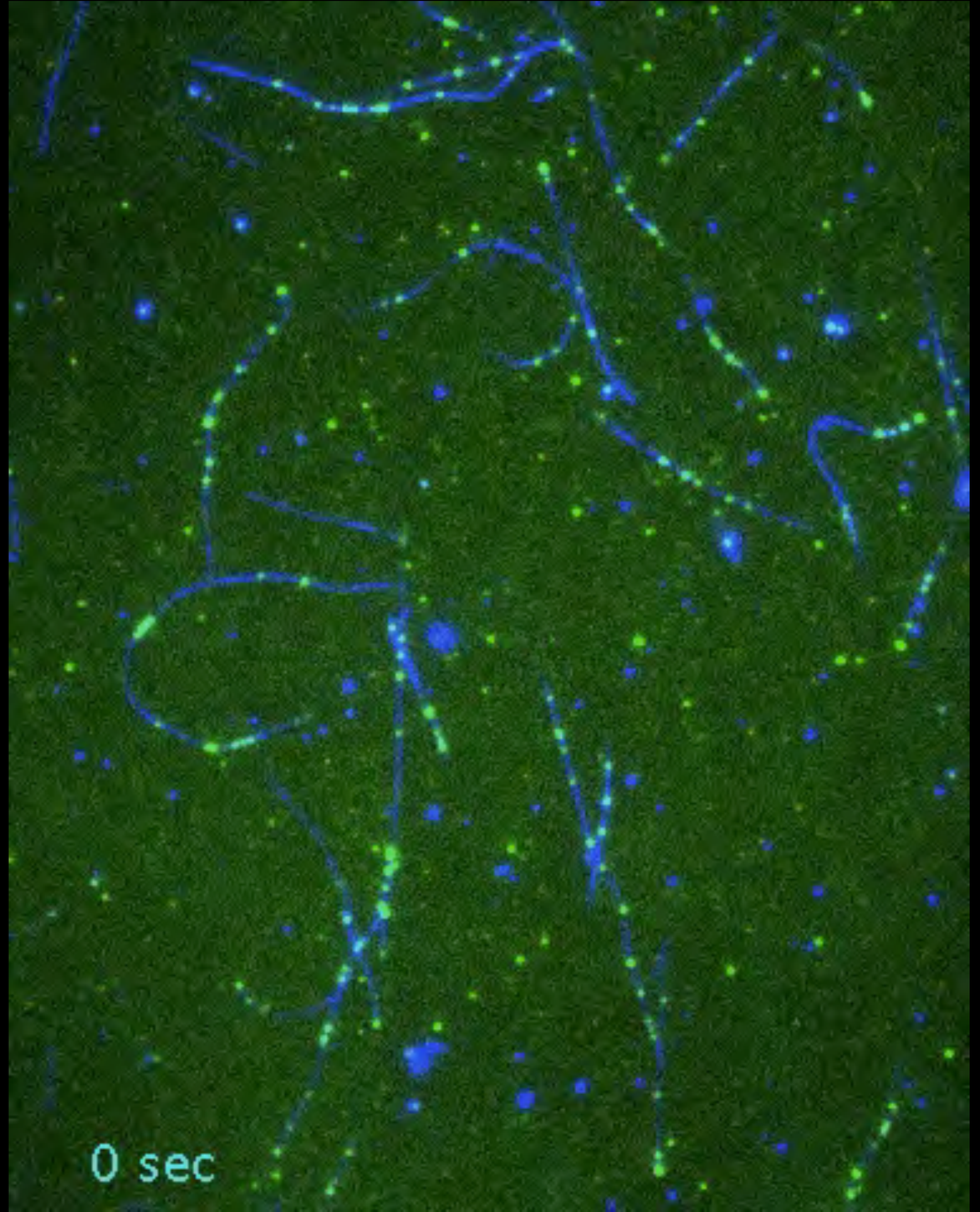
Established as a hands-on teaching conference in 2003, a biennial workshop on molecular electron microscopy at The Scripps Research Institute (TSRI) has evolved into an intense, high-level forum on cutting-edge issues, distinguished by a spirit of generosity and collegiality among its expert lecturers and participants.

Now considered one of the most important and useful meetings in the rapidly maturing field of molecular electron microscopy, each six-day workshop has been organized by Professors Bridget Carragher, Clint Potter and Ron Milligan under the auspices of the National Resource for Automated Molecular Microscopy (NRAMM).

Professors Clint Potter, Bridget Carragher and Ron Milligan

Professor Richard Henderson (MRC LMB)

Professors Bob Glaeser (UC-Berkeley) and David DeRosier (Brandeis University)



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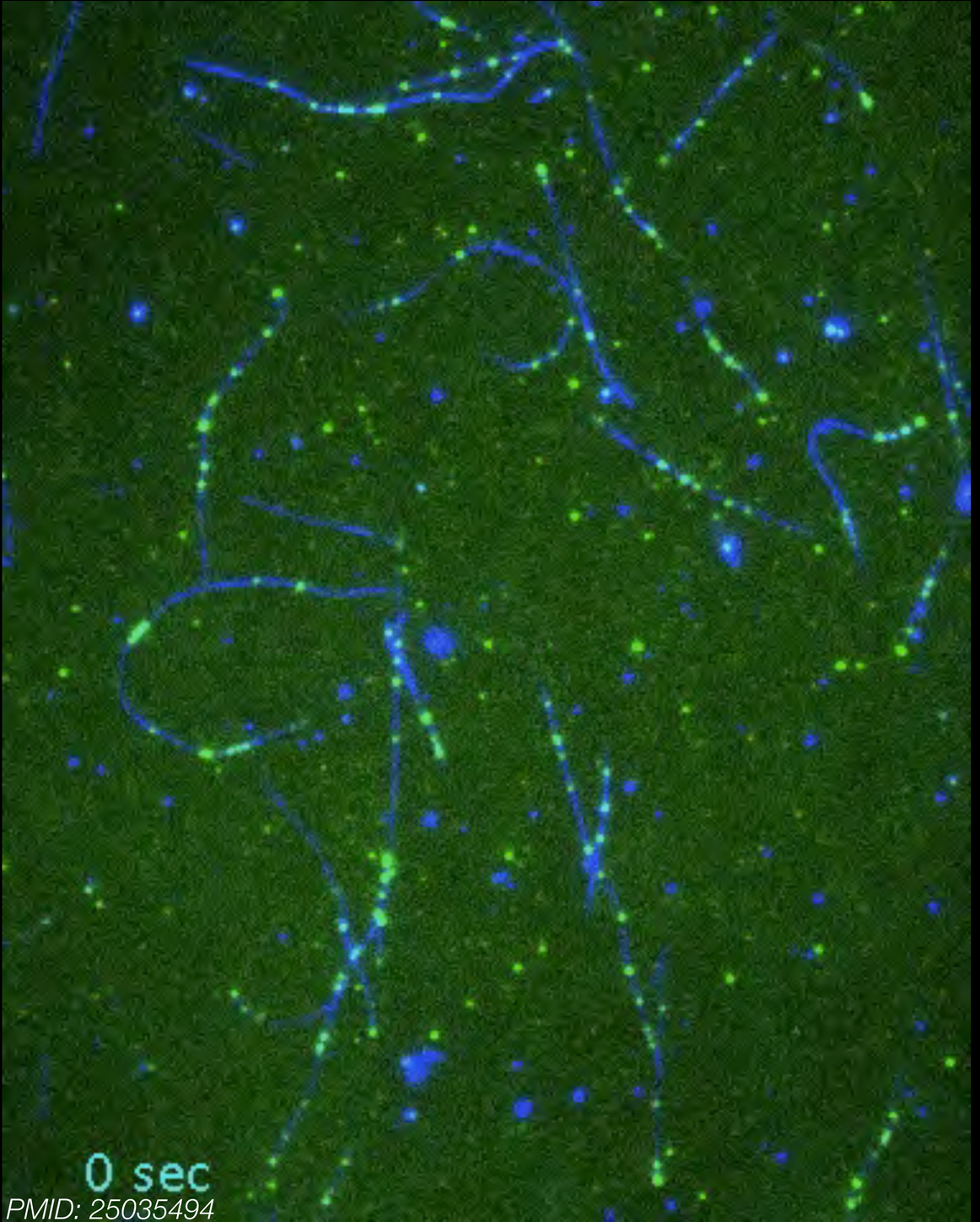

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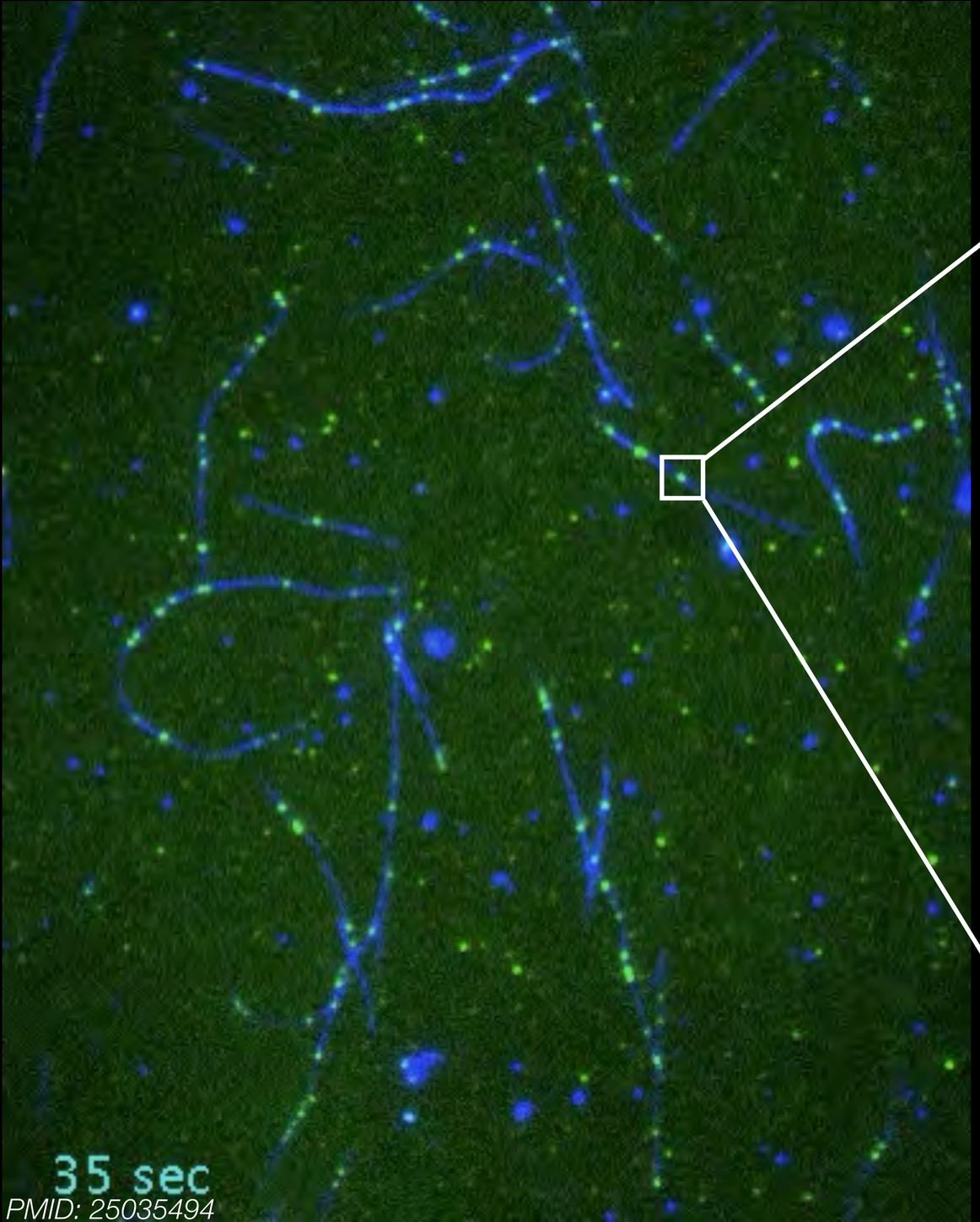
Dynein
The ‘train’ of the cell

Microtubules
The ‘train tracks’ of the cell



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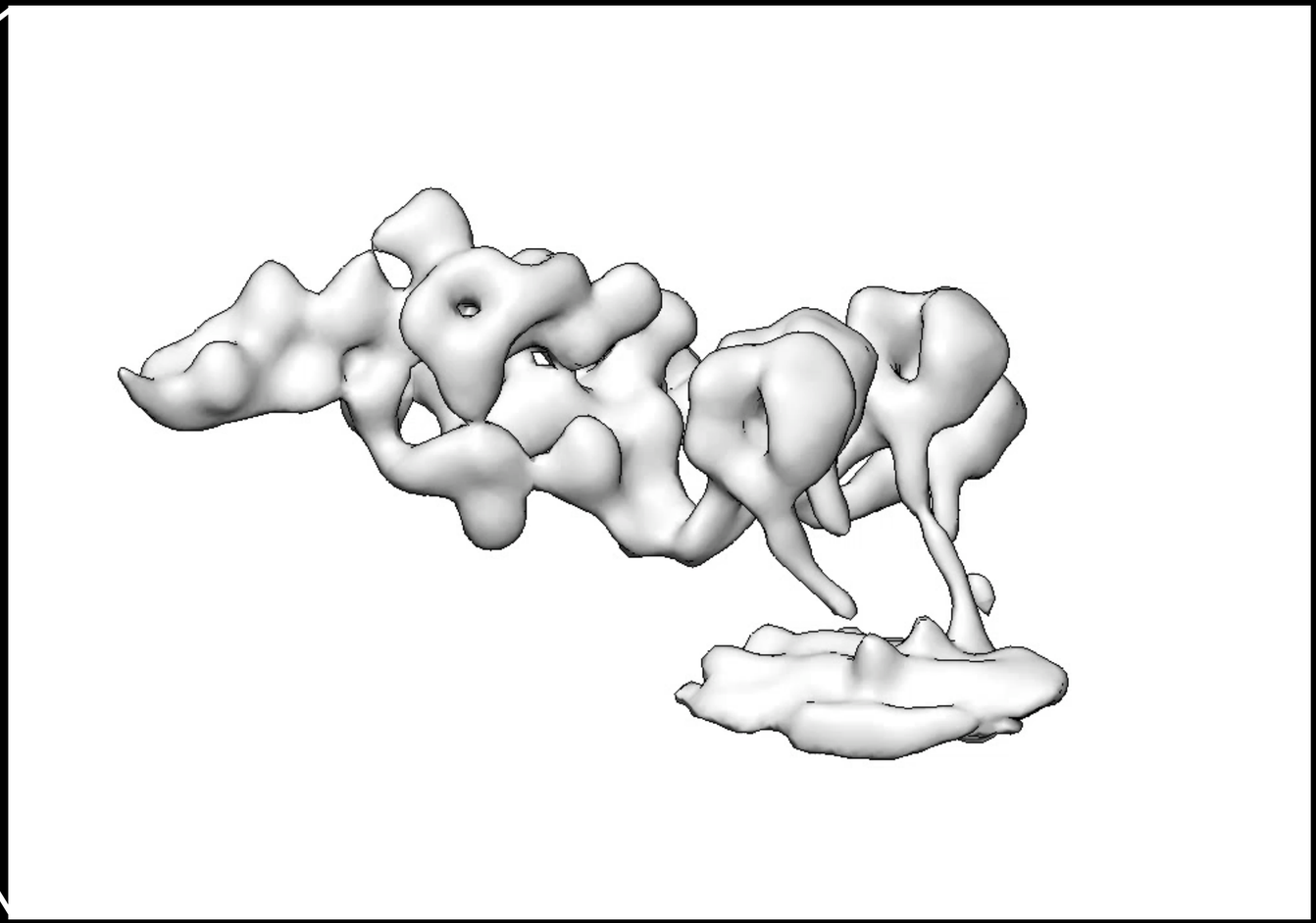

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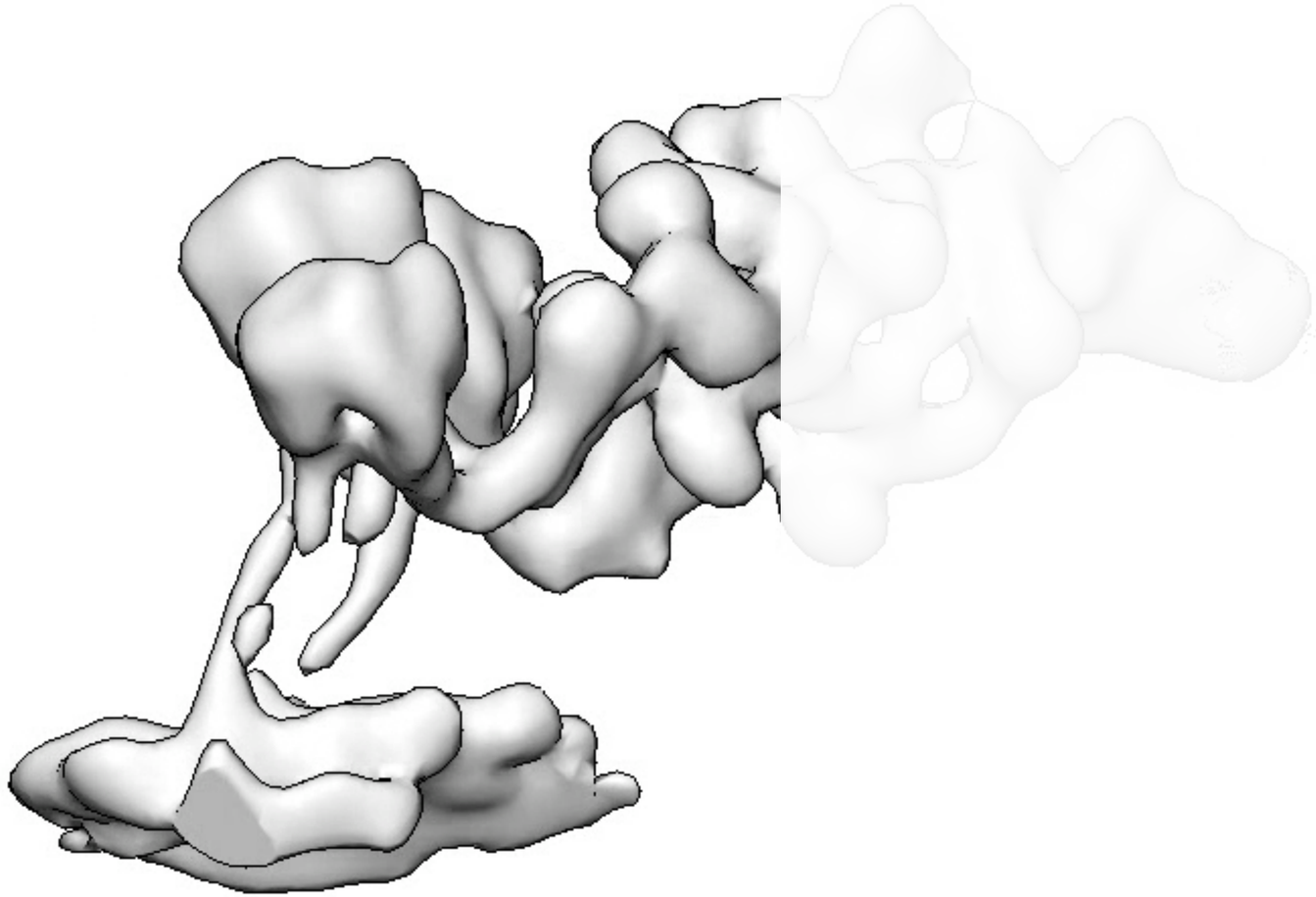

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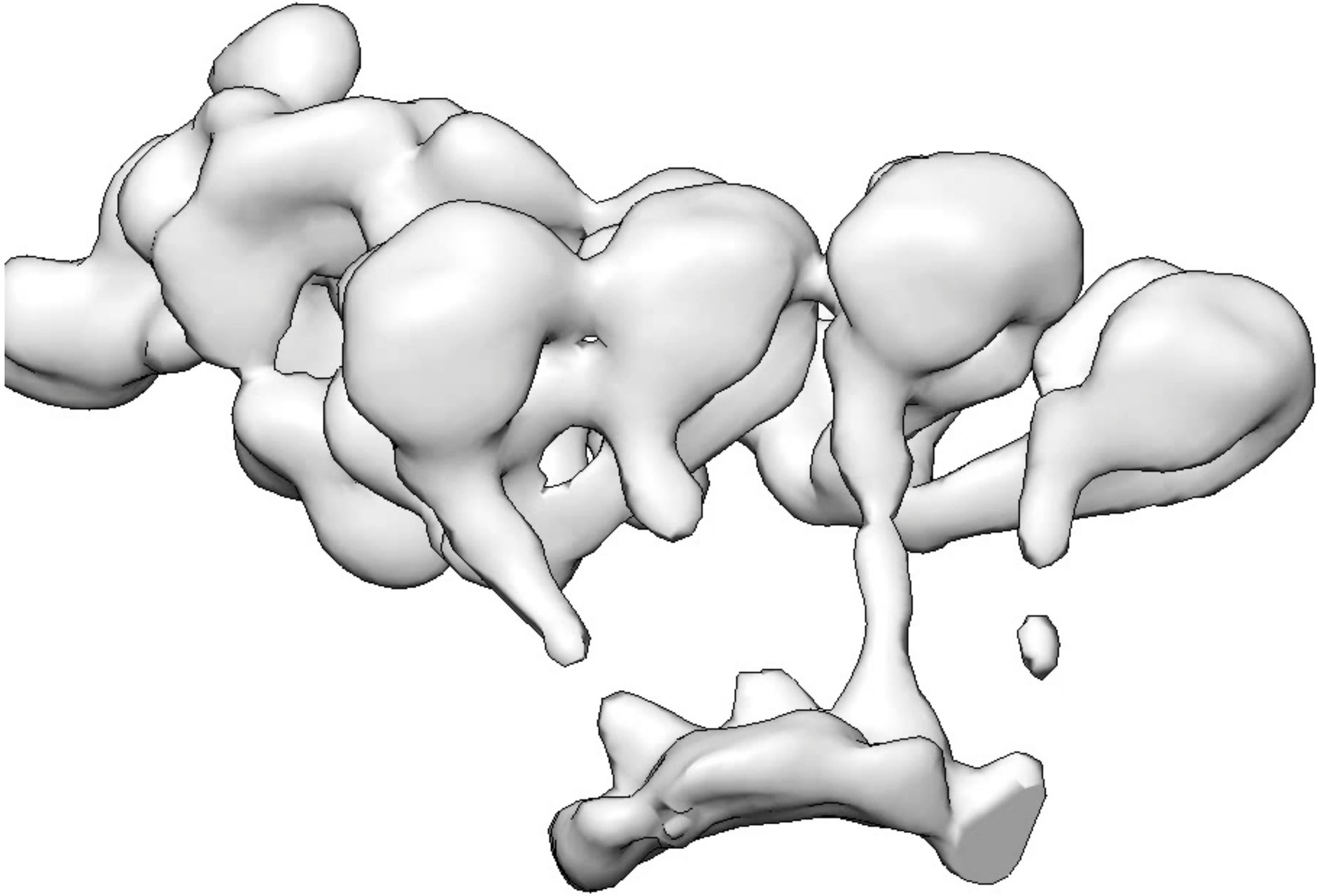

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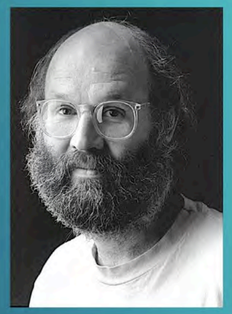
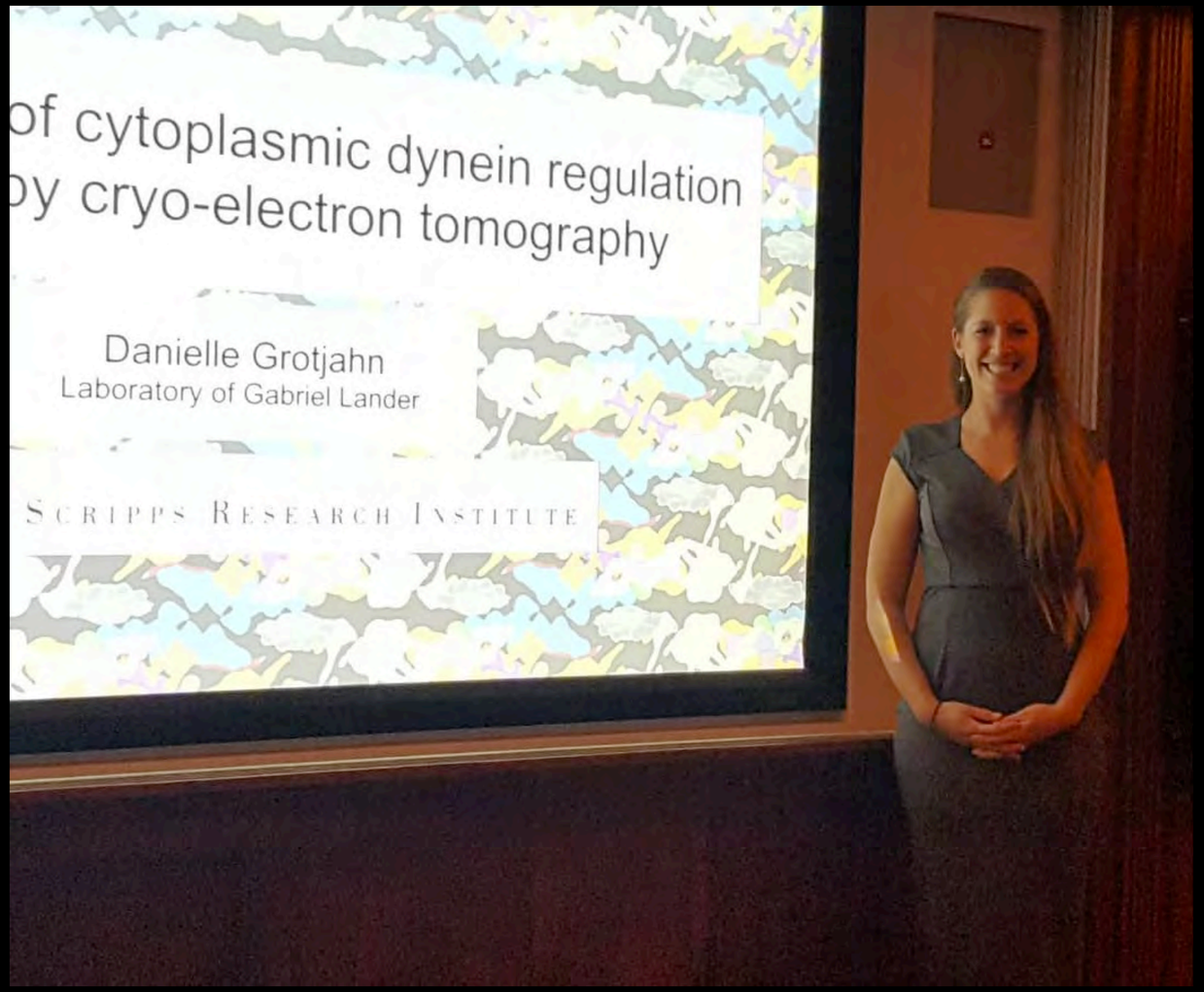
The Chariot Race from Ben-Hur (1959)



Harold M. Weintraub
Graduate Student Awards

"The Harold M. Weintraub Graduate Student Award recognizes outstanding achievement during graduate studies in biological sciences.
Fred Hutch established this annual award to honor the bold, creative, pioneering spirit embodied by Hal Weintraub."


of cytoplasmic dynein regulation
by cryo-electron tomography
Danielle Grotjahn
Laboratory of Gabriel Lander
Scripps Research Institute

The Scripps Fellows Program

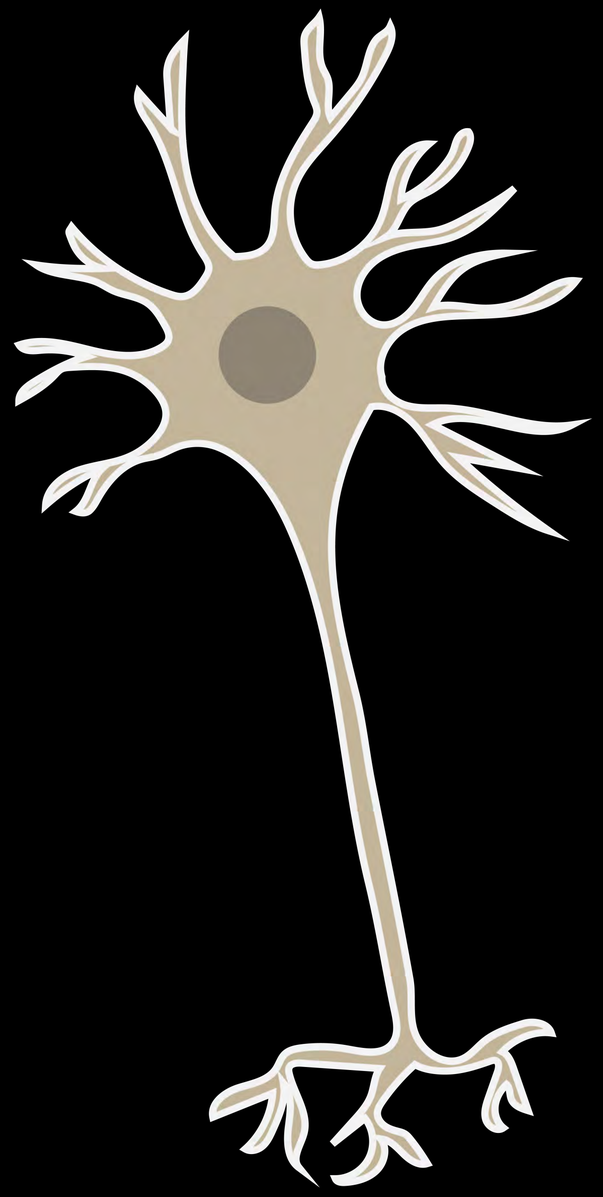
Extraordinary scientists launching impactful careers

November 07, 2018

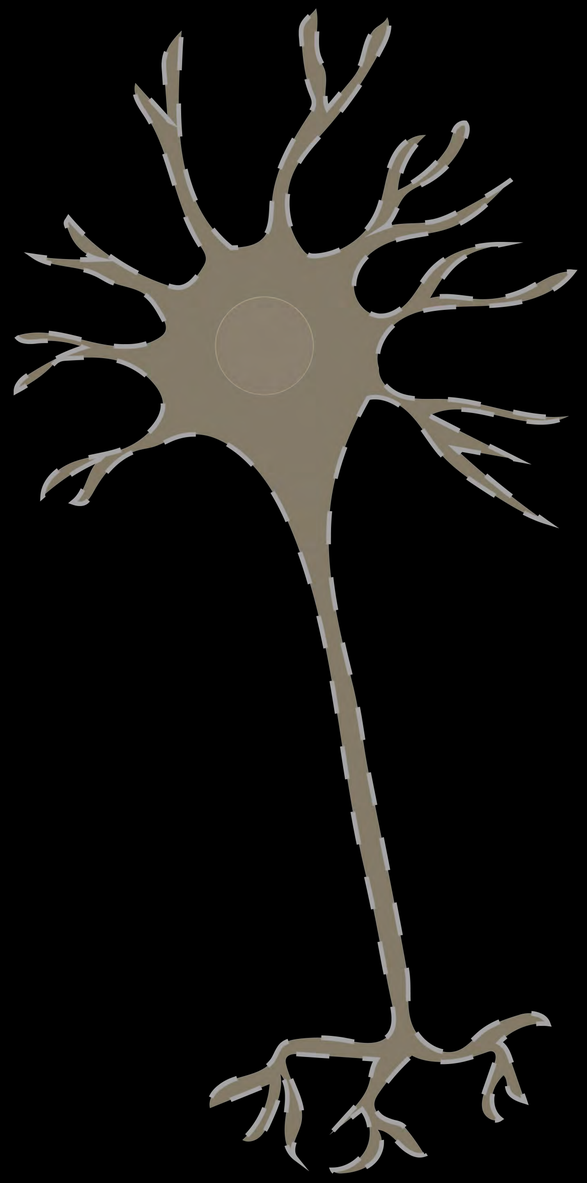
Scripps Fellows Danielle Grotjahn, PhD, Michael Bollong, PhD, and Michael Erb, PhD.

Photo Credit: Michael Jach

Photo Credit: Michael Jach



Neurodegeneration

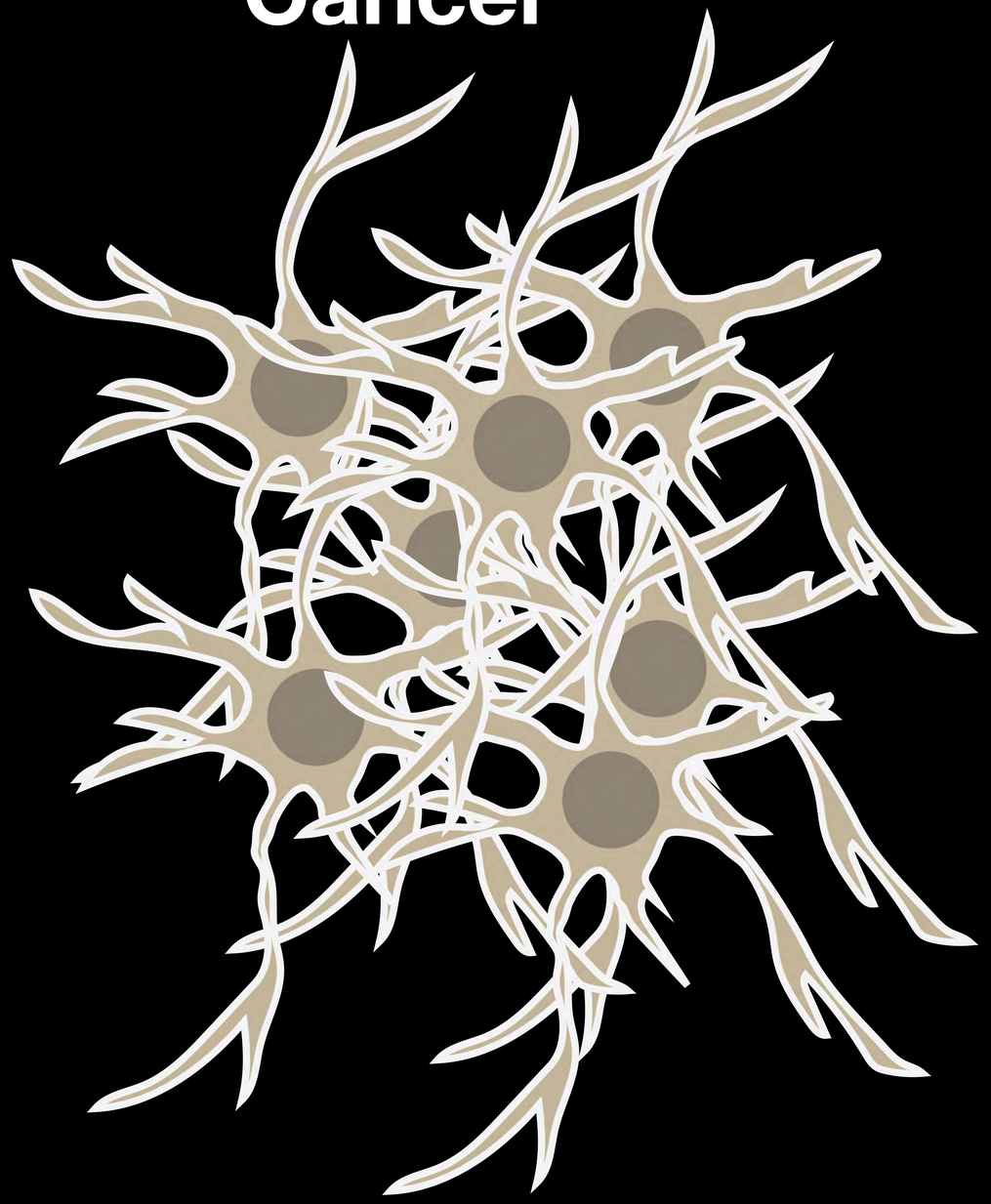


Progressive loss of cells

Neurodegeneration

Progressive loss of cells

Cancer

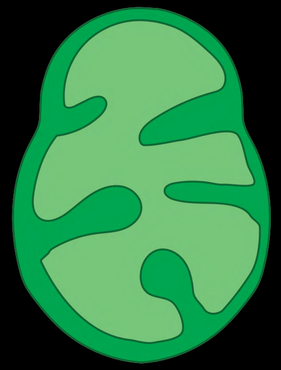


Uncontrolled growth of cells

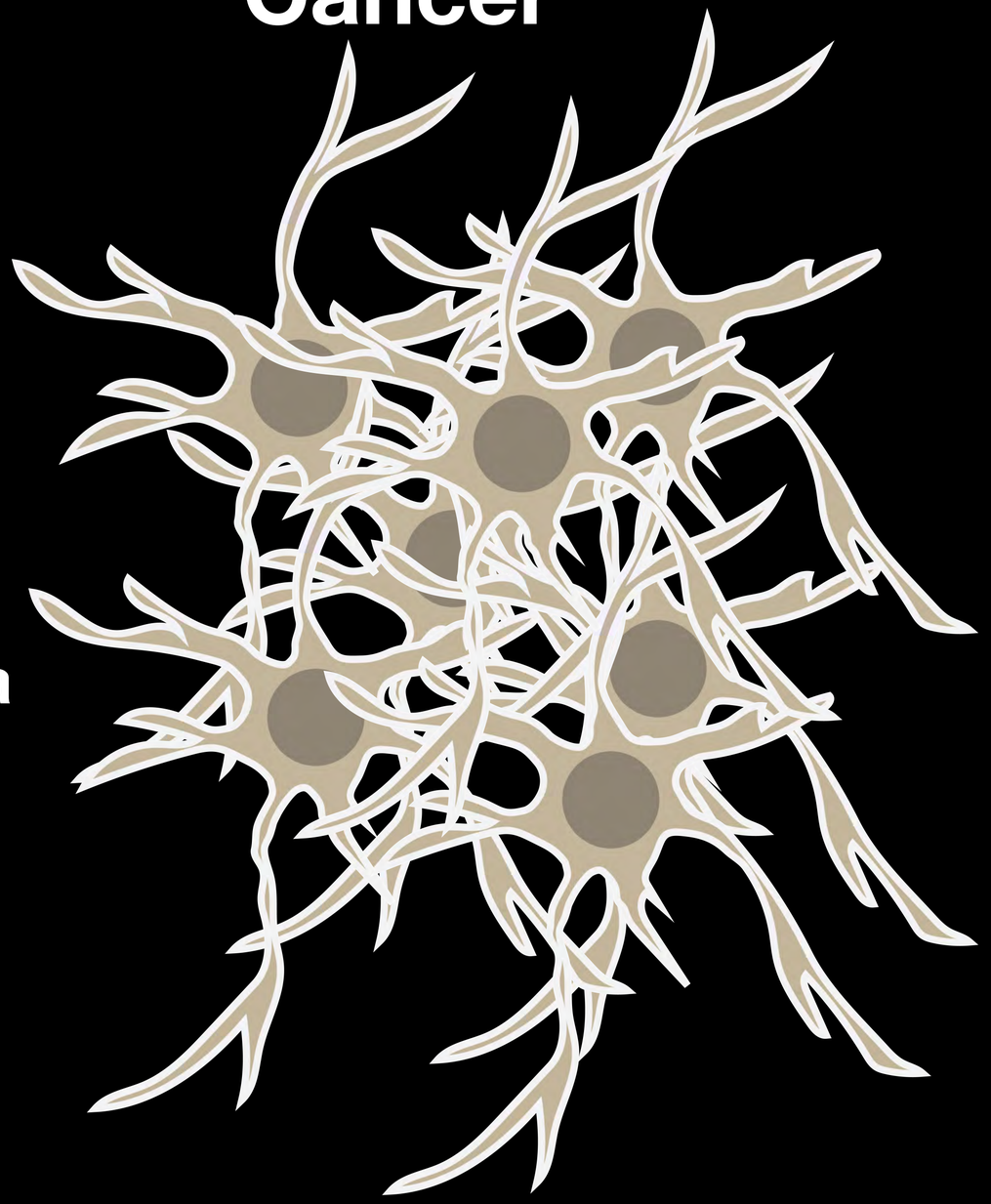
Neurodegeneration

Progressive loss of cells

Mitochondria

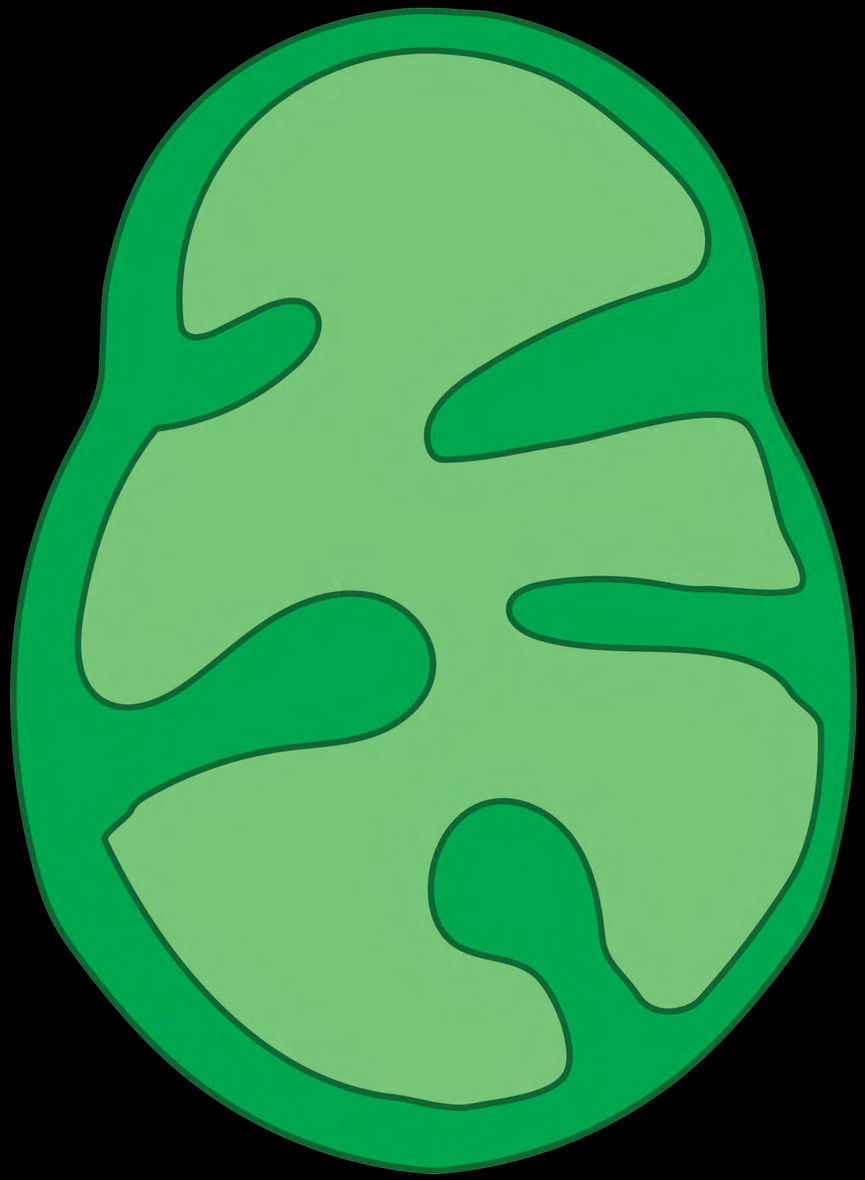


Cancer

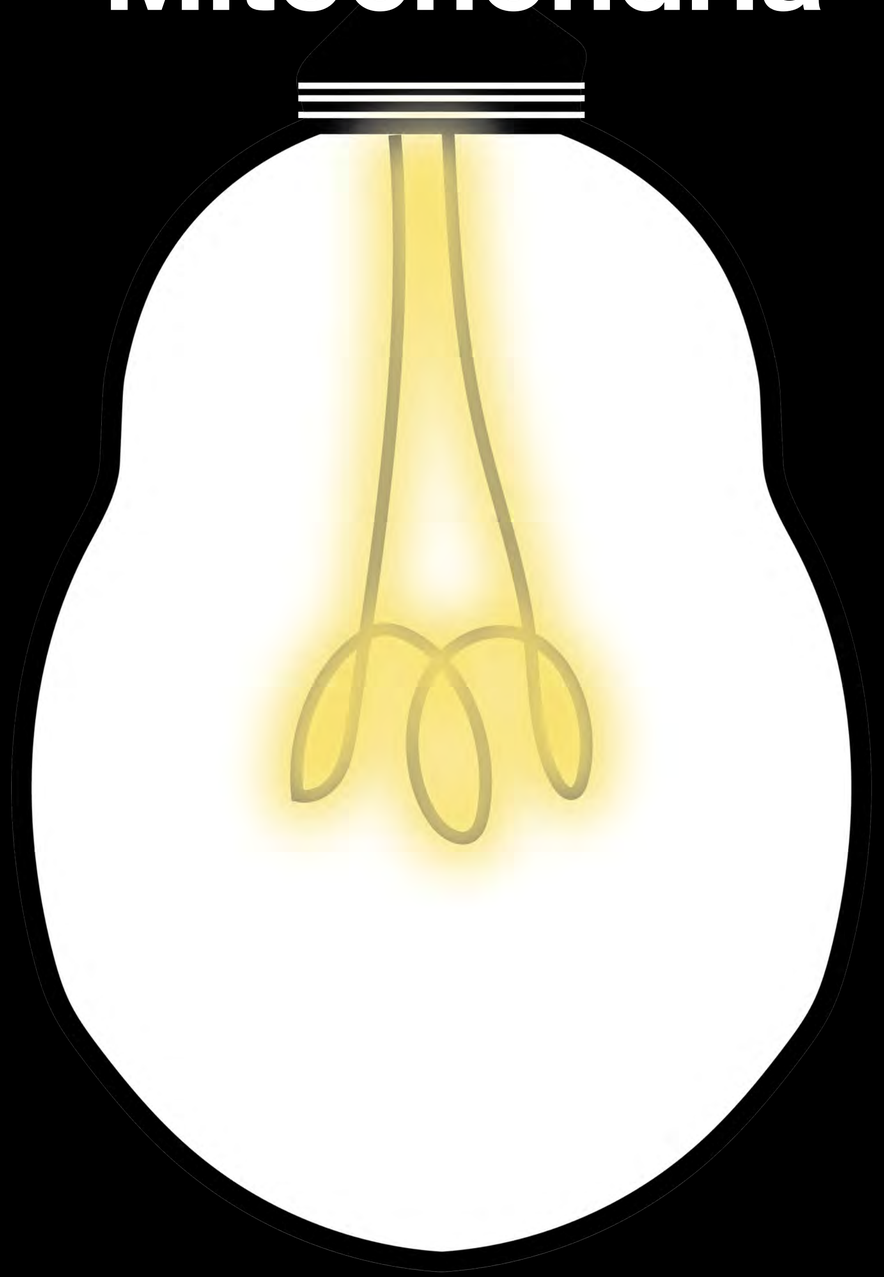


Uncontrolled growth of cells

Mitochondria



Mitochondria



‘Powerhouse of the cell’

Mitochondria

Power
Cellular
Life

Trigger
Cellular
Death

This image was created with the assistance of DALL·E 2

Mitochondria

Neurodegenerative diseases

Alzheimer's disease

Parkinson's Disease

Huntington's disease

Amyotrophic lateral sclerosis (ALS)

Metabolic disorders

Diabetes

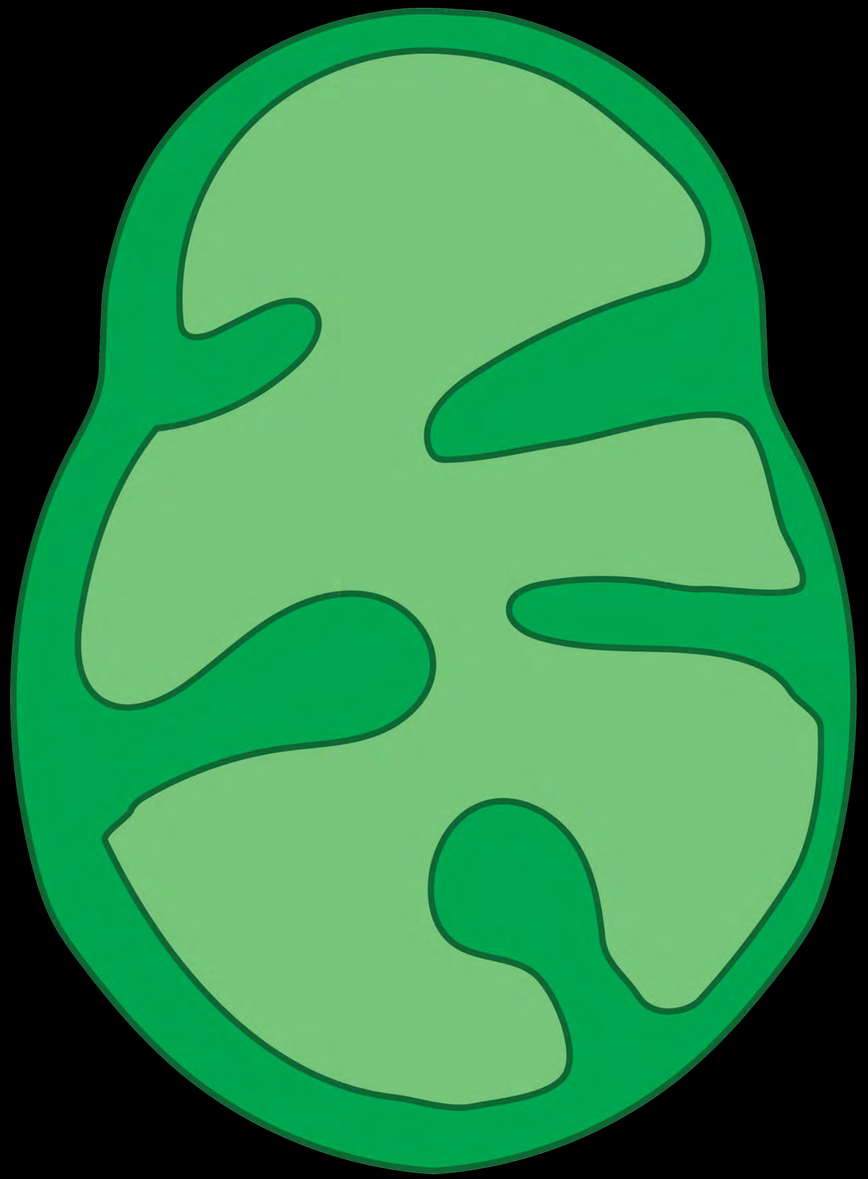
Obesity

Cardiovascular Diseases

Heart Failure

Ischemic heart disease

Cardiomyopathy



Cancer

Renal cell carcinoma

Pancreatic cancer

Ovarian cancer

Breast cancer

Colorectal cancer

Prostate cancer

Brain cancer

Age-related diseases

Osteoarthritis

Age-related macular degeneration

Autoimmune disorders

Multiple Sclerosis

Inflammatory bowel disease

Systemic lupus erythematosus

Mitochondria

Neurodegenerative diseases

Alzheimer's disease

Parkinson's Disease

Huntington's disease

Amyotrophic lateral sclerosis (ALS)

Cancer

Renal cell carcinoma

Pancreatic cancer

Ovarian cancer

Breast cancer

Colorectal cancer

Prostate cancer

Brain cancer

Limited success in targeting mitochondria for therapeutics (medicine)

Metabolic disorders

Diabetes

Obesity

Age-related diseases

Osteoarthritis

Age-related macular degeneration

Cardiovascular Diseases

Heart Failure

Ischemic heart disease

Cardiomyopathy

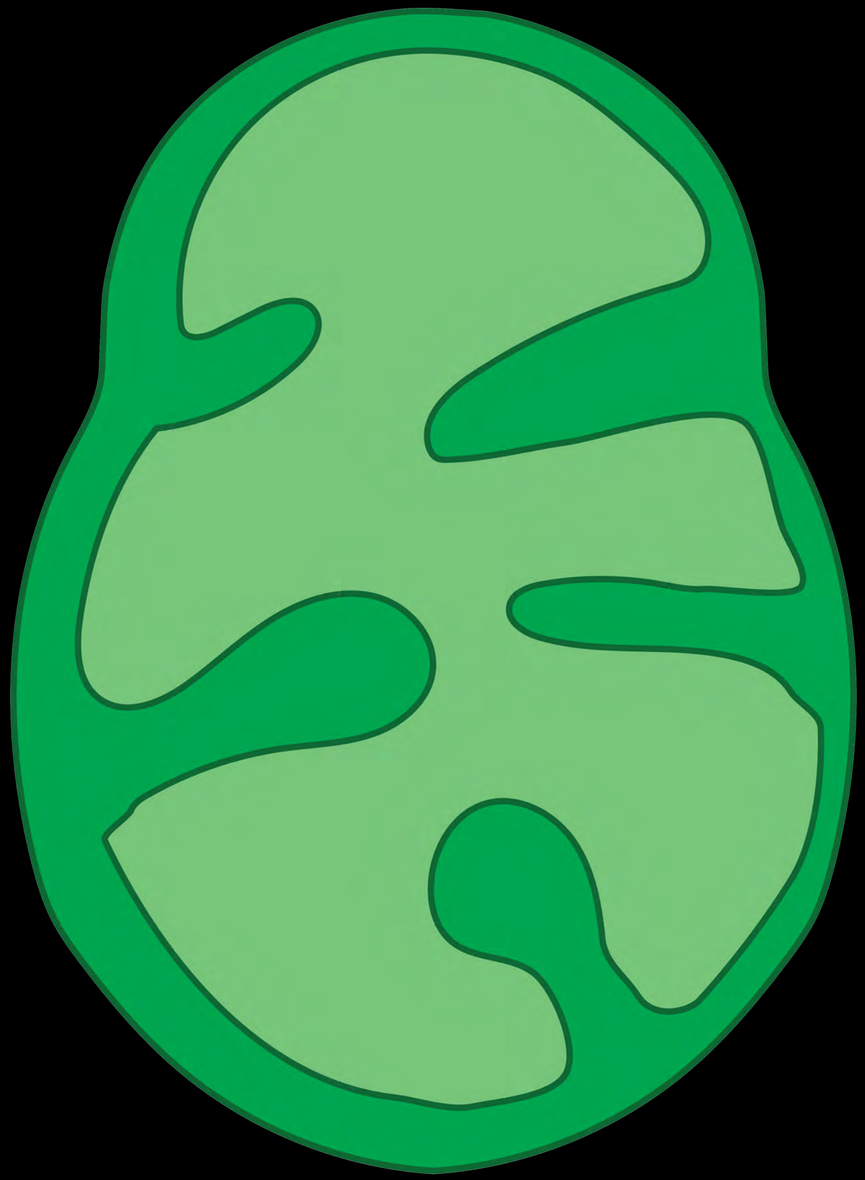
Autoimmune disorders

Multiple Sclerosis

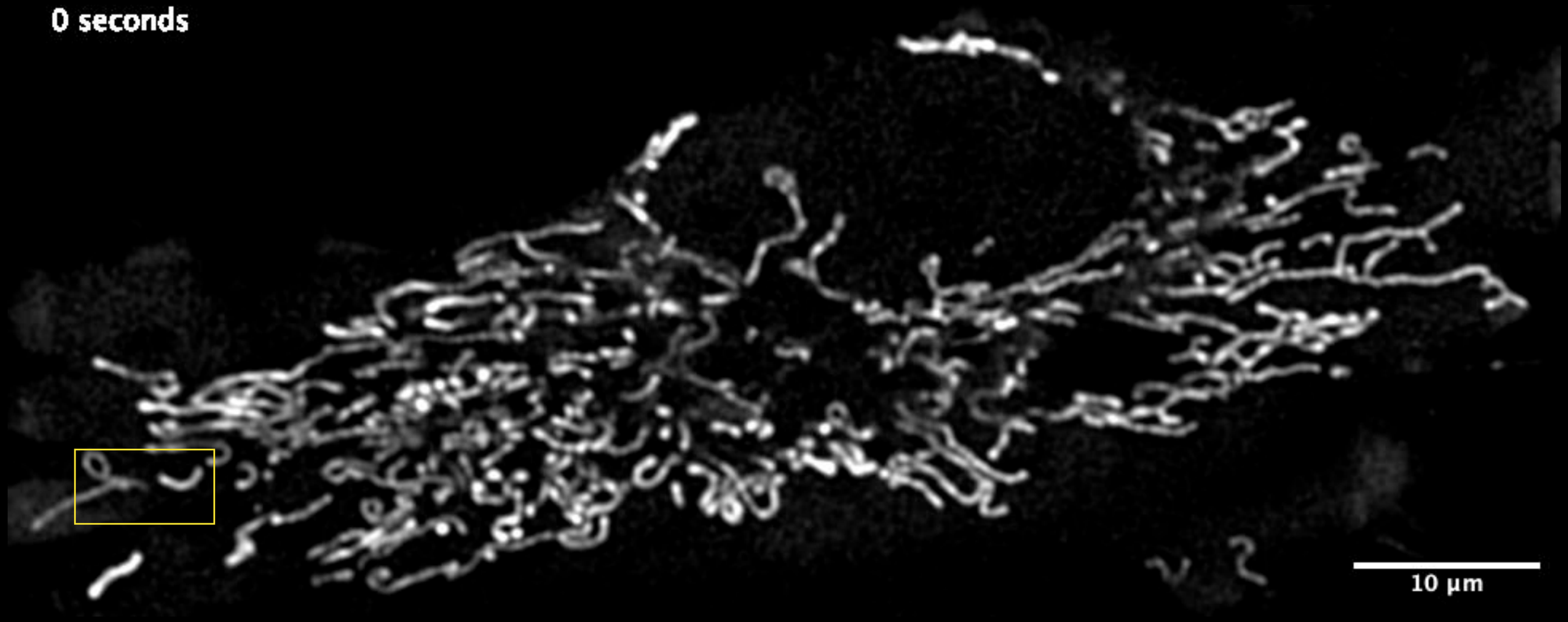
Inflammatory bowel disease

Systemic lupus erythematosus

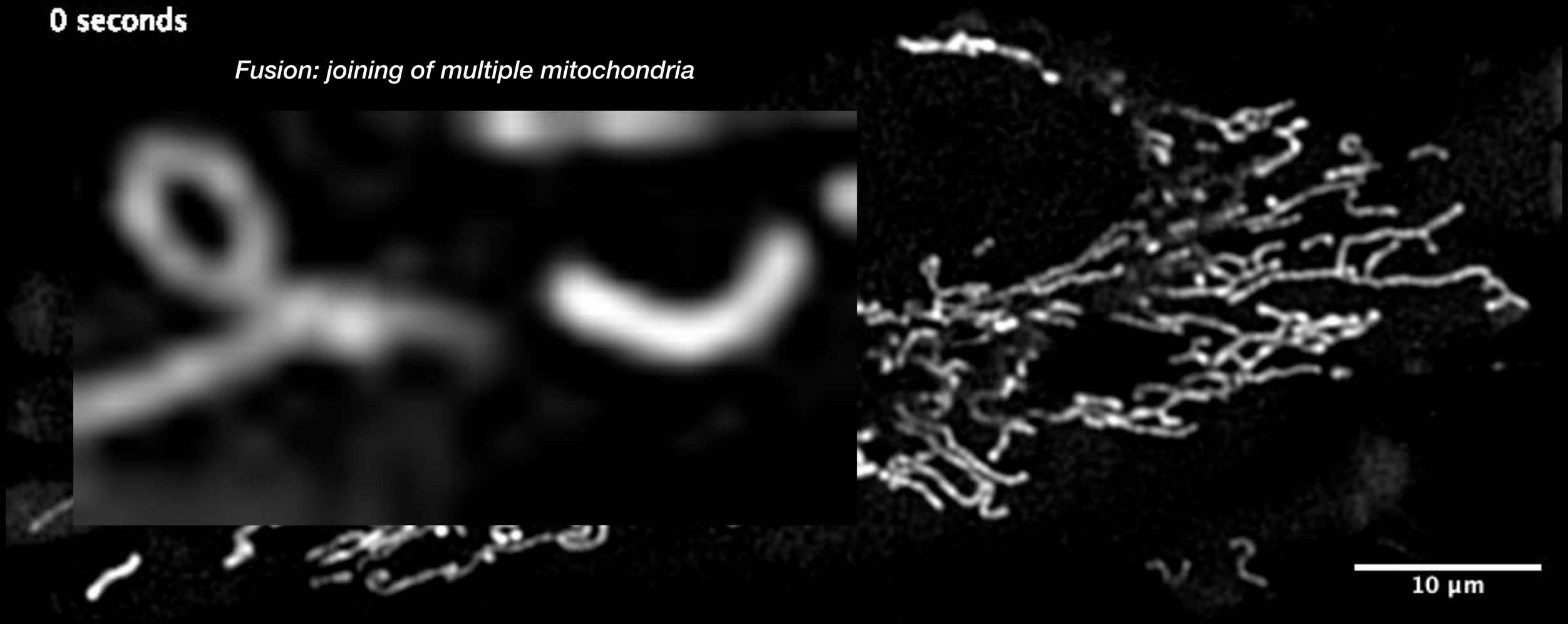
Mitochondria



Mitochondria are constantly moving (dynamic)

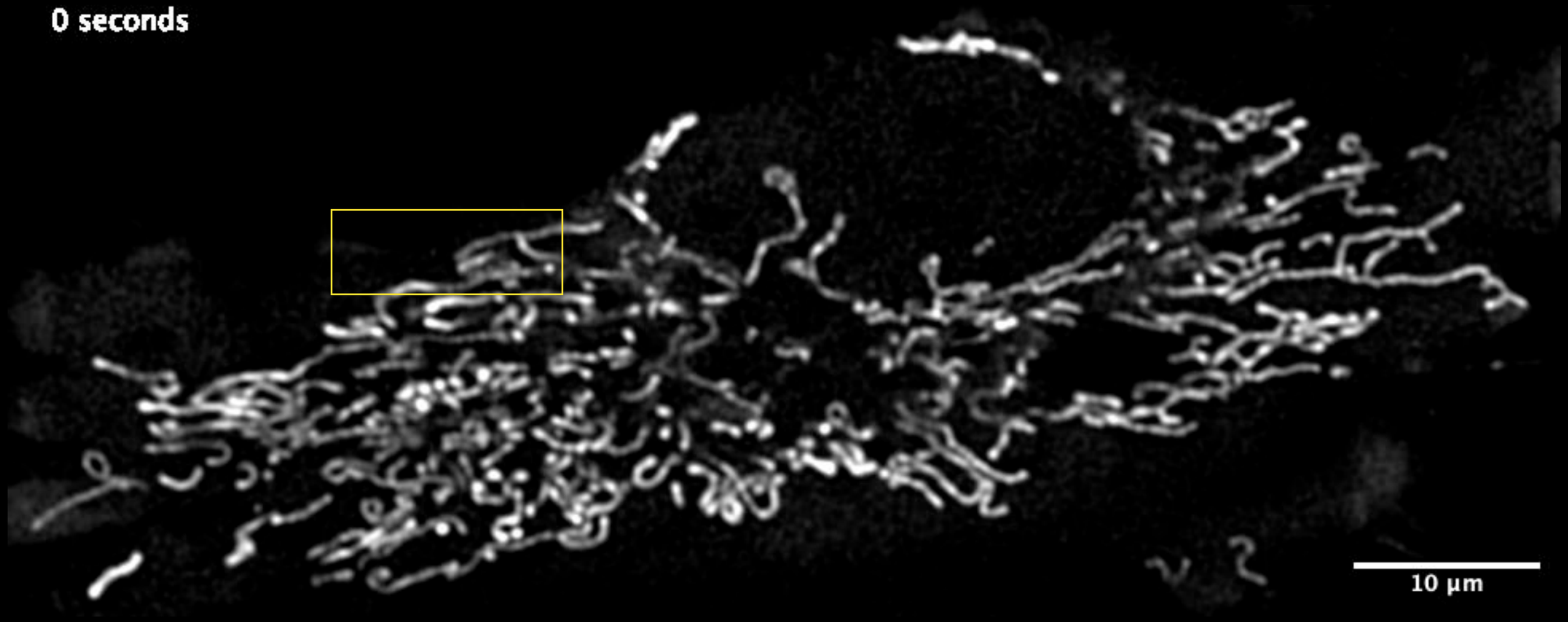


Mitochondria are constantly moving (dynamic)

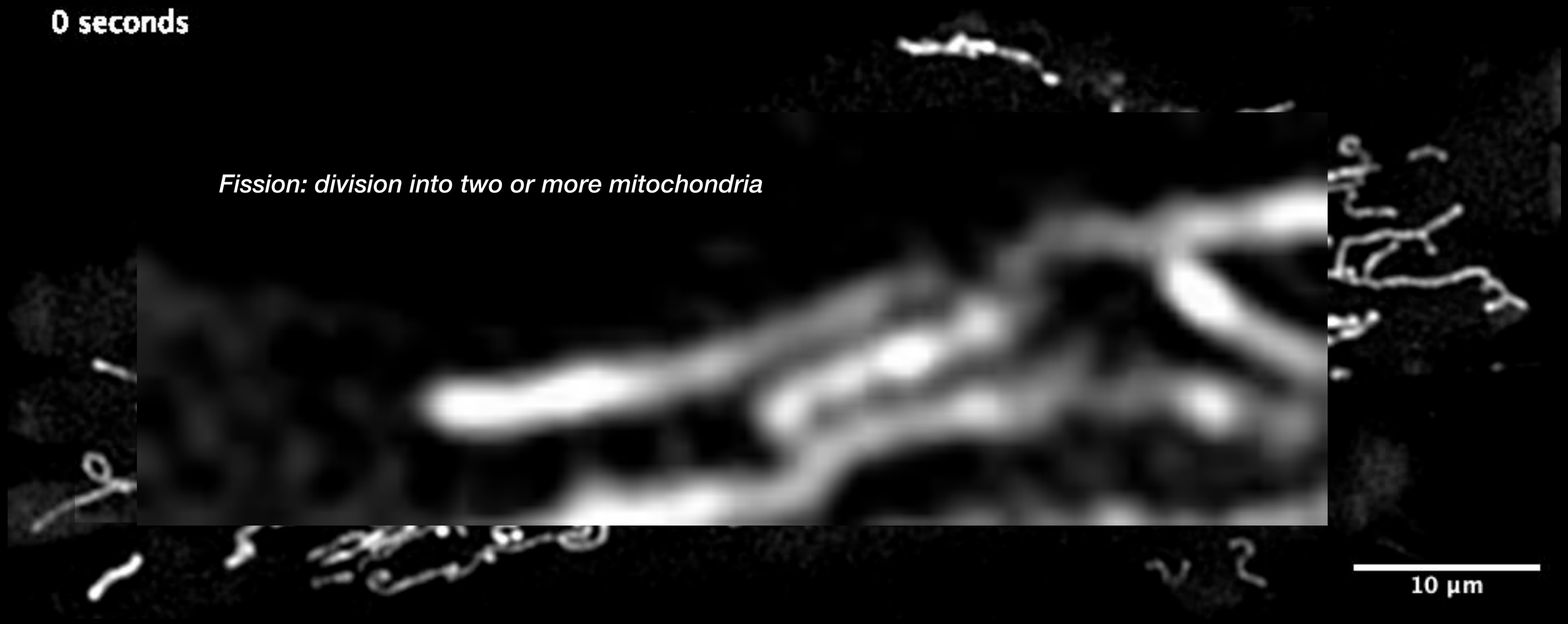


Fusion: joining of multiple mitochondria

Mitochondria are constantly moving (dynamic)

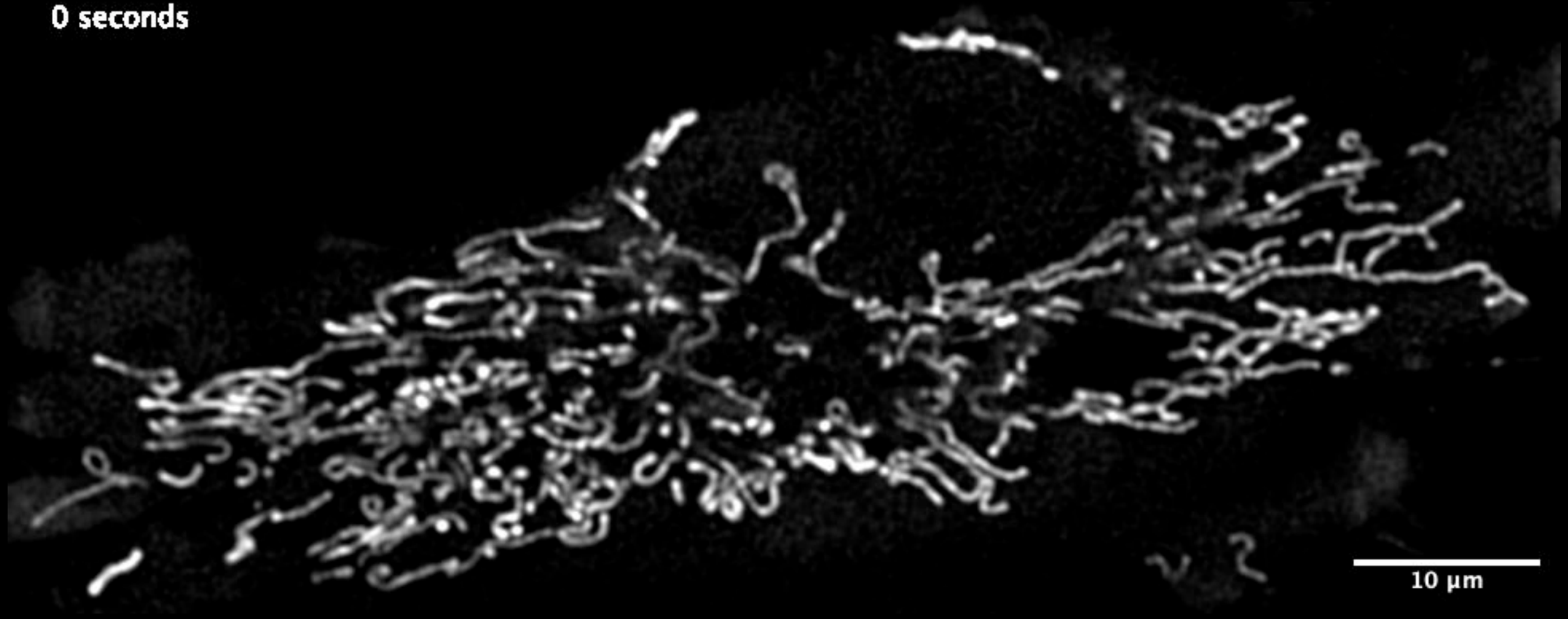


Mitochondria are constantly moving (dynamic)



Fission: division into two or more mitochondria

Mitochondria are constantly moving (dynamic)



Mitochondria change shape (morphology) in response to different cellular conditions

Homeostasis

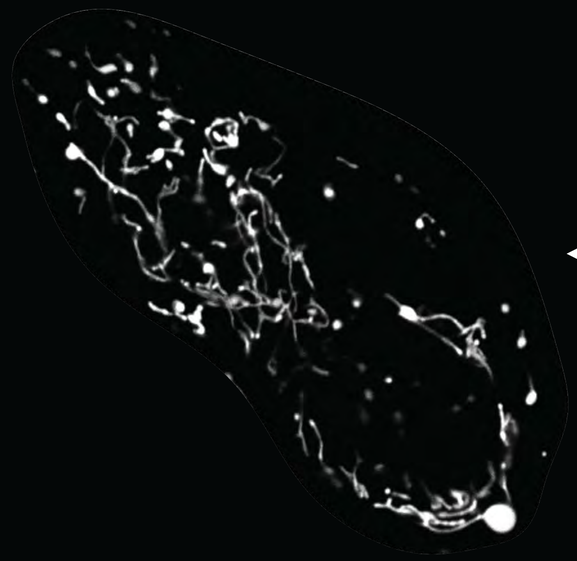
Cellular mitochondrial network

Mitochondria change shape (morphology) in response to different cellular conditions

Hyperfusion

Homeostasis

Hyperfragmention

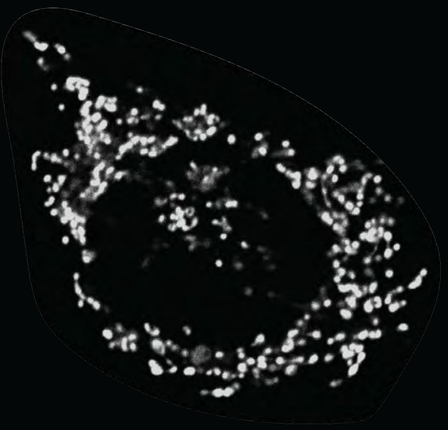


Fusion

Fission

Fission

Fusion



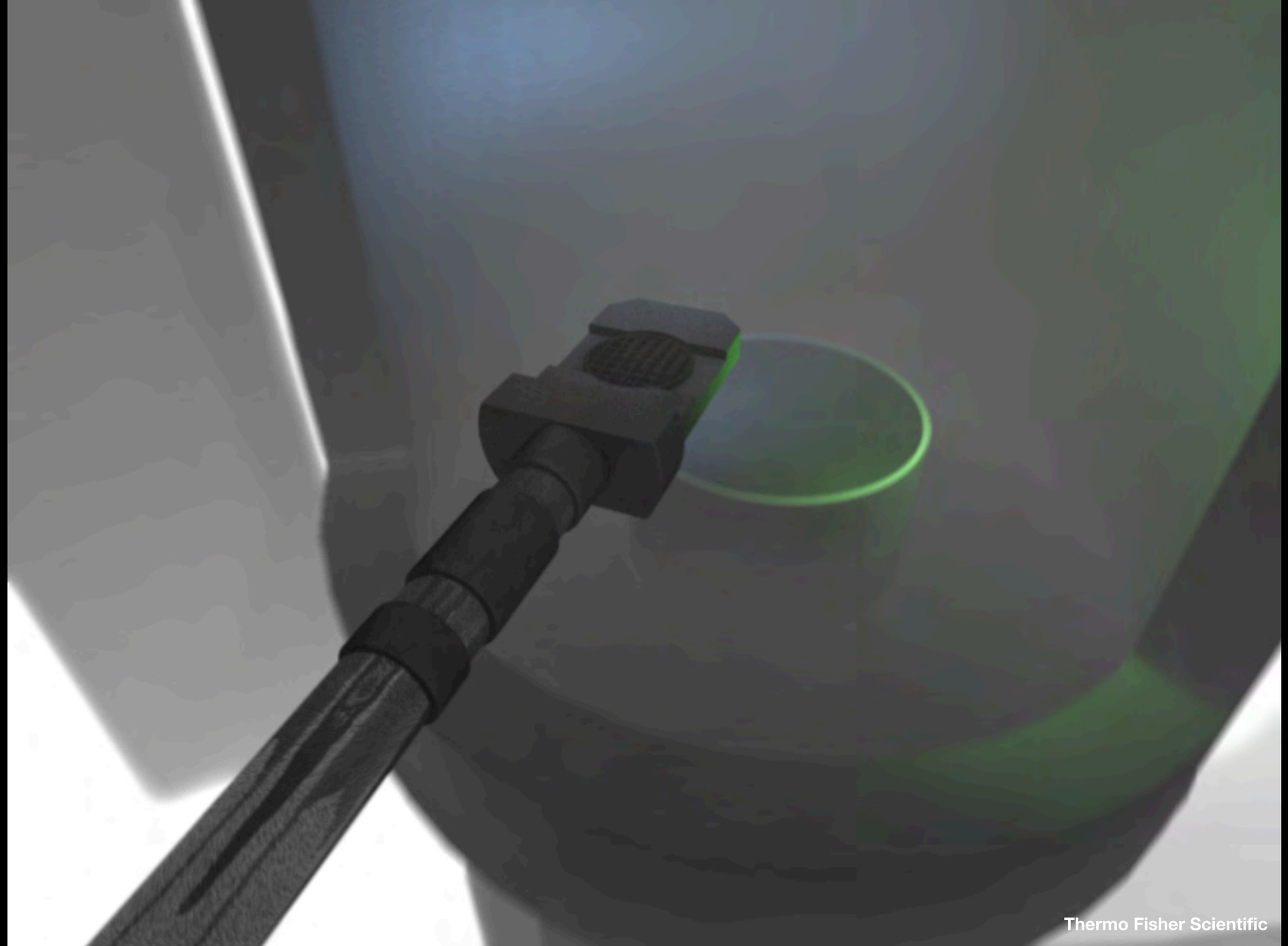
Cell Survival

Cell Death

“Functional”

“Damaged or dysfunctional”


Thermo Fisher Scientific


Thermo Fisher Scientific

Scripps Research Institute among the first to invest in this cutting-edge imaging technology

Scripps Research

Mitochondria change shape in response to different cellular conditions

Elongated

Tubular

Fragmented

Fusion

Fission

Fission

Fusion

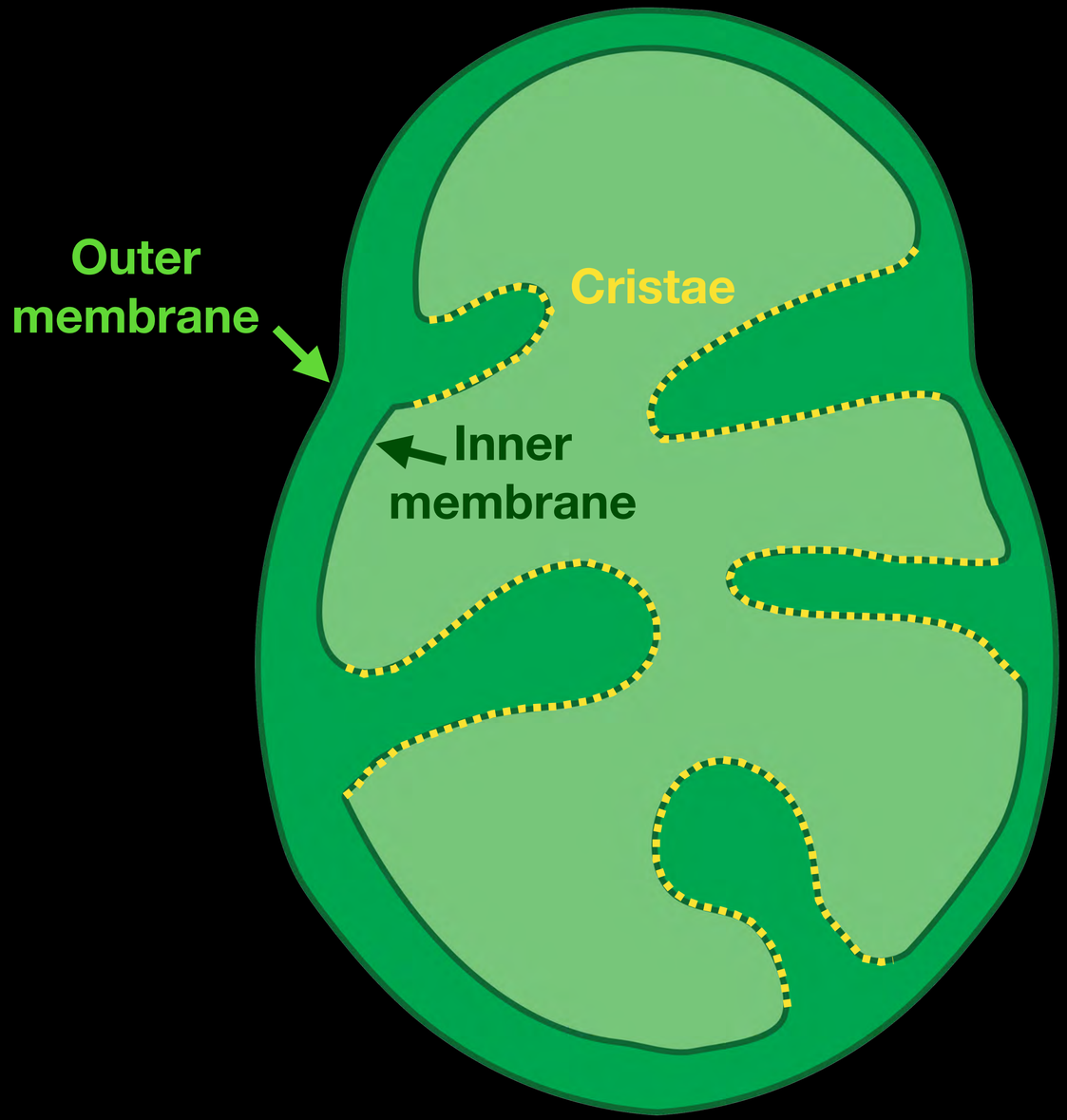
Cell Survival

Cell Death

“Functional”

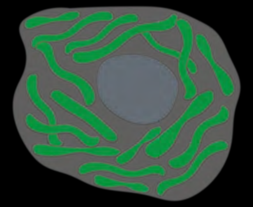
“Damaged or dysfunctional”

Mitochondria

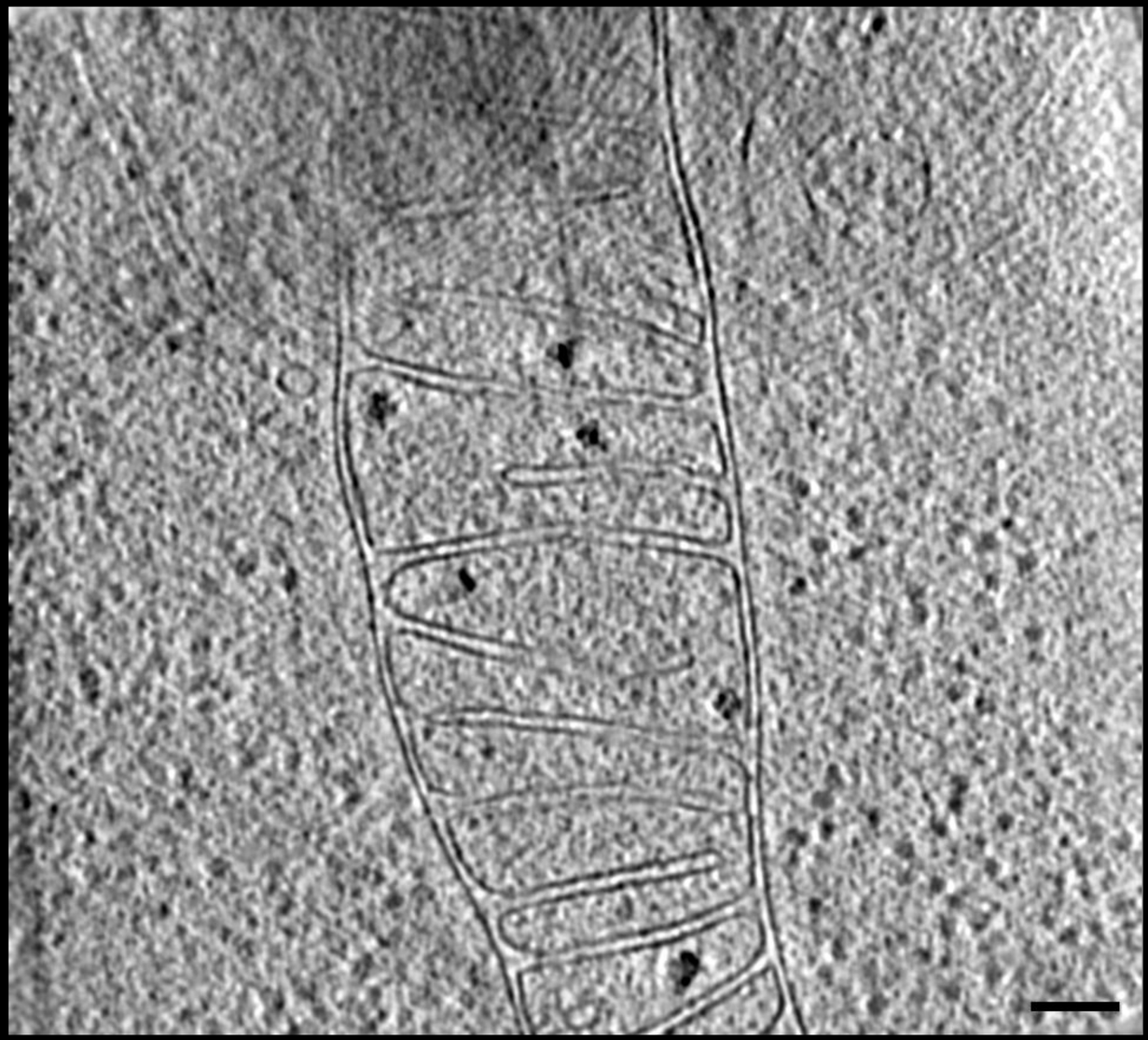


Cryo-electron tomography captures mitochondrial membrane ultrastructure

Cellular
Network
Morphology



Organellar
Membrane
Ultrastructure



PMID: 36786771

Elongated Mitochondria ('functional, pro-survival mitochondria')

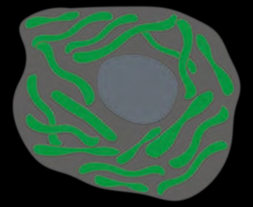
Scale bar = 100 nm

Jackson Pollock

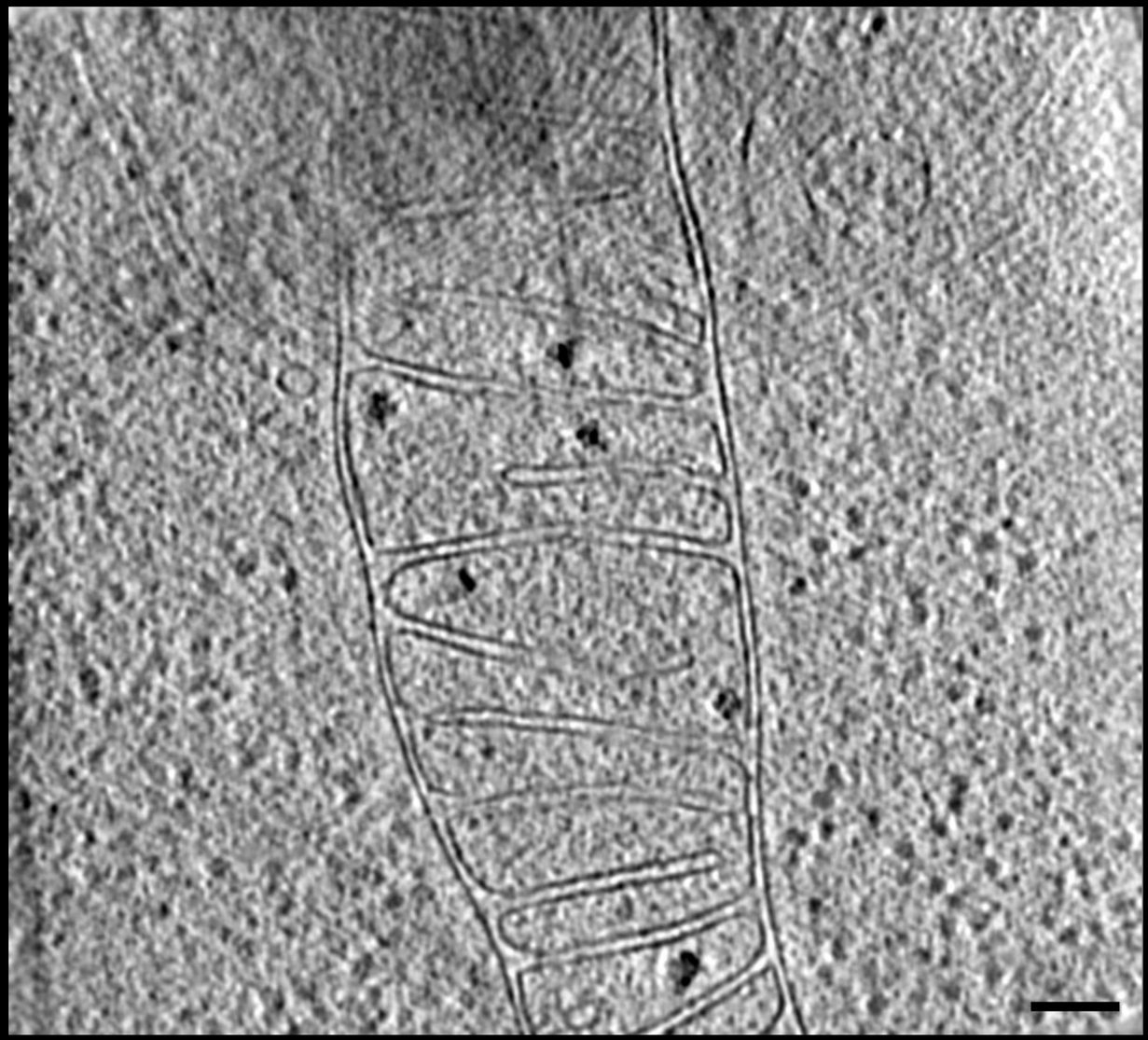
Number 14: Gray, 1948

Cryo-electron tomography captures mitochondrial membrane ultrastructure

Cellular
Network
Morphology



Organellar
Membrane
Ultrastructure



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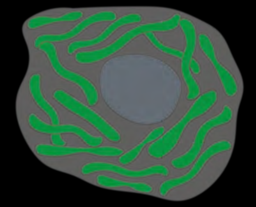
Elongated Mitochondria ('functional, pro-survival mitochondria')

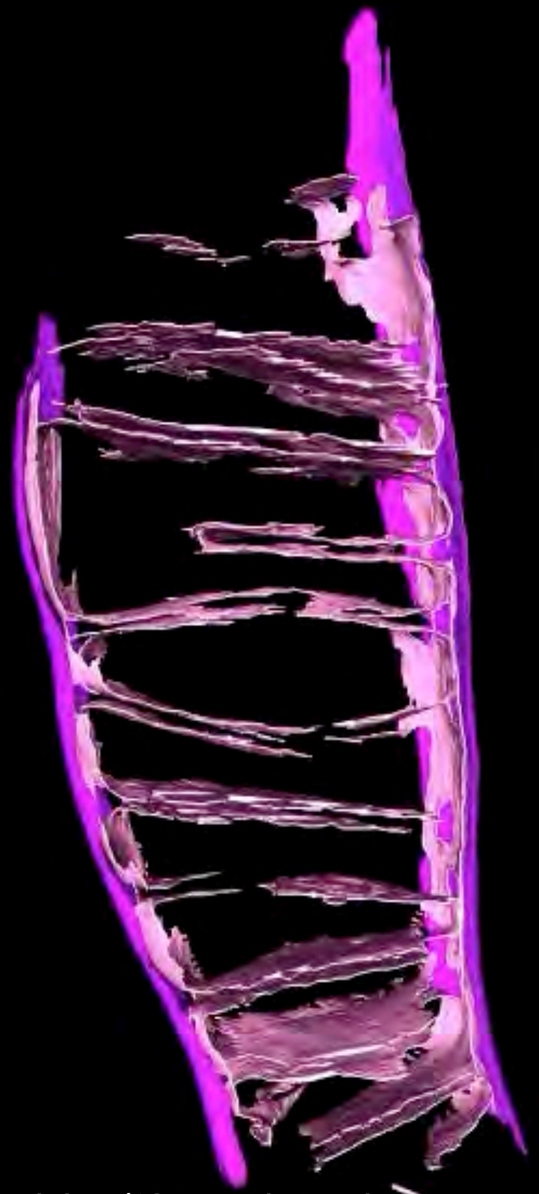
Scale bar = 100 nm

Cryo-electron tomography captures mitochondrial membrane ultrastructure

Cellular
Network
Morphology



Organellar
Membrane
Ultrastructure



PMID: 36786771

Elongated Mitochondria ('functional, pro-survival mitochondria')

Scale bar = 100 nm

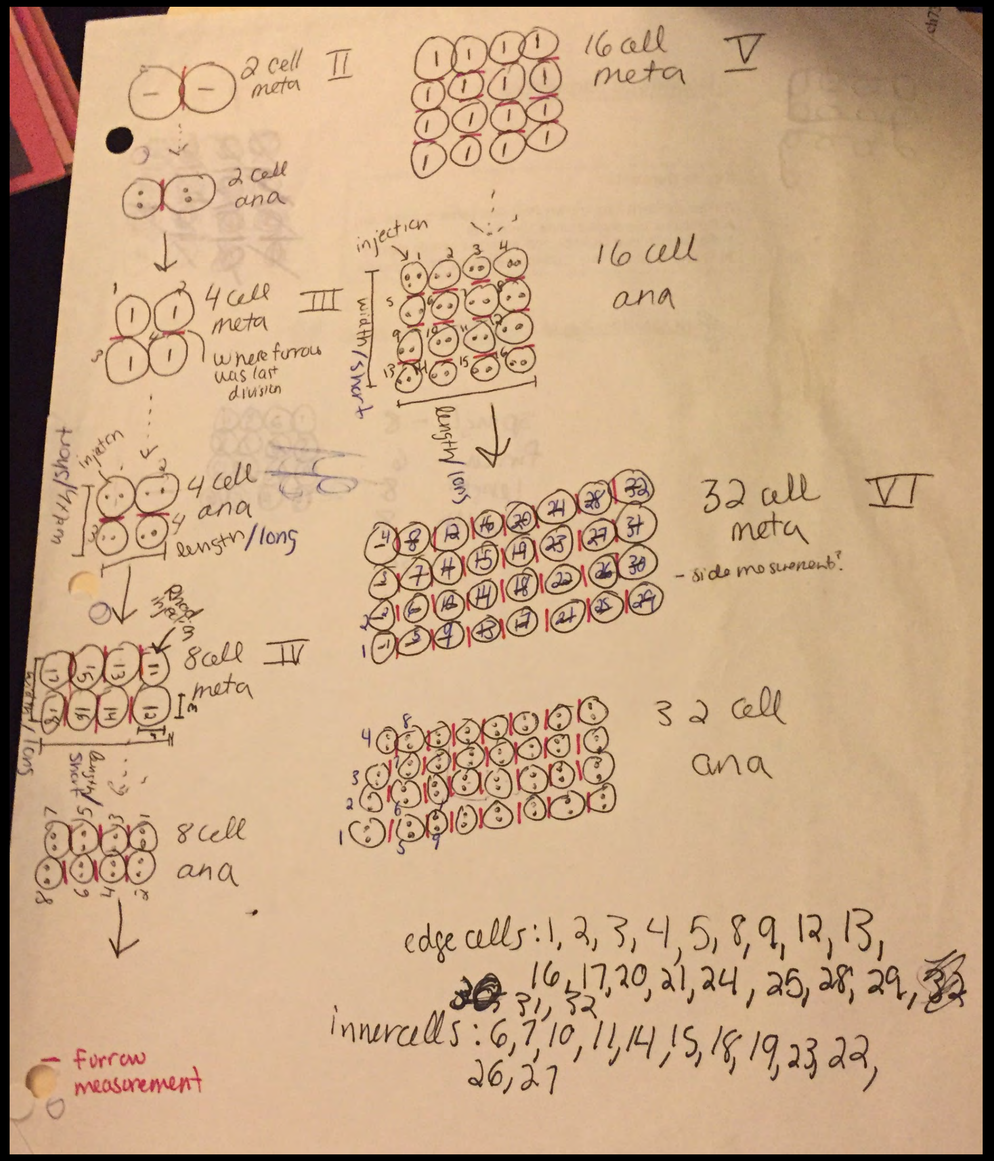
“Pro-cell death” mitochondria contain swollen cristae

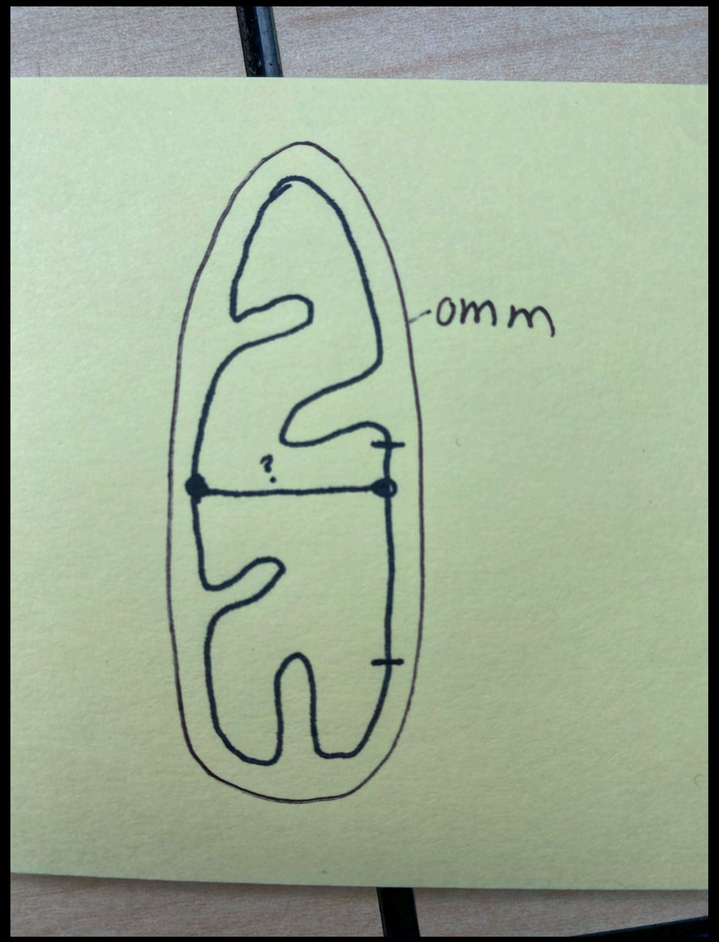
PMID: 36786771

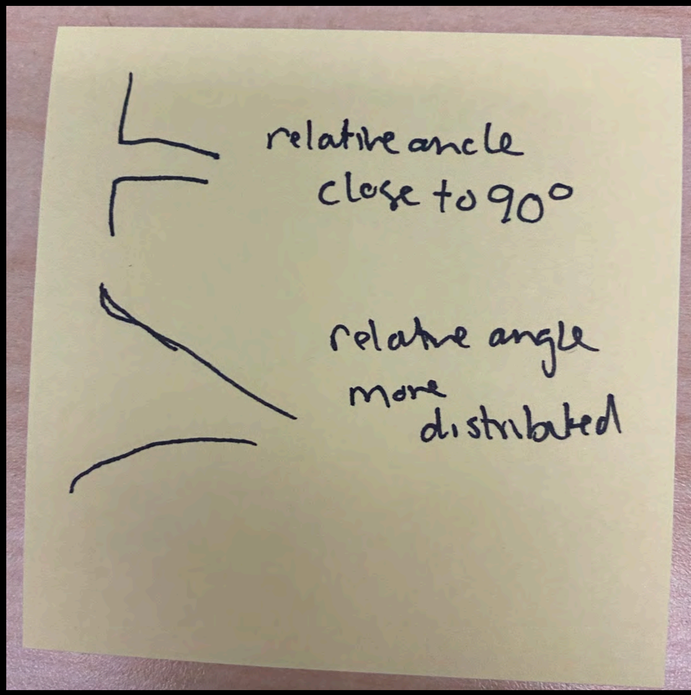
Fragmented Mitochondria (‘damaged, pro-cell death mitochondria’)

Scale bar = 100 nm

Transform beautiful pictures into meaningful numbers





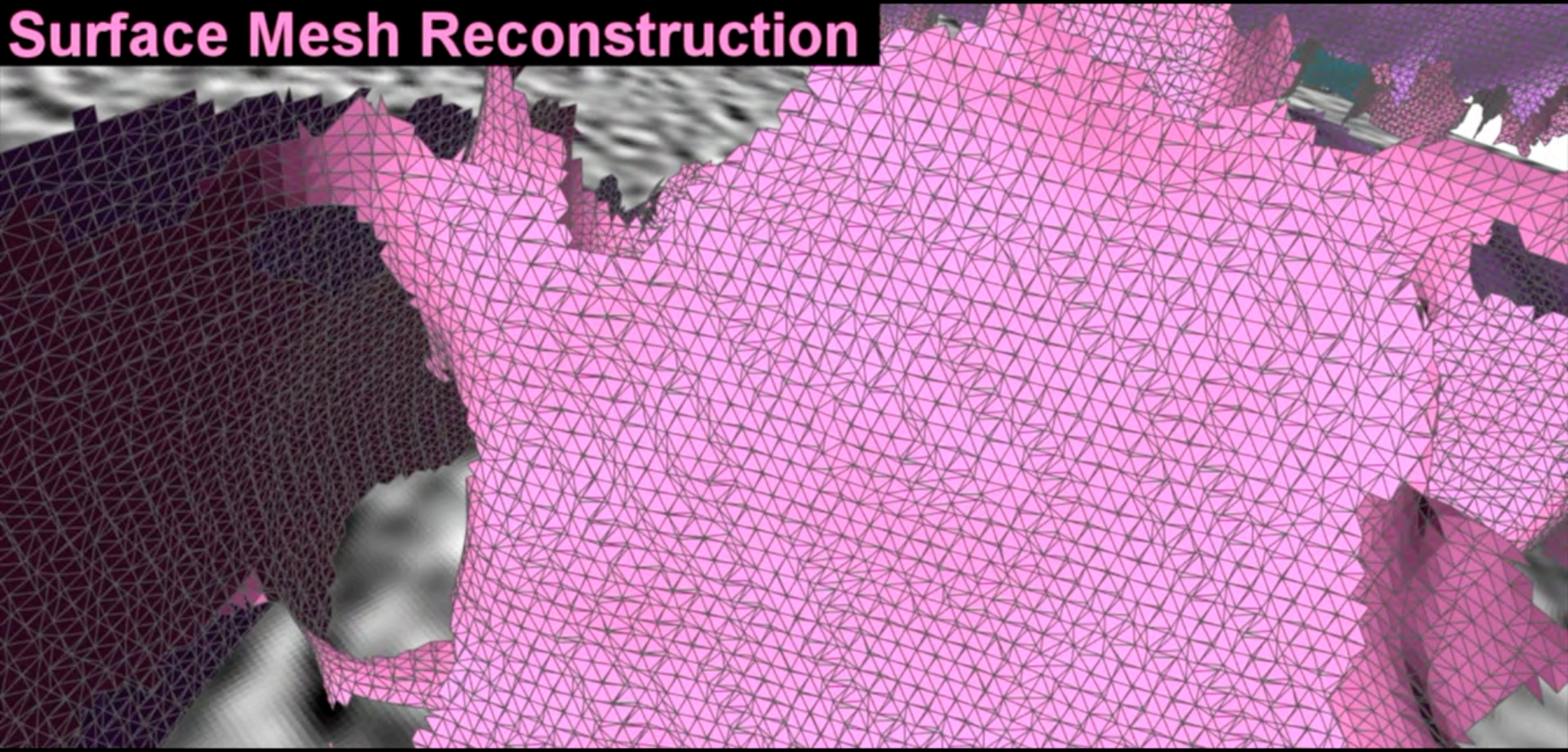


Borrowing methods from the computer vision community

Mimicking LIDAR data from self driving car

PMID: 36786771

Surface Mesh Reconstruction



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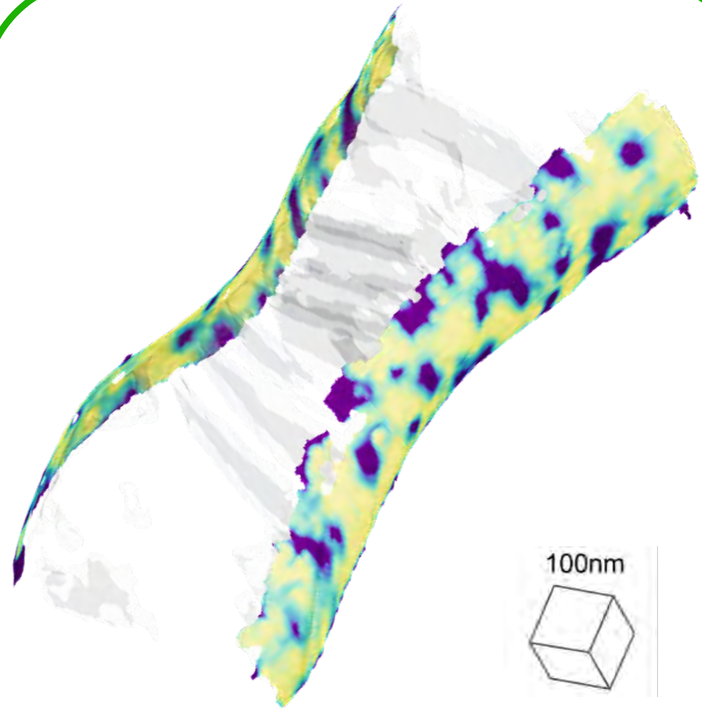
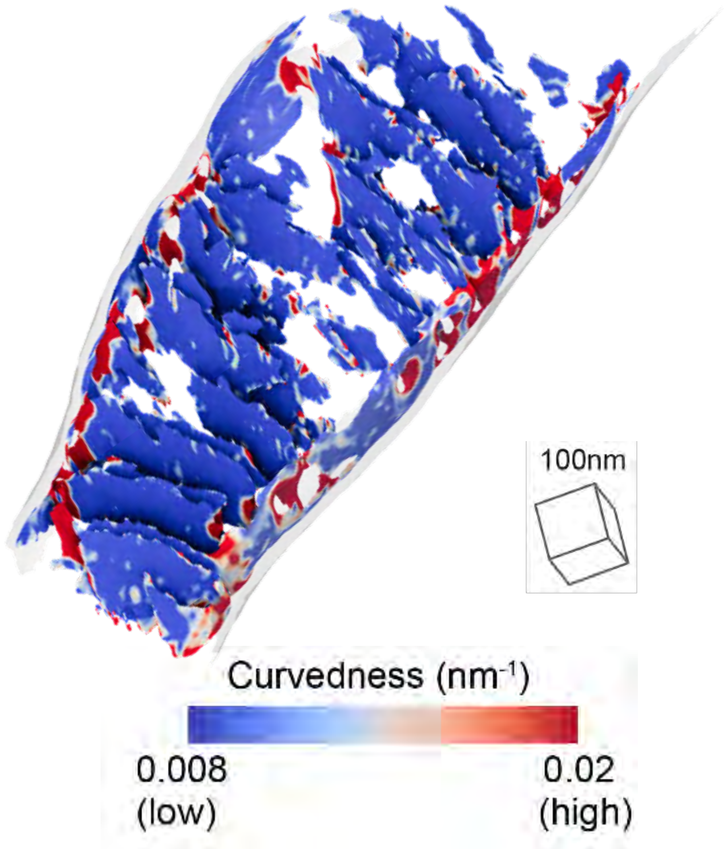
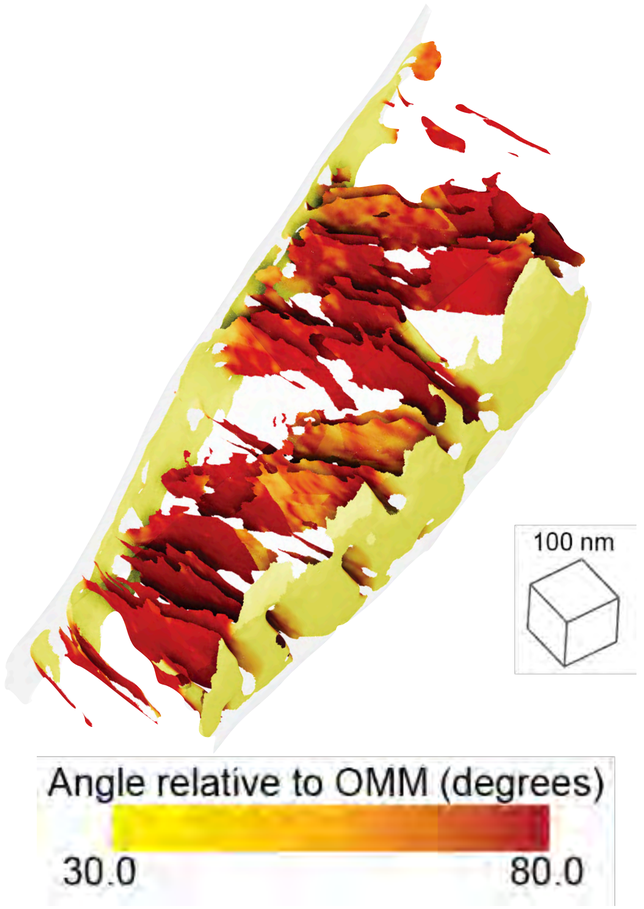
Software to make very precise measurements of membrane architecture



Distance



Curvature



Orientation

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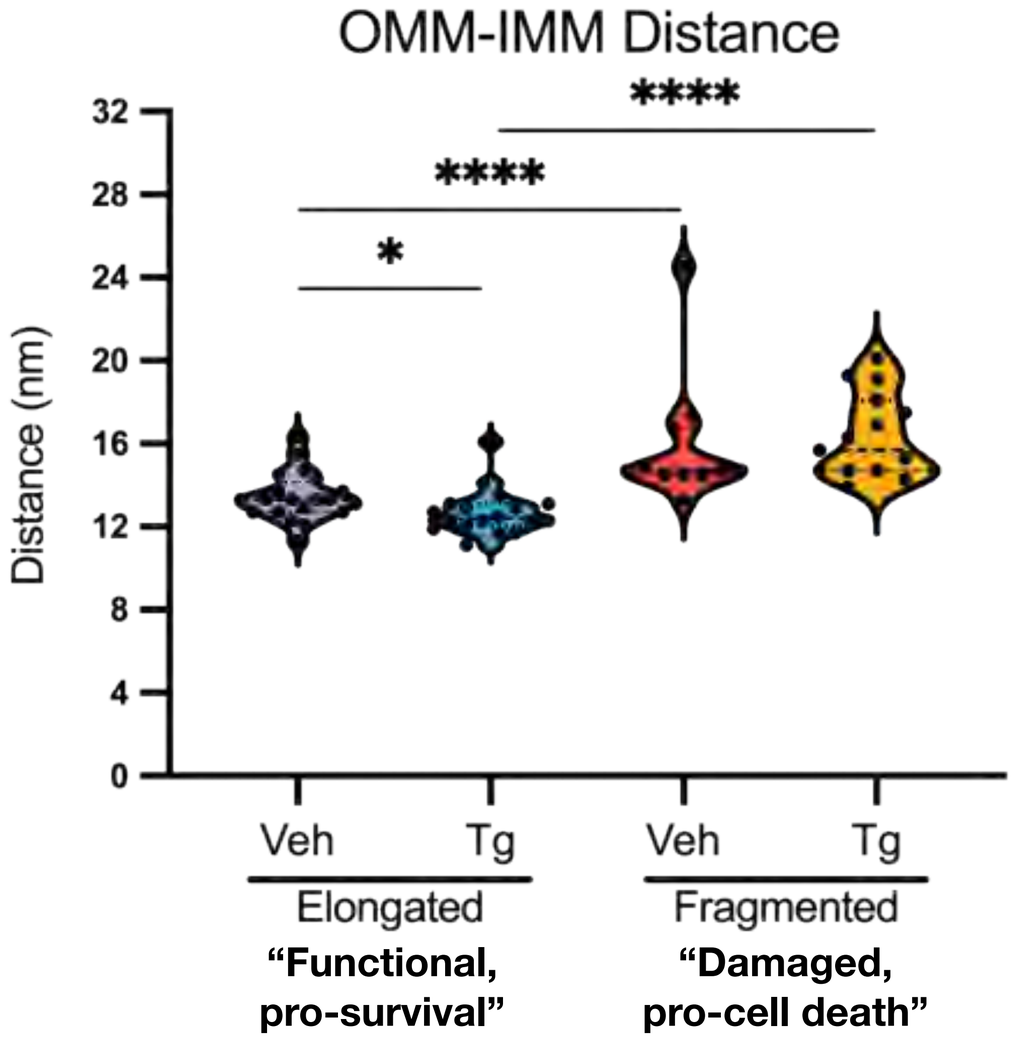
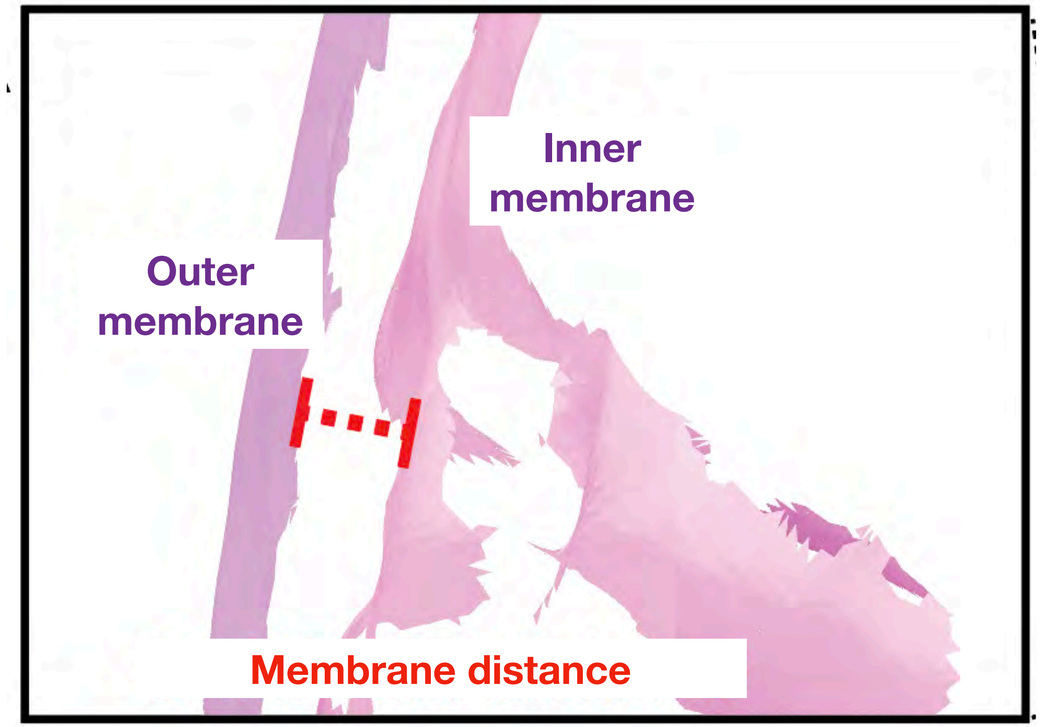
Cellular conditions induce opposing changes in outer-to-inner membrane distance between distinct network morphologies



*Detecting statistically significant differences of **0.8-3.6 nm!***



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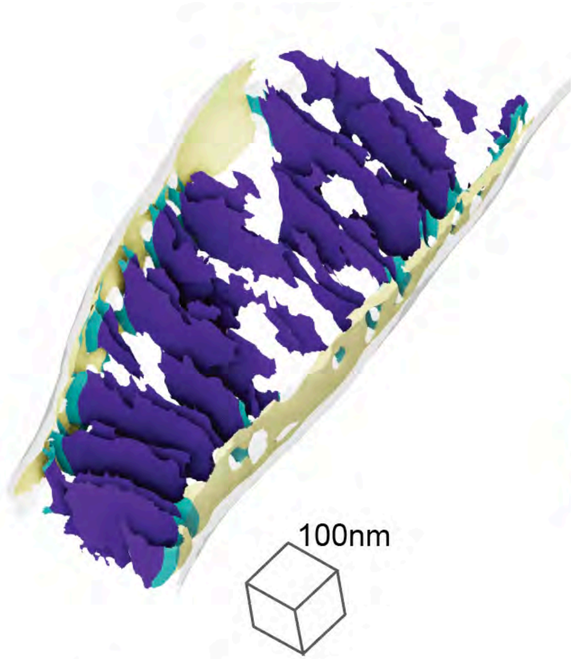
Elongated and fragmented mitochondria are very different at the detailed membrane level

Elongated
"Pro-survival"



OMM-IMM Distance
- Inner membrane boundary (IBM) (<19 nm)
- Crista junction (19-40 nm)
- Crista (>40 nm)

↓ OMM-IMM distance ↑

↓ Intra-crista distance ↑

↓ Crista curvedness ↑

↑ Junction curvedness ↓

↓ Crista angle variability ↑

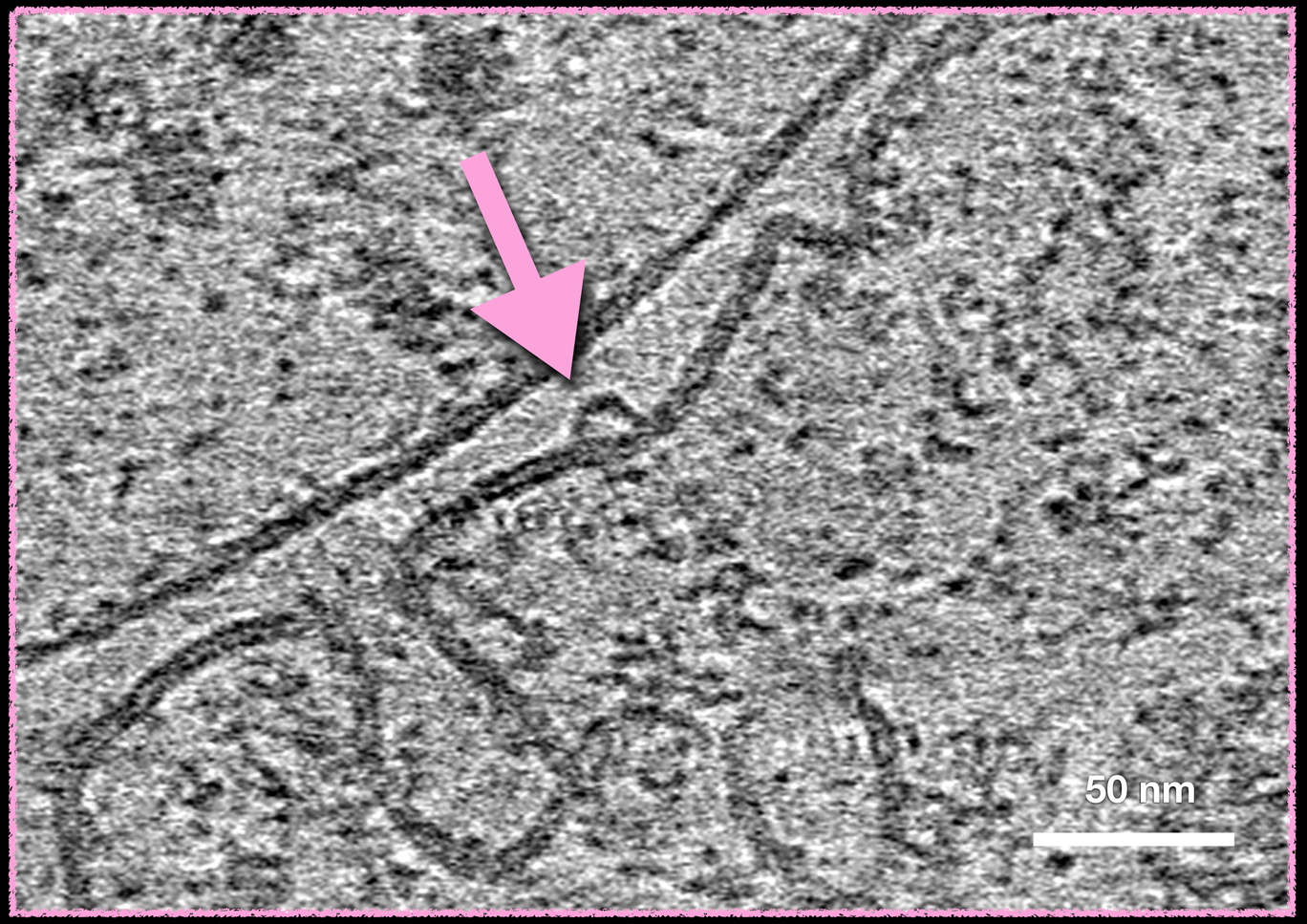
Fragmented
"Pro-cell death"

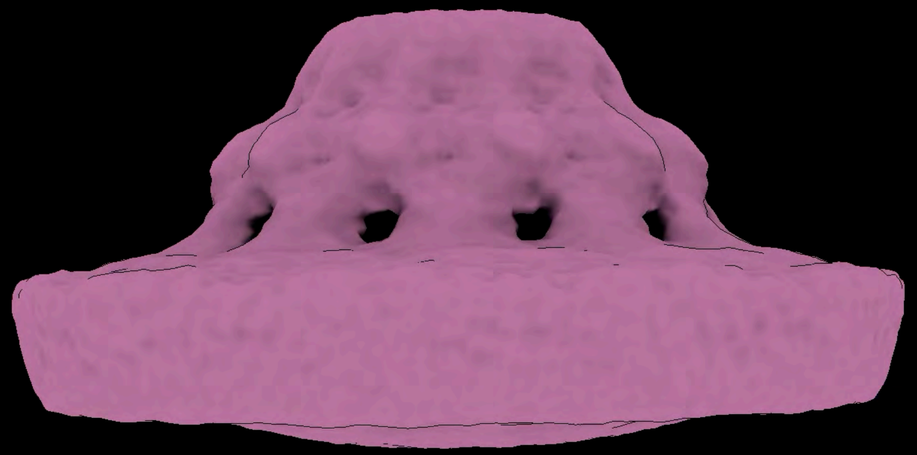
This suggests that learning what shapes the structure of membranes might be the key to understanding what controls how mitochondria work

PMID: 36786771

Scale bar = 100 nm

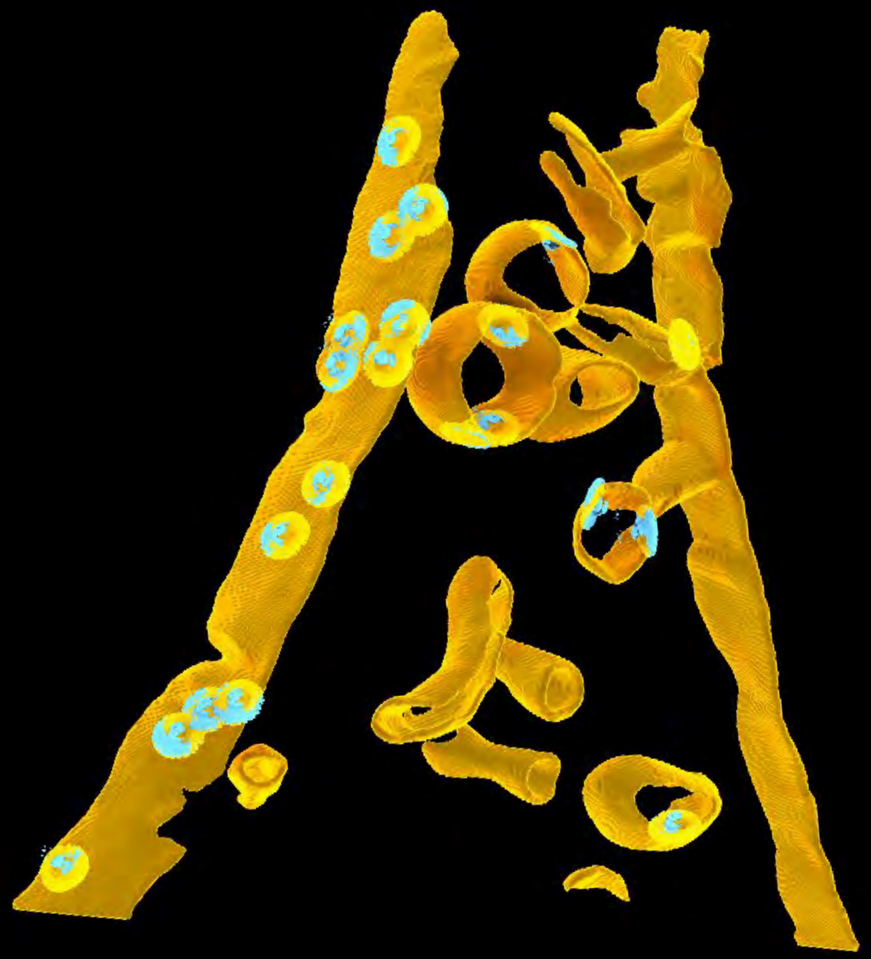
Unidentified “volcano” structure hidden within mitochondria





Unidentified “volcano” structure hidden within mitochondria

‘functional, pro-survival mitochondria’



‘damaged, pro-cell death mitochondria’

Mitochondria change shape in response to different cellular conditions

Elongated

Tubular

Fragmented

Fusion

Fission

Fission

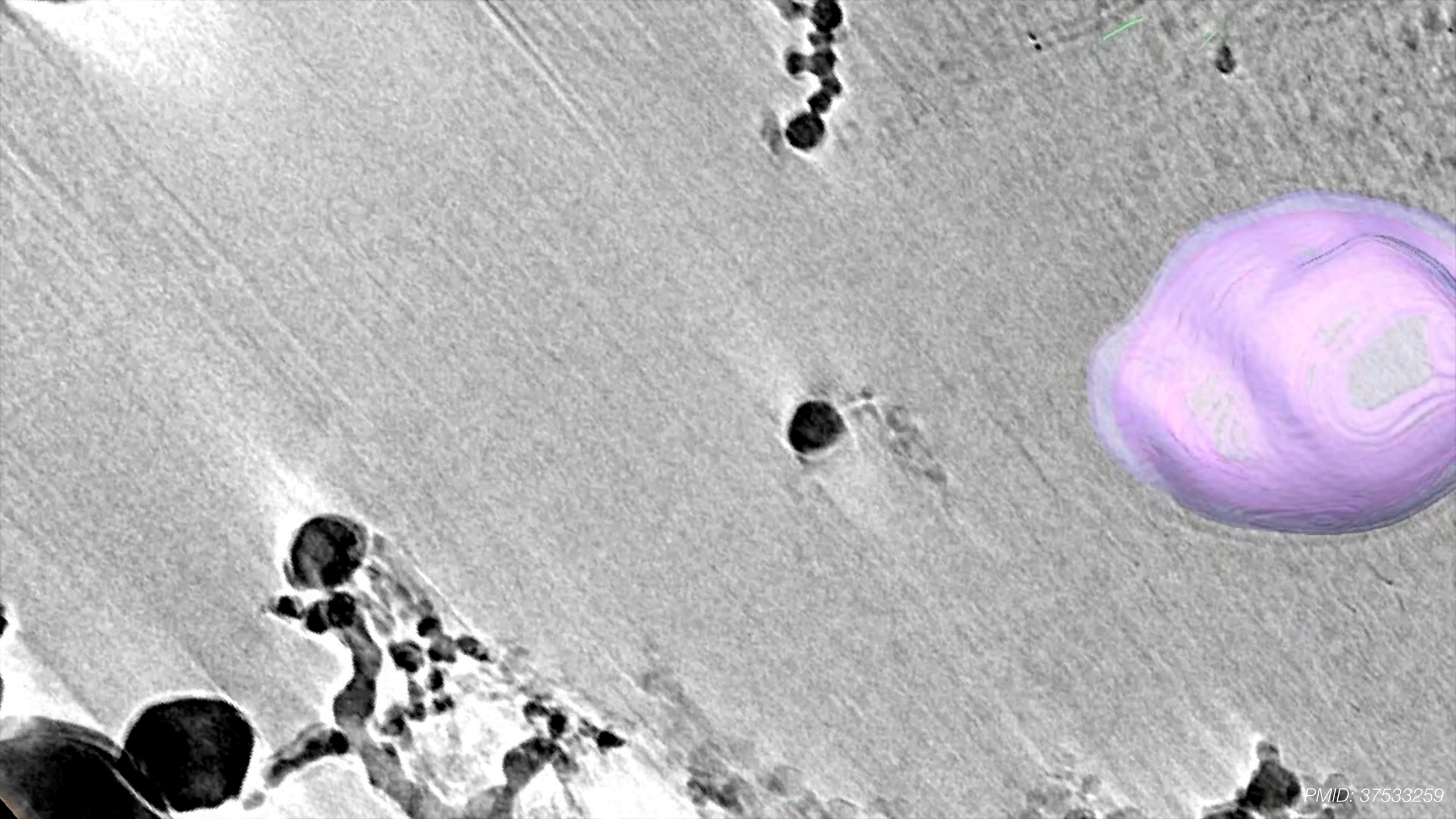
Fusion

Cell Survival

Cell Death

“Functional”

“Damaged or dysfunctional”



PMID: 37533259

Mitochondria change shape in response to different cellular conditions

Elongated

Tubular

Fragmented

Fusion

Fission

Fission

Fusion

Cell Survival

Cell Death

“Functional”

“Damaged or dysfunctional”

Mitochondria change shape in response to different cellular conditions

Elongated *Tubular* *Fragmented*

Fusion **Fission**

Fission Fusion

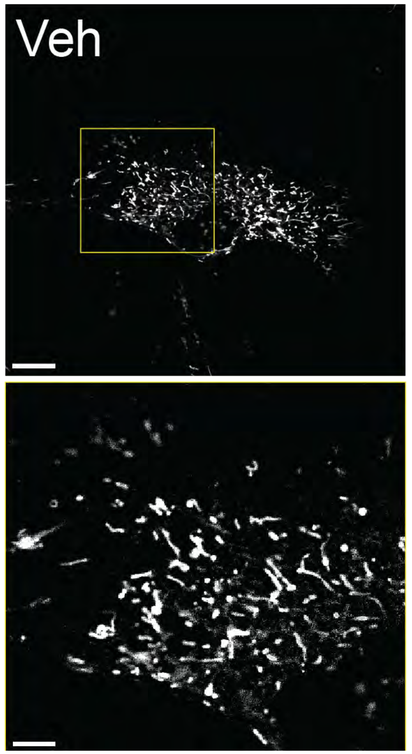
Can we reverse or prevent mitochondria fragmentation?

Cell Death

Cell Survival

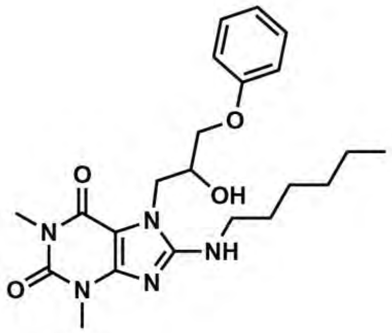
Designing molecules to promote healthy mitochondrial shapes and function

Patient Cells (MFN2^{D414V})



PMID: 38915623

Designing molecules to promote healthy mitochondrial shapes and function



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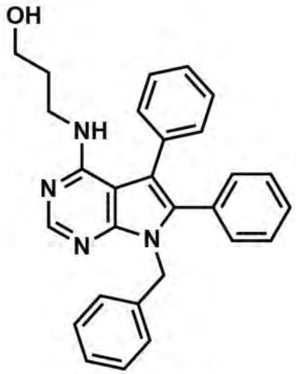
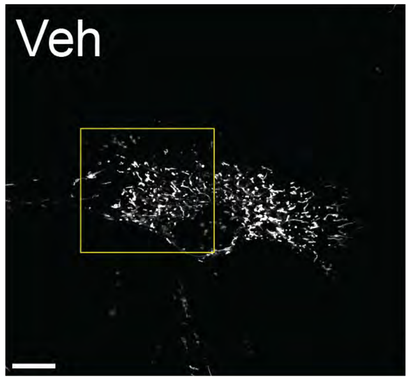
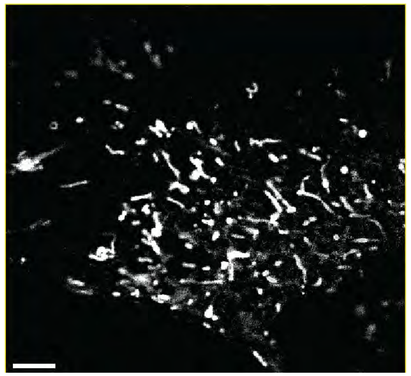


3610

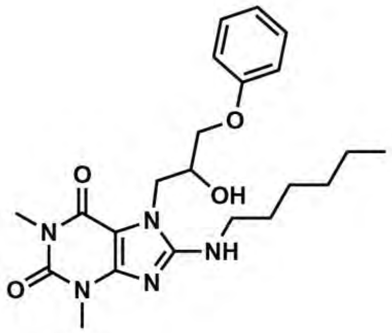
Patient Cells ($MFN2^{D414V}$)





PMID: 38915623

Designing molecules to promote healthy mitochondrial shapes and function



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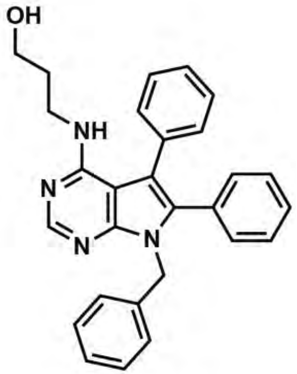

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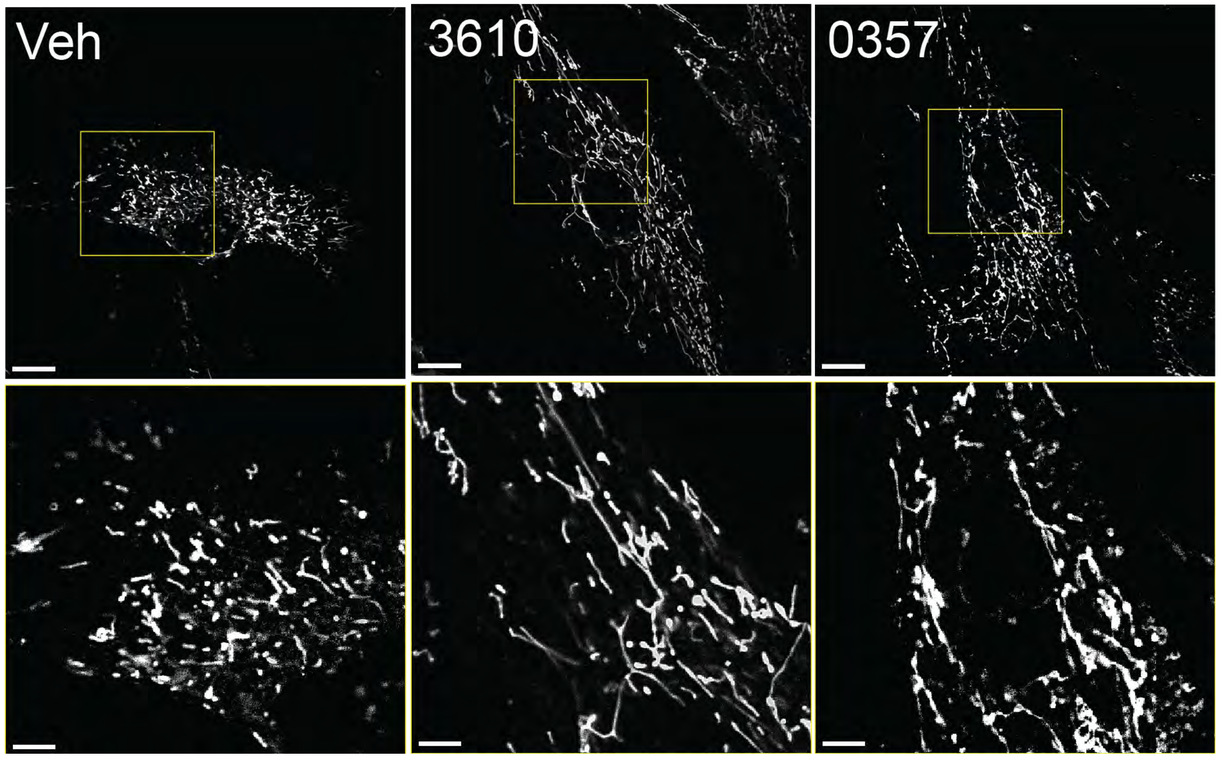

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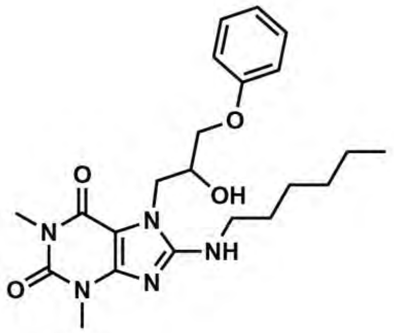
Designing molecules to promote healthy mitochondrial shapes and function



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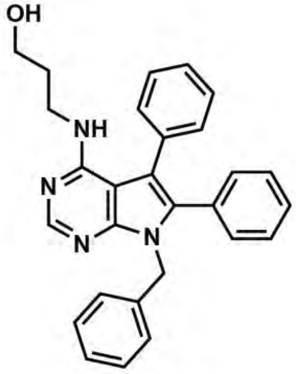

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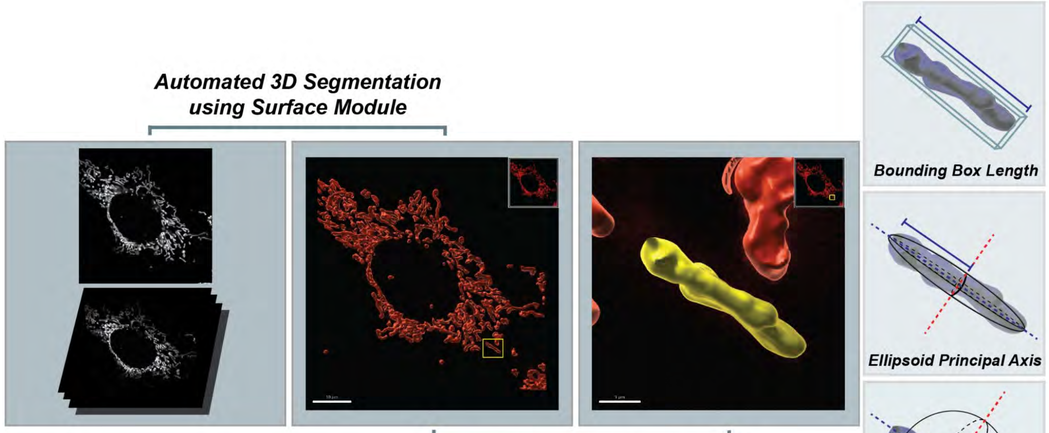

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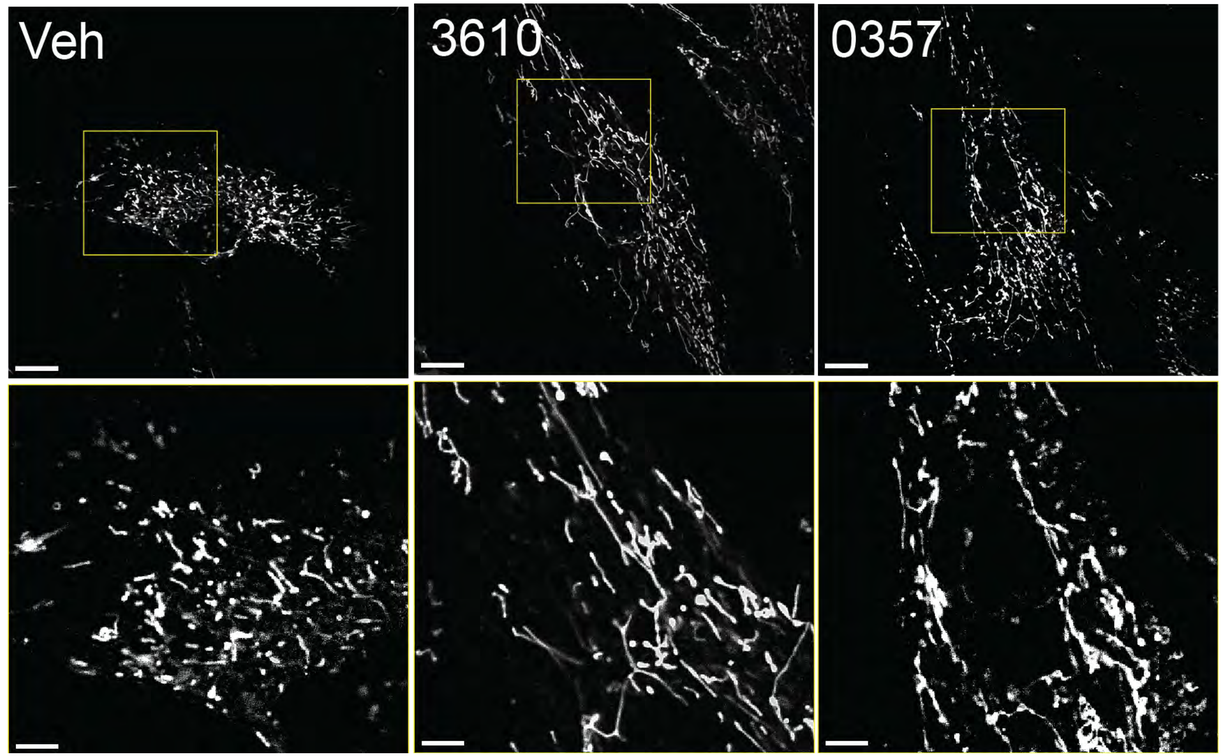
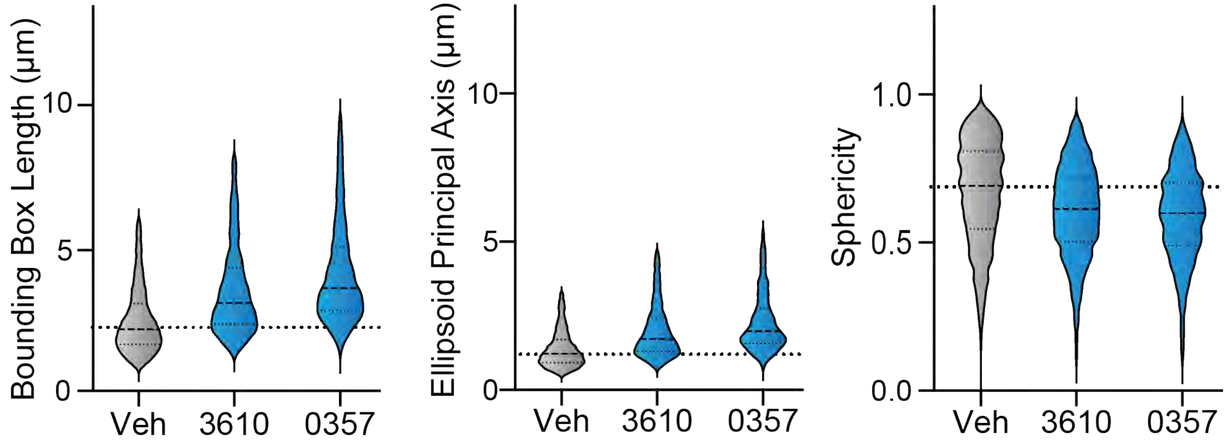
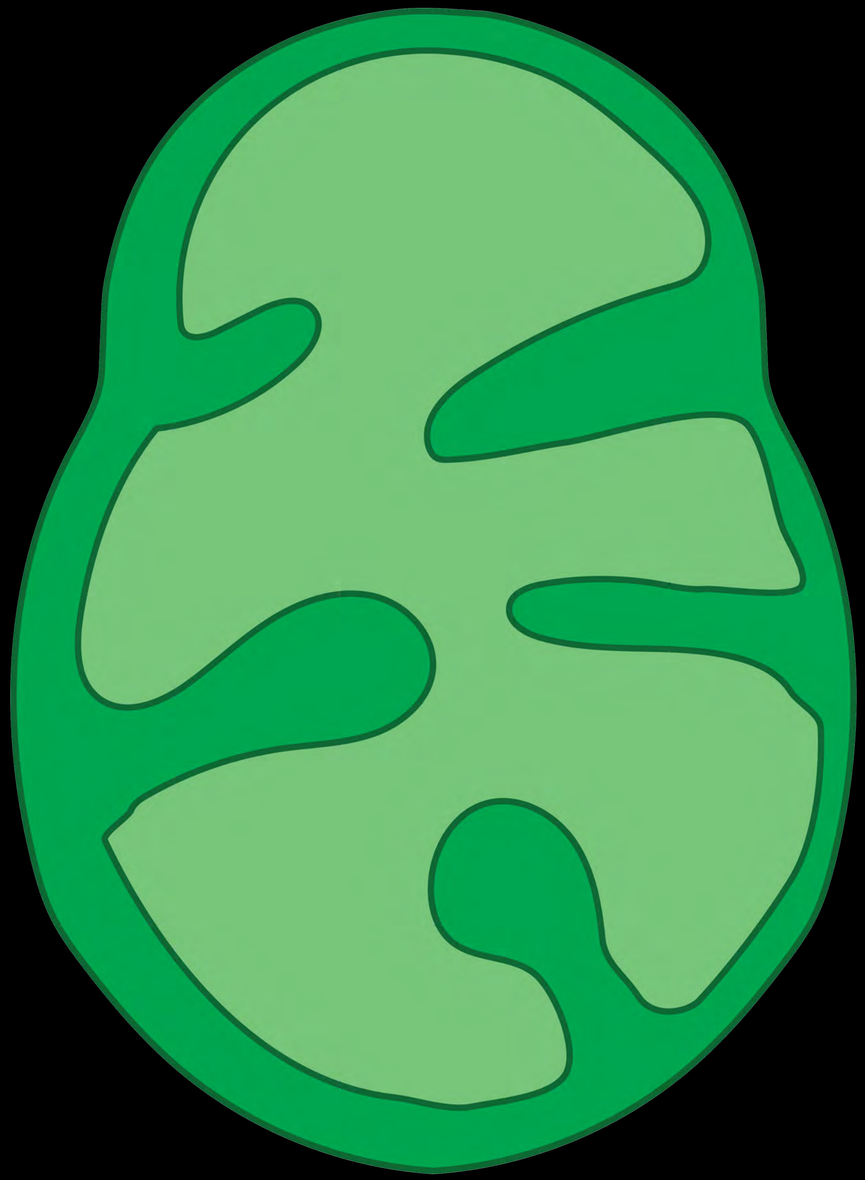
Patient Cells ($MFN2^{D414V}$)



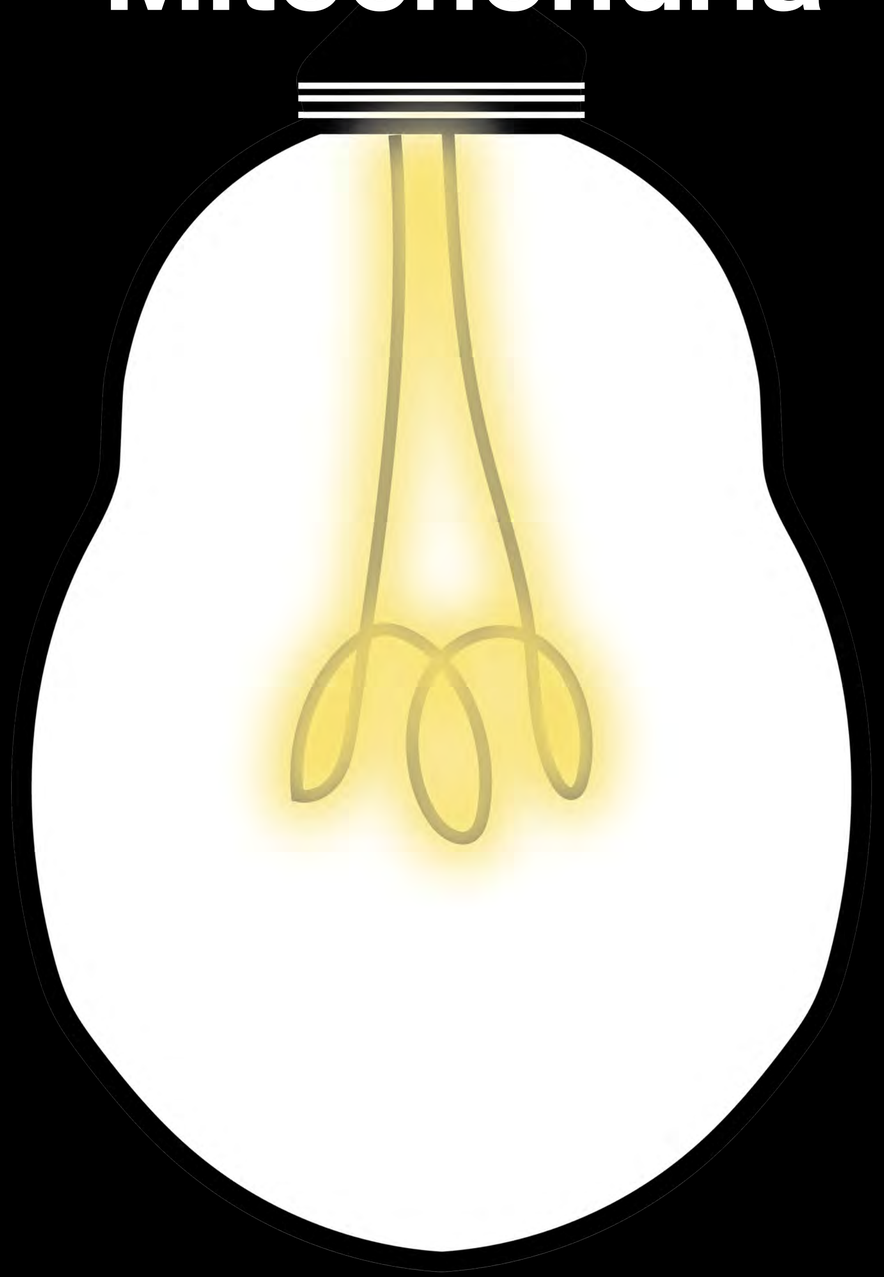
Patient Cells ($MFN2^{D414V}$)



Mitochondria

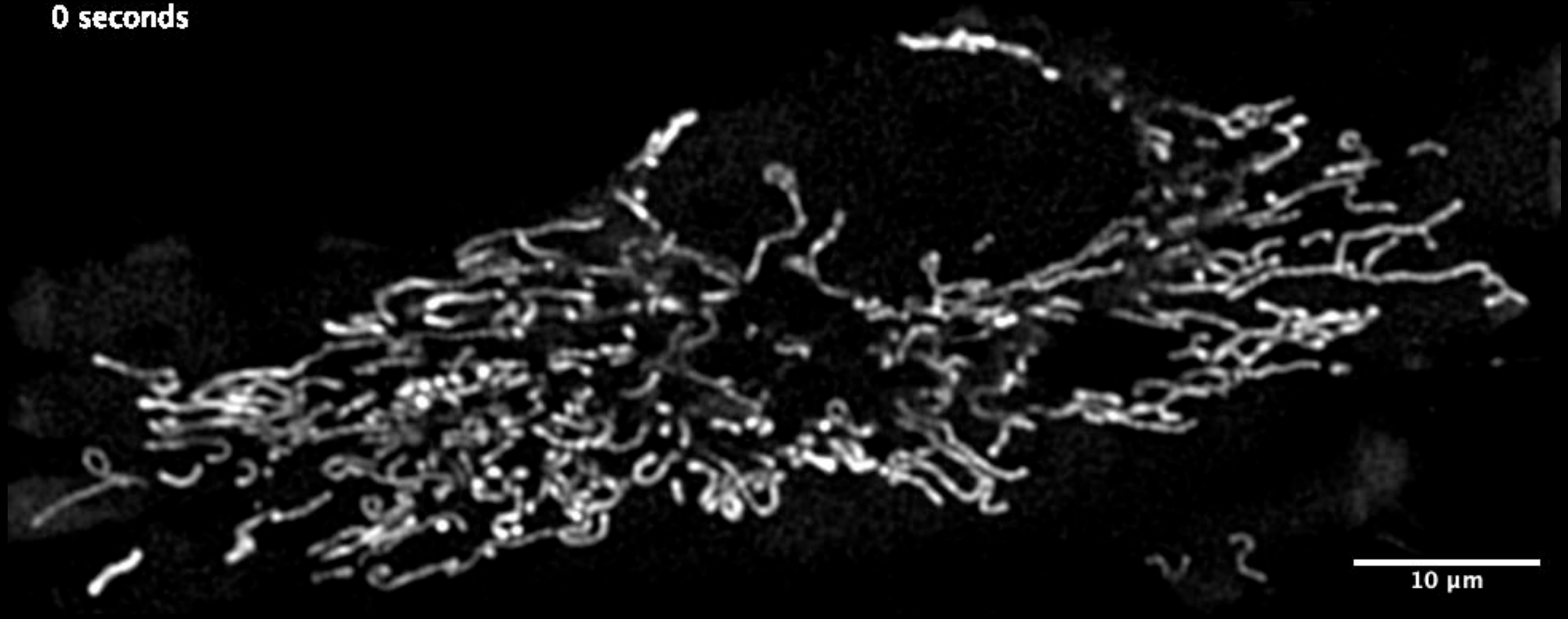


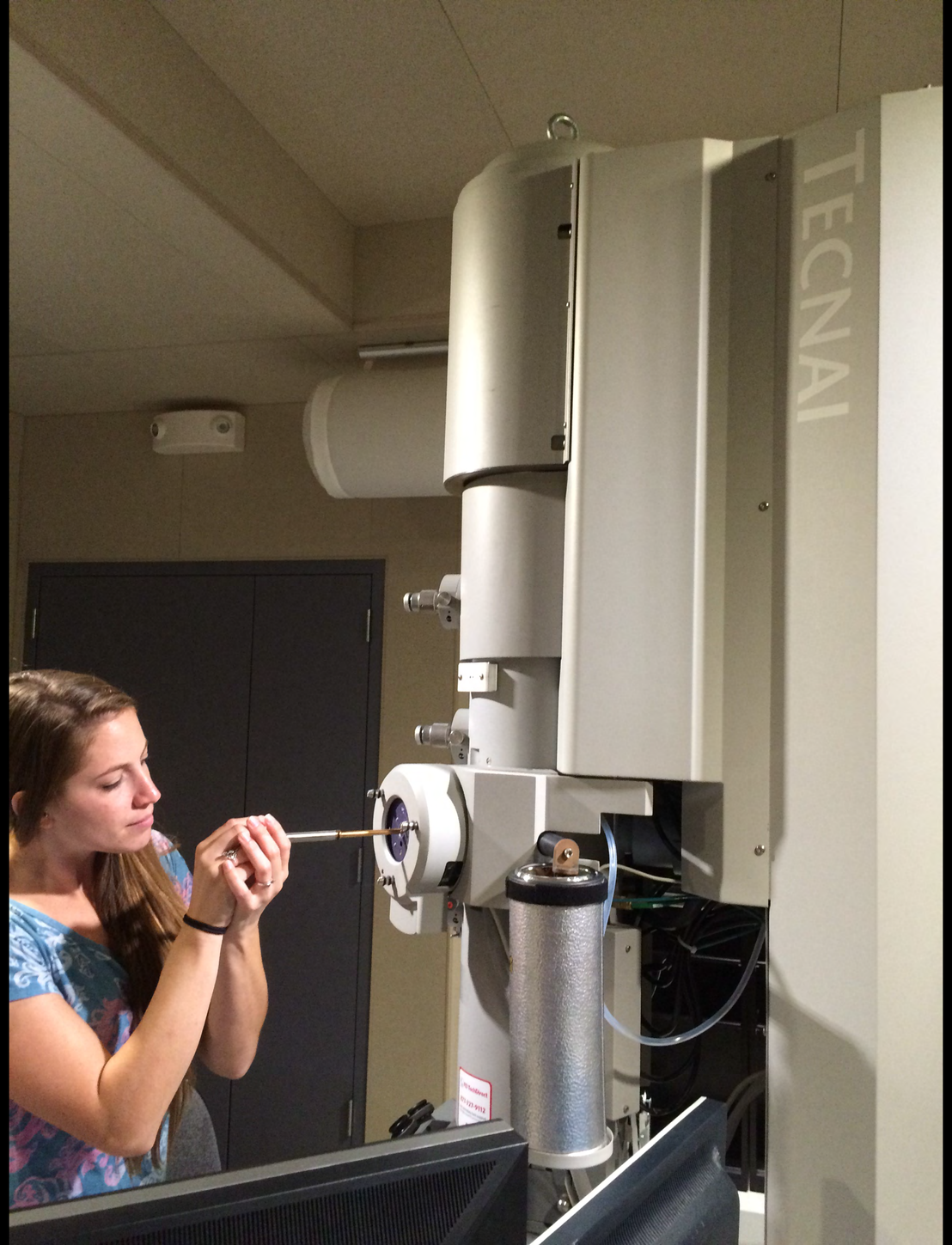
Mitochondria



‘Powerhouse of the cell’

Mitochondria are constantly moving (dynamic)

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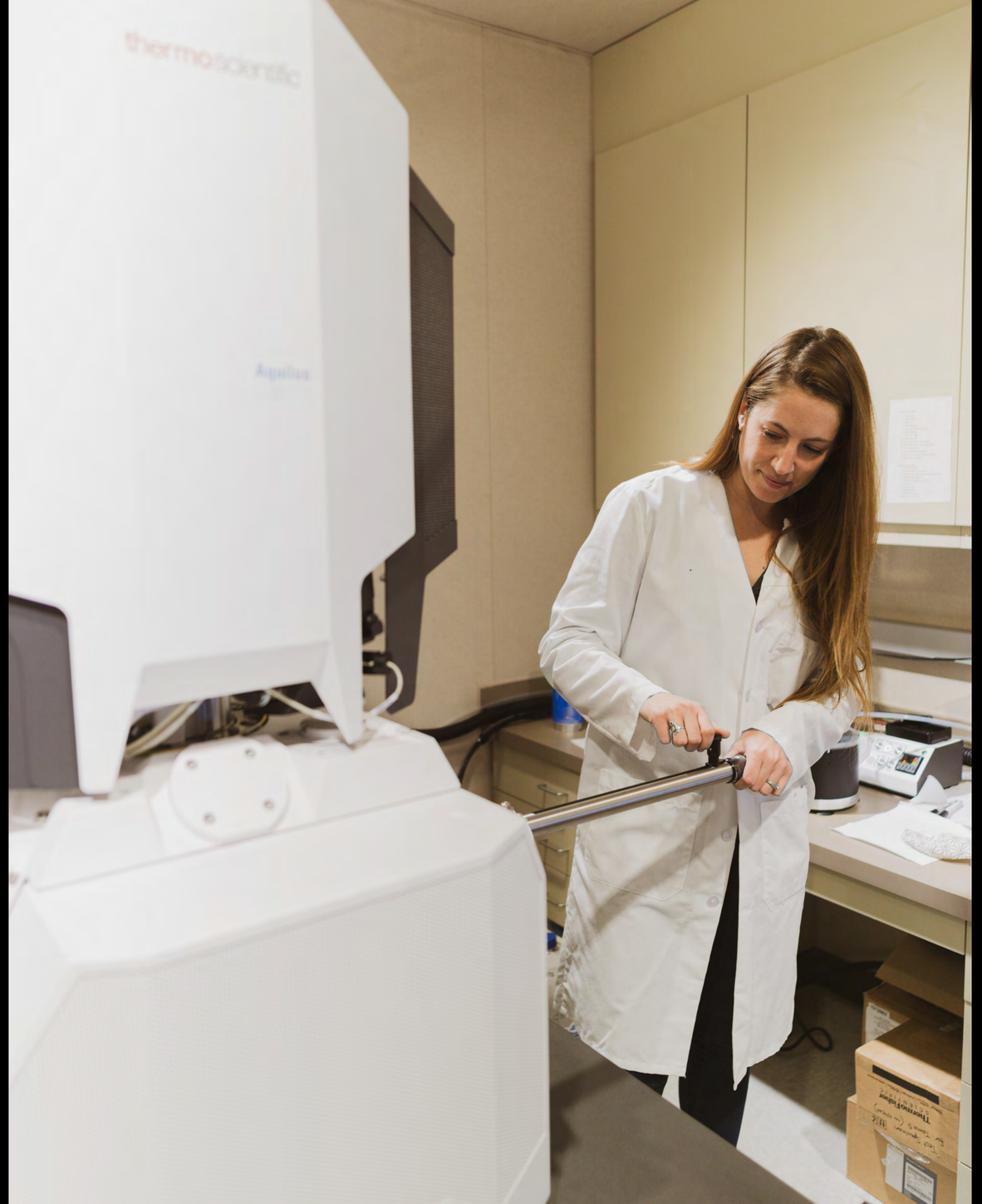
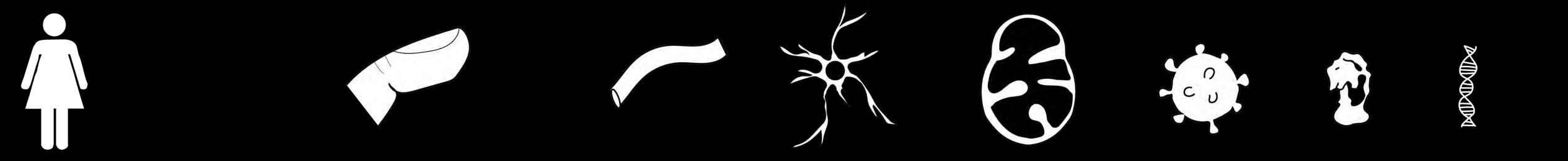
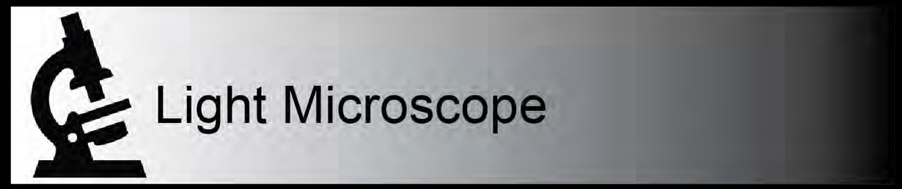
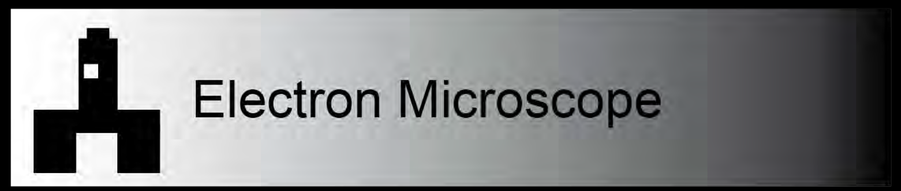

thermoscientific
Aquilus


TITAN

Visualizing Life Across Scales







Support Across Scales

Support Across Scales

Research Team

Michaela Medina *Hamid Rahmani* *Atty Chang* *Tumara Boyd* *Michaela Horger* *Sam Oviedo* *Nitish Dua*

Ben Barad *Ashim Rai* *Daniel Fuentes* *Marina Youngblood* *Philipp Gerlof* *Joan Lee*

Support Across Scales

Friends and Family

Research Team

Support Across Scales

Community

Friends and Family

Research Team

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THE PEW CHARITABLE TRUSTS | Scholars Program *in the* Biomedical Sciences

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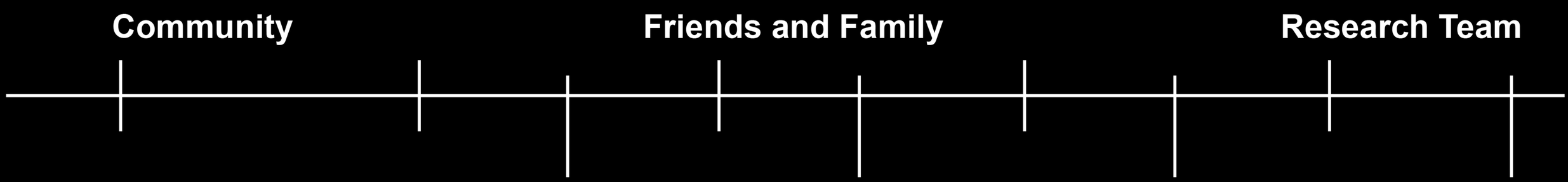
BACHRACH FAMILY FOUNDATION

NIH National Institutes of Health

National Institute of Neurological Disorders and Stroke

Support Across Scales



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