3Rs Change with the 3Rs Collaborative

Evidence-Based, Practical, and Impactful

Lauren Young | Sarah Thurston

CALAS 2024

Hello!

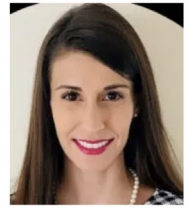
I'm Lauren Young

Program Manager of The 3Rs Collaborative

MSc in Animal Behavior & Welfare
University of Guelph

The 3RsC's mission is to advance better science – for both people & animals

3RsC members span across the scientific field.



abbvie Genentech GSK Lilly scientist.com VERISIMLife

charles river Roper Toxicology Consulting Limited AZAR innovations University of Colorado Anschutz Medical Campus EMORY UNIVERSITY

UF UNIVERSITY of FLORIDA UNIVERSITY of WASHINGTON PRINCETON UNIVERSITY USDA AWIC NIH National Institutes of Health Office of Laboratory Animal Welfare FASEB Federation of American Societies for Experimental Biology NC 3Rs

The 3RsC's Strategy has 3 Goals:

1. Promote the 3Rs Broadly by creating a research landscape that is knowledgeable & supportive of the 3Rs

2. Promote Specific 3Rs Strategies by advancing implementation of high-impact, evidence-based, & practical 3Rs techniques.

3. Promote Our Organization by building collaborations & awareness of resources and programs from The 3Rs Collaborative.

To promote specific high-impact 3Rs strategies, we

1. **Choose the right topics & create strategic working groups** of diverse stakeholders to lead our efforts.
2. **Work to understand the status quo** through longitudinal surveys and discussions with stakeholders.
3. **Accelerate implementation** through creating resources for implementation (SOPs, tech hubs), demonstrating social proof, and addressing any misconceptions or operational challenges.

Our current specific 3Rs efforts:

We have done the work to evaluate which 3Rs strategies are evidence-based, high-impact, & practical:

1. Microphysiological Systems (MPS)
2. Refined Mouse Handling
3. Translational Digital Biomarkers
4. Microphysiological Systems
5. Artificial Intelligence
6. Environmental Health Monitoring
7. Compassion Fatigue Resiliency

TODAY'S AGENDA: 9:15am-10am

High-level intro to MPS

Lauren Young

9:15 – 9:30

Refined Mouse Handling

Sarah Thurston

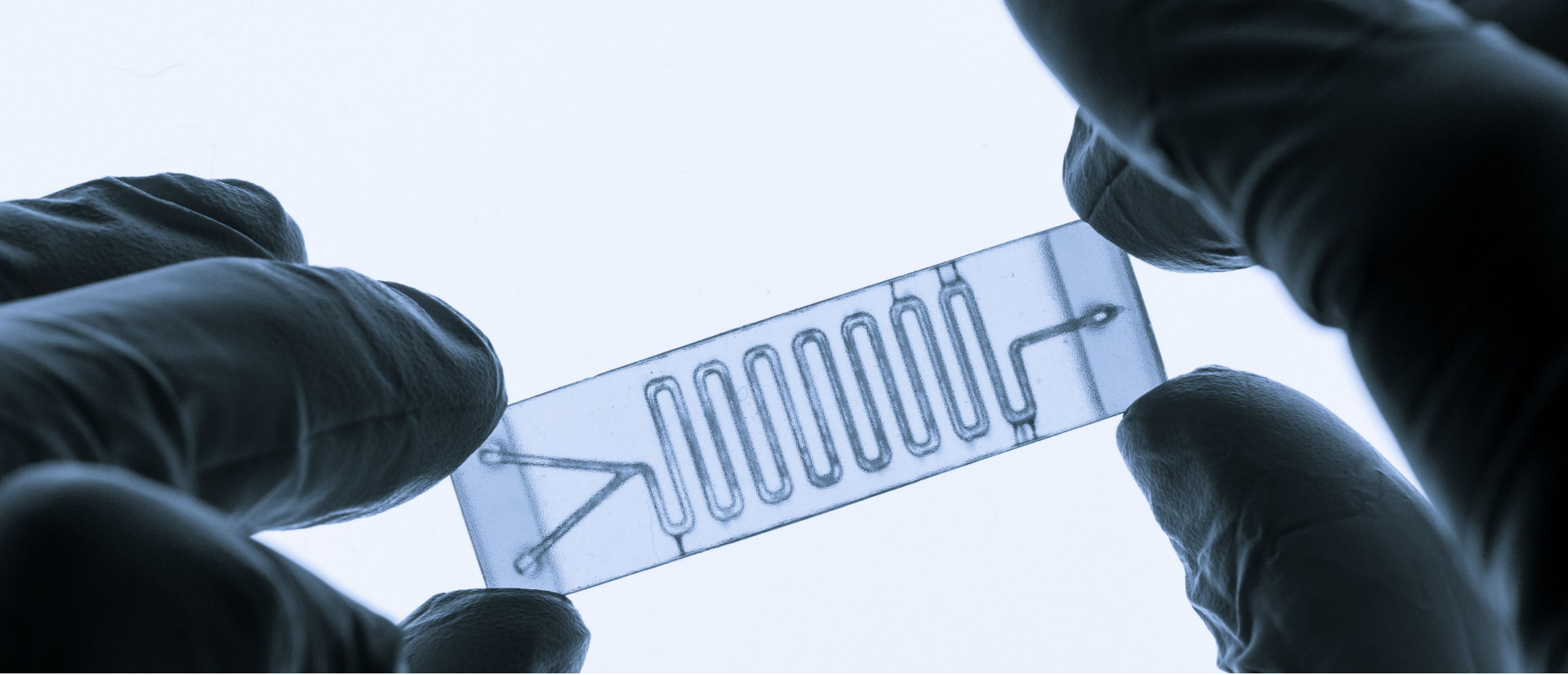
9:30 – 9:45

Compassion Fatigue Resiliency

Lauren Young

9:45 - 10

Questions will be taken at the end of each section



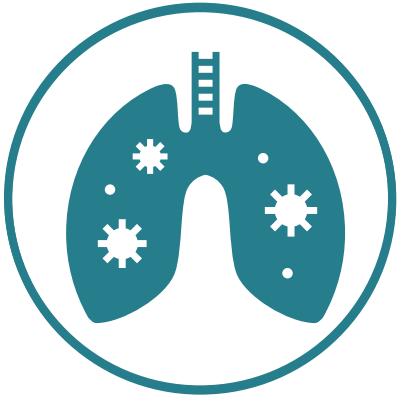
An introduction to Microphysiological Systems


Much of our animal research, we hope to eventually impact the human population

We believe that microphysiological systems are a key application of the 3Rs as part of continuous scientific progress.

So…what are microphysiological systems?

Miniaturized systems of organ-specific cell types that mimic physiology

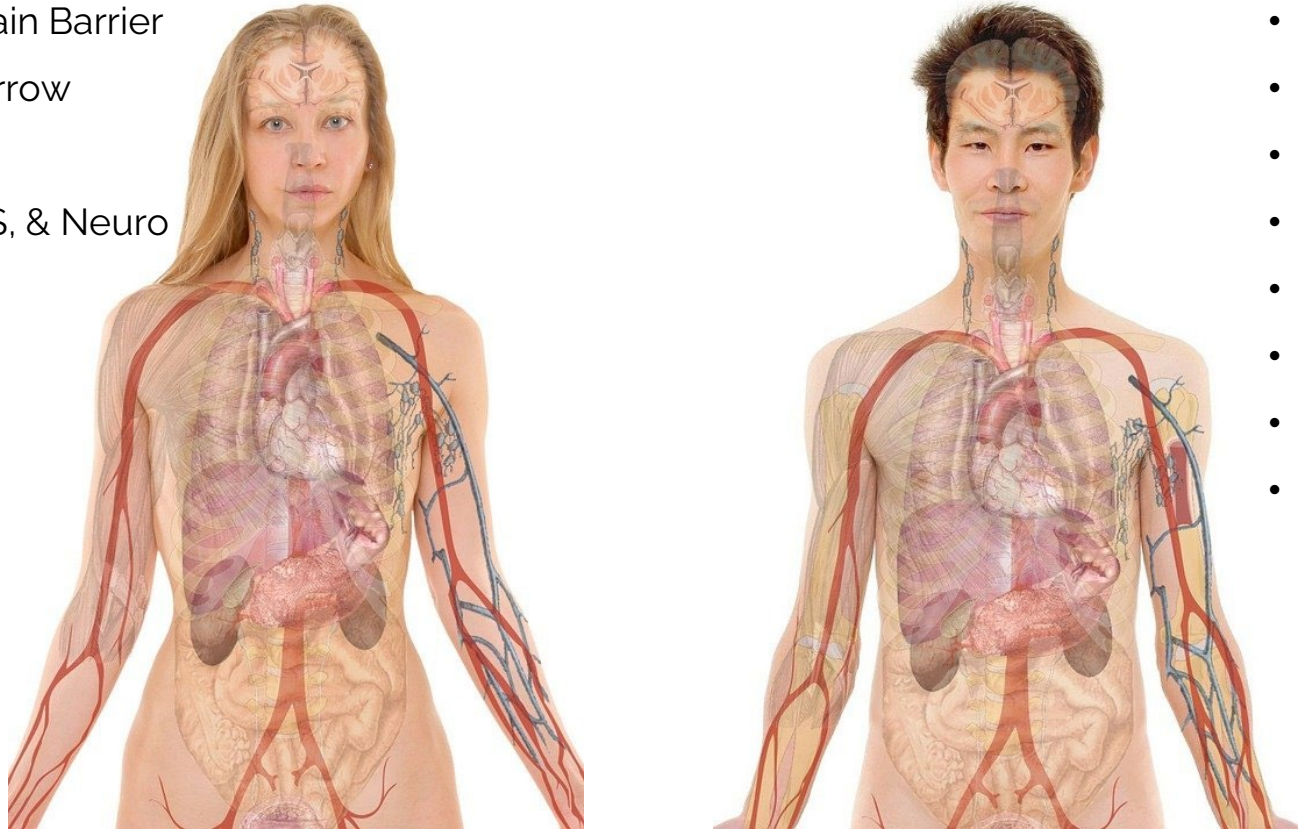


Can model healthy or diseased tissues

Some systems are viable for up to 3 months

Microphysiological systems have been created for almost **every organ.**

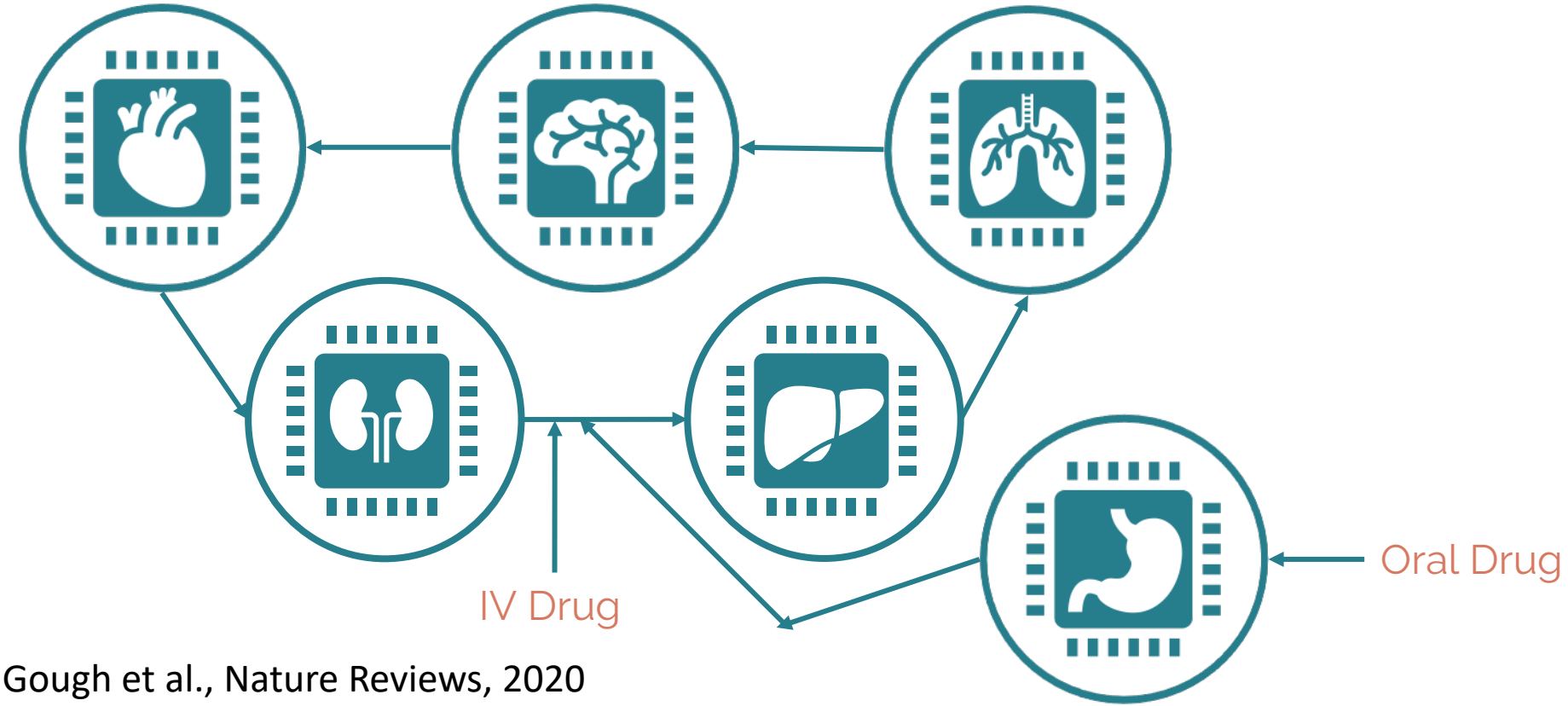
- Blood Brain Barrier
- Bone Marrow
- Cartilage
- CNS, PNS, & Neuro
- Fat
- Gut
- Heart
- Kidney
- Liver



- Lung
- Ocular
- Pancreas
- Reproductive
- Skeletal Muscle
- Skin
- Tumor
- Vasculature

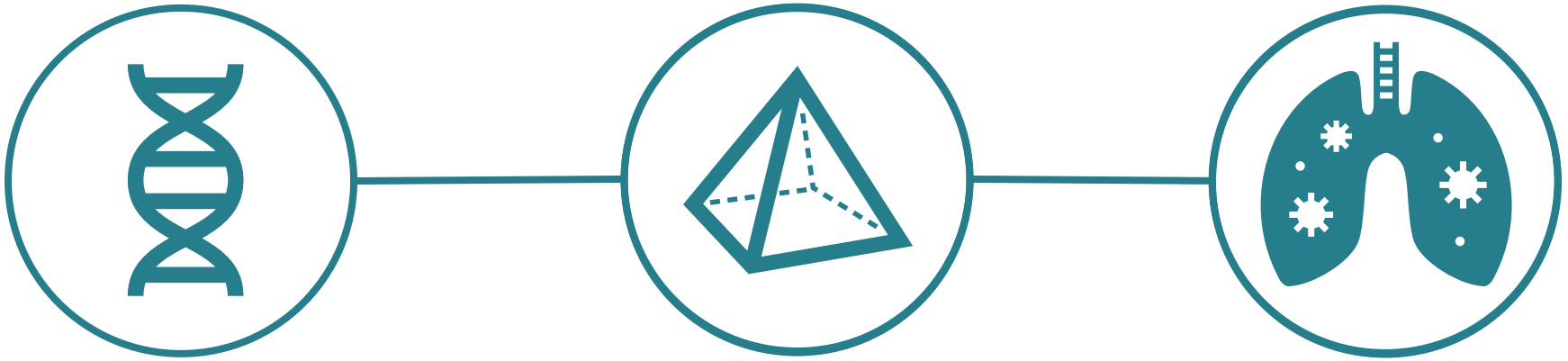
Journal Of Laboratory Automation
20(3) 2015

MPS can be linked in multi-organ systems & mimic drug administration route.



Gough et al., Nature Reviews, 2020

Microphysiological systems show translational promise.



Recapitulation

Toxicity

Disease replication & efficacy

MPS can recapitulate disease-related phenotypes.

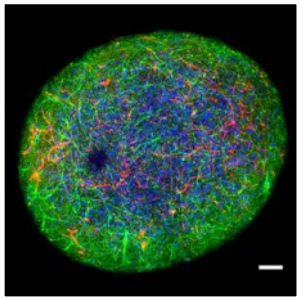
Neuro MPS Example

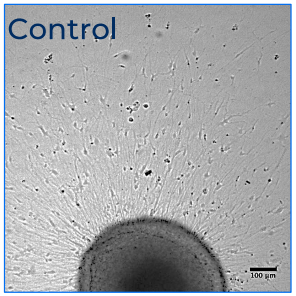
Neurite Outgrowth

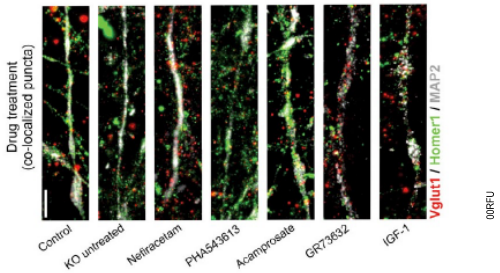
Synapse Formation

Neural Function

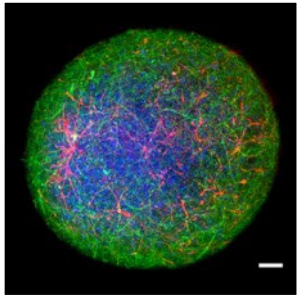
Control

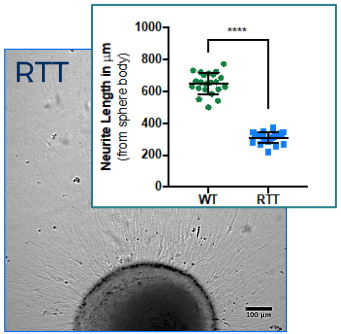


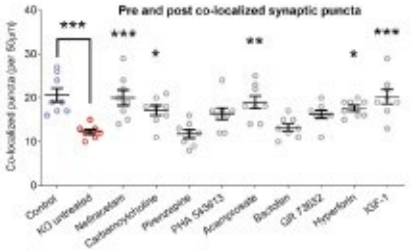




Rhett Disease



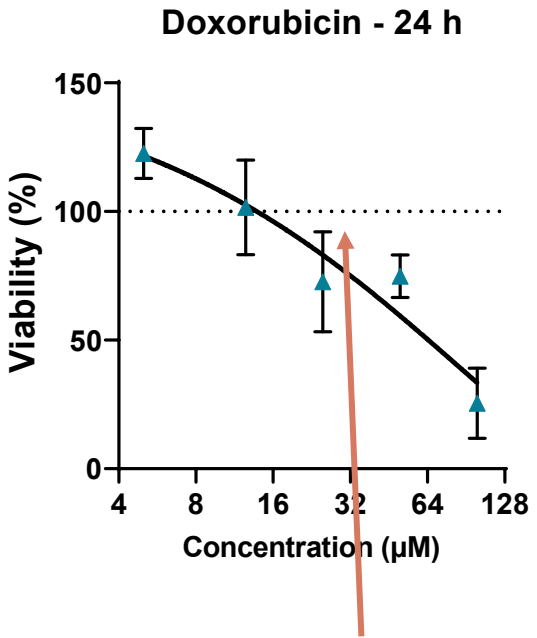




Trujillo et al., 2020

Some MPS can predict toxicity.

Cytotoxic



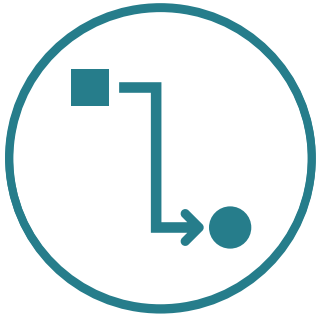
Cells viability decreases in a dose-dependent manner to known toxins

(Dr Valeria Chichagova & Dr. Carol de Santis)

Key promises for MPS & other NAMs

- **New approach methodologies**: MPS, artificial intelligence, etc...

Elimination of compounds likely to fail



Basic research into mechanisms

Precision medicine

Rare diseases & no relevant animal models

How does this relate to the 3Rs?

- Microphysiological systems primarily address replacement, although they can sometimes contribute to refinement & reduction too.

Microphysical systems have limitations too.

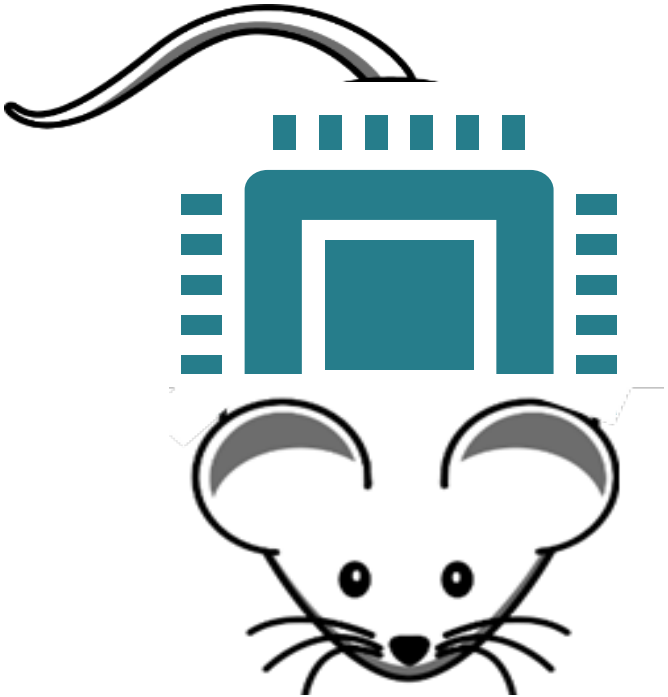
More independent characterization & validation needed

Not appropriate for all paradigms: Behavior, mental health issues, modeling fractures of large bones, cardiac output

Not shaped by external stimuli

Don’t recapitulate all organ features Interactions with other organs are limited

Ultimately, microphysiological systems can be integrated with animal studies to advance science.



Encourage investigators to check out our MPS website hub

Donate

Micro

We collaborat

systems.

JOIN OUR I

VISIT OUR

Microphysiological Systems Technology Hub

Commercially available microphysiological systems.

Overview | Tech Hub | Presentations | MPS & the FDA Modernization Act | Conferences | Initiative FAQ & How to Join

Microphysiological Systems (MPS) are *in vitro* models composed of cells, tissue explants, or stem-cell derived 'organoid' formations of human or animal origin. These models provide translational biochemical, electrical, and/or physiomechanical responses to represent organ and tissue function, with great potential to replace some animals used in research.

Below you can explore Microphysiological System Companies offering commercially available advanced in vitro models across a variety of organs as well as enabling technologies. This includes organ-on-a-chip, organoid, and spheroid companies. Individual technology providers may offer products or services, share key publications, and encourage contact and questions via the outreach buttons.

To learn more about a particular organ system, check out our MPS presentation page. So far we've hosted presentations on liver, kidney, neuro, blood-brain-barrier, and vascular MPS.

Overview | Tech Hub

FAQ & How to Join

Overview of Microphysiological Systems

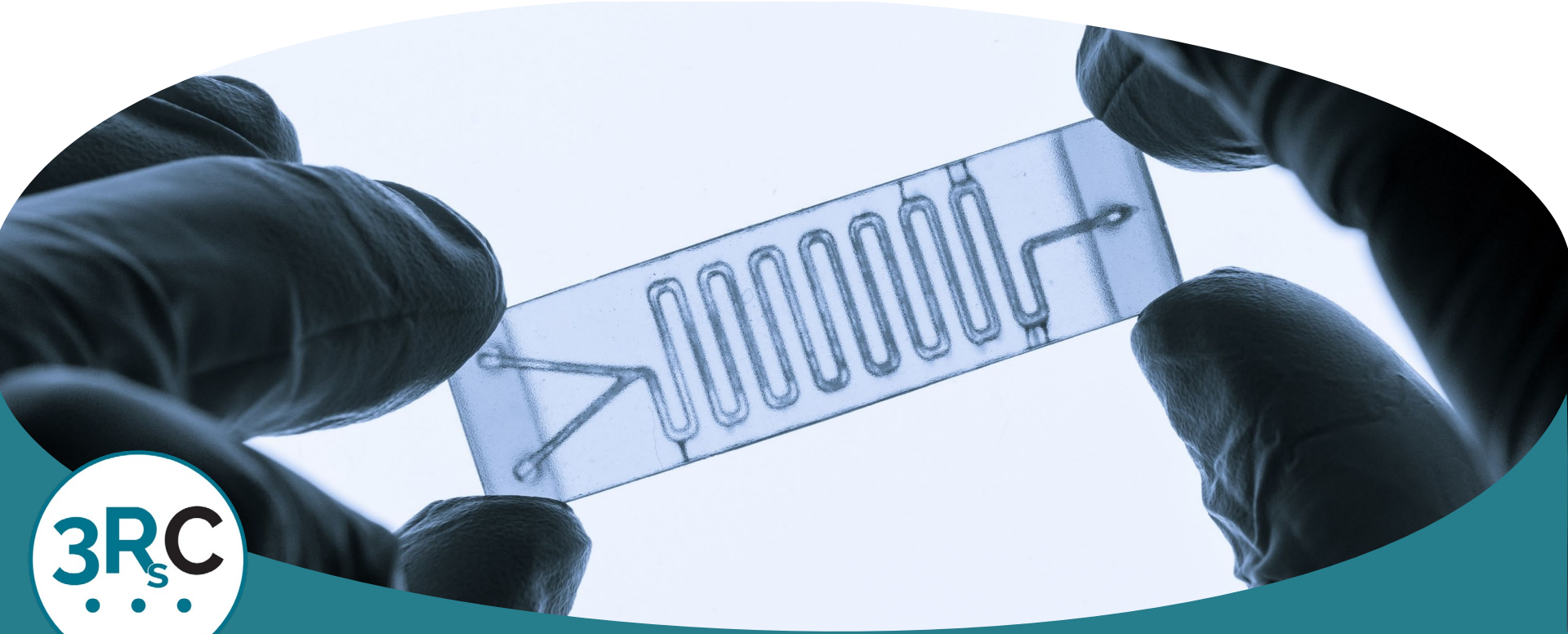
If you are new to microphysiological systems or a particular MPS organ model, start with the videos below. They give an introduction to MPS, a 2022 status update, and webinars that give a broad overview of each organ system. To connect with commercial technology providers, check out our MPS Technology Hub.

Playlist 2 Videos

- An Introduction to Microphysiological Systems
- North America MPS Update, 2022

Thank you to our current MPS initiative members

Questions?



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Refined Mouse Handling

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Compassion Fatigue Resiliency

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Refined Mouse Handling

Sarah Thurston BS, LAT, CLABP
Coordinator, Animal Behavior and Welfare Management Programs
Charles River Laboratories

Refined handling may also be called non-aversive handling or low stress handling and refers to the method used to *remove mice from their home cage* while avoiding lifting mice by the tail.

Traditionally, mice have been lifted by the base of the tail with fingers or forceps.

However, research started by Professor Jane Hurst in 2010 has shown us a better way to handle mice.

Strong evidence indicates that refined handling is advantageous.

(>25 publications across 14 years from independent labs)

What does refined handling look like?

Tunnel Handling

Video credit: CRL-GAW&T

Cup Handling

Video credit: Hurst & West 2010

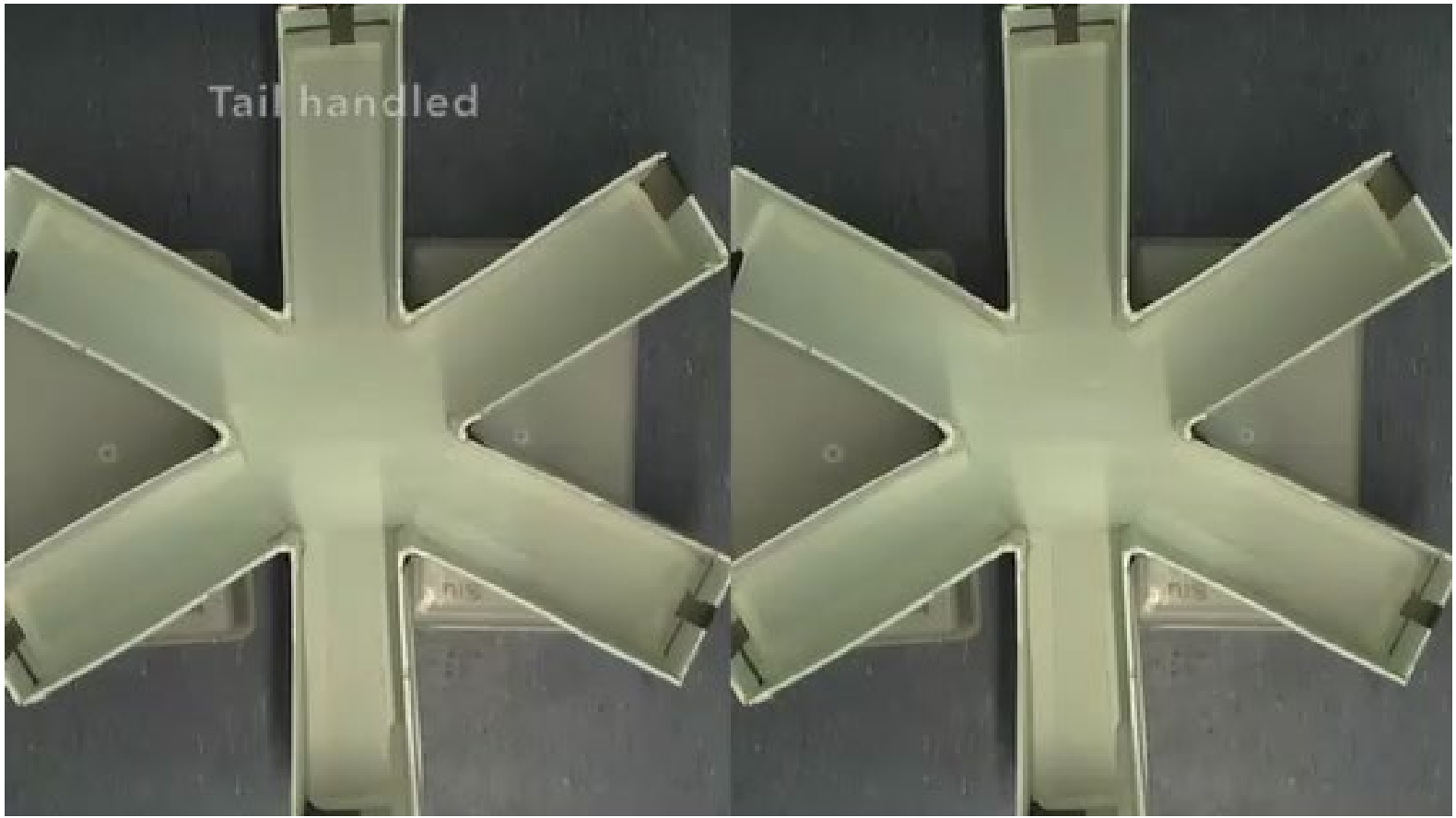
Benefits to mouse welfare

Mice handled with refined handling have improved behavioral and physiological responses compared with tail handled mice including...

- Reduced stress and anxiety
- Reduced depressive-like states
- Reduced fear

For full list of studies: https://www.nc3rs.org.uk/3rs-resources/mouse-handling/mouse-handling-research-papers

Benefits to mouse welfare



Video Credit: Jane Hurst – NC3Rs

Benefits to scientific outcomes

- Handling methods impact physiological data parameters and test reliability
  - Improved glucose tolerance, reduced stress hormones and smaller adrenal glands in mice handled with refined handling techniques

Ghosal et al., 2015, Clarkson et al., 2020

Benefits to breeding outcomes

- Mice handled with refined handling have improved breeding outcomes as shown by larger pups, more pups born and weaned, and a longer reproductive lifespan
  - In one study, tunnel handled animals averaged 1 extra pup per pair born and weaned.

Hull et al., 2022, 2024

Benefits to handlers

Refined handling reduces handling stress, lowers bite risk, and encourages voluntary interaction which encourages more **positive human-animal interactions.**

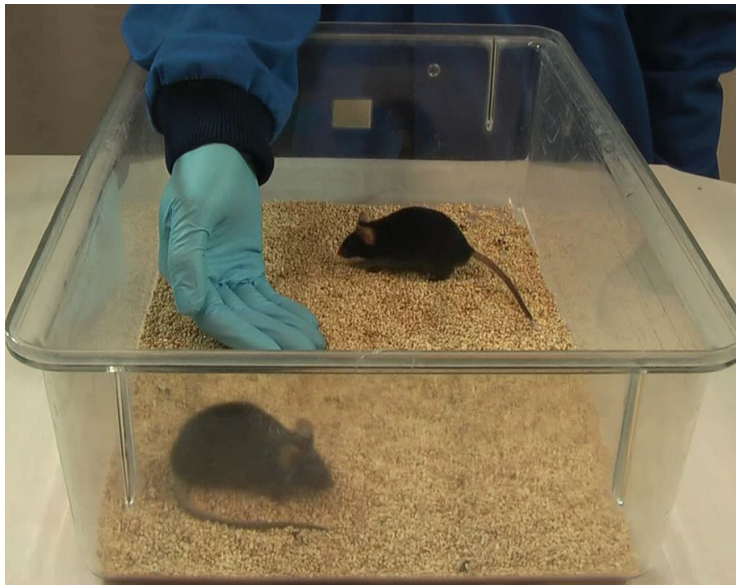
In a study, most personnel engaged in **positive human-animal interactions** report higher levels of **compassion satisfaction.**

Increased **compassion satisfaction** has been linked to lower levels of burnout and higher rates of retention among animal research personnel.

LaFollette et al, 2020, Cake and Bell, 2019, Young et al., 2024

The only difference in the mice below is in how they were picked up

After tail handling



After tunnel handling

Hurst & West 2010

Will it take too long?

- One pilot study found cage change times were 10-25 minutes **faster** per 100 cages when comparing tunnels to forceps after 1-2 change cycles (Reynolds, 2022)
- 2023 data from a study at AMGEN, found that **tunnel handling took less time** than tail handling for a number of mouse strains with Balb/c being the only outlier

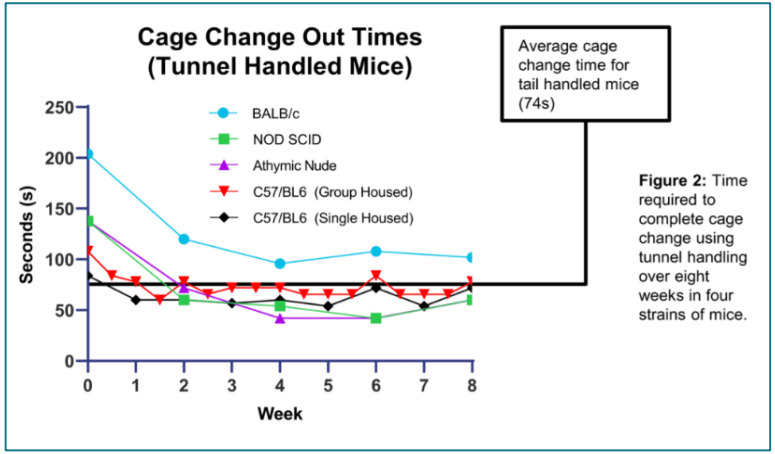
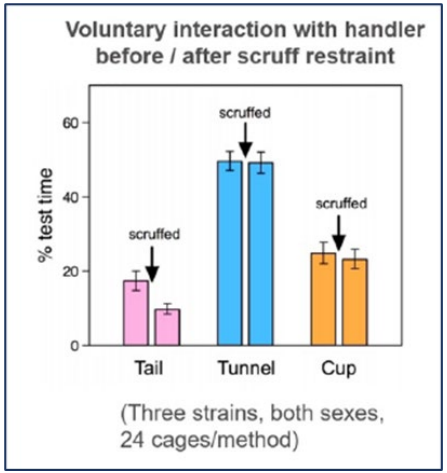


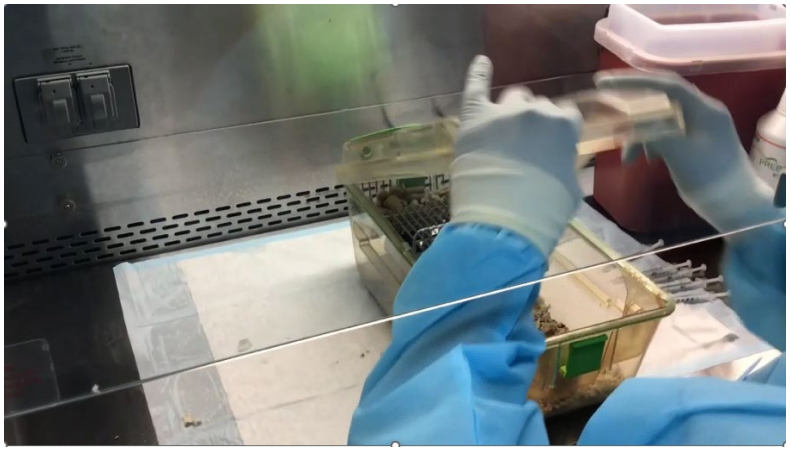
Figure 2: Time required to complete cage change using tunnel handling over eight weeks in four strains of mice.

Arnott et al., 2023

Can I still restrain for procedures?

- You can restrain via scruff or tail for procedures *after removing from enclosure via refined handling* without counteracting the positive benefits of refined handling!
- **How mice are removed from the home enclosure is most important**



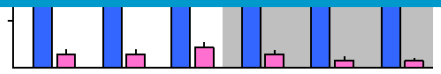


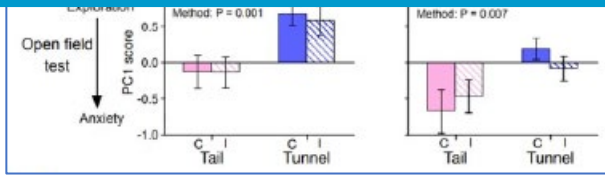
Hurst & West, 2010, Gouveia & Hurst, 2019, Henderson et al., 2020

Can I still perform procedures?

- Refined handling is beneficial prior to performing routine

Research shows that it's not restraint or procedures alone that are stressful. Rather, the combination of these procedures + tail handling is stressful.





Gouveia & Hurst, 2019, Nakamura & Suzuki, 2018

3RCs Study

- Research personnel in diverse roles (e.g., veterinarians, managers, caretakers, researchers, etc.) were surveyed about their current use, knowledge, and beliefs about refined handling in 2021
- Asked quantitative and qualitative questions to get a holistic picture of participant's beliefs

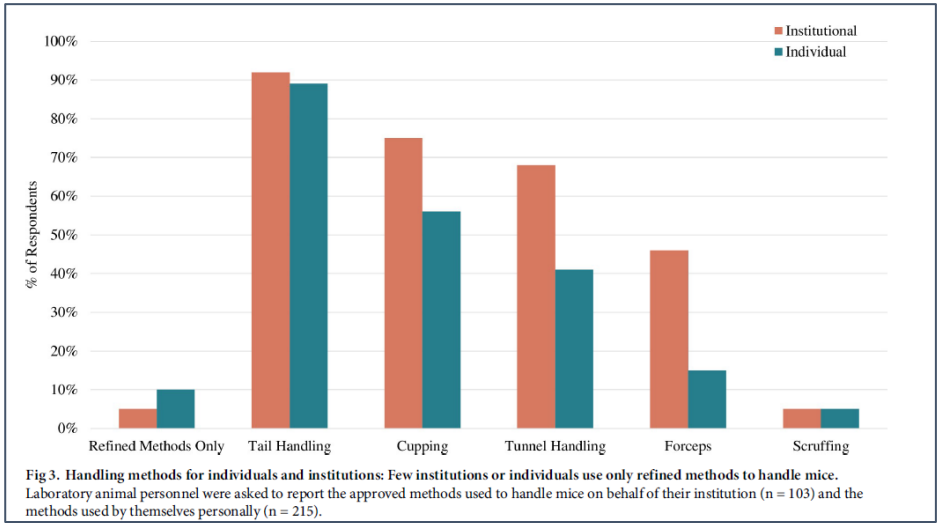


Fig 3. Handling methods for individuals and institutions: Few institutions or individuals use only refined methods to handle mice. Laboratory animal personnel were asked to report the approved methods used to handle mice on behalf of their institution (n = 103) and the methods used by themselves personally (n = 215).

Young et al., 2023

Barriers to implementation

- 65% of participants described individual “barriers” considered to be misconceptions
- 32% of the situations that participants described as institutional “barriers” are considered to be misconceptions

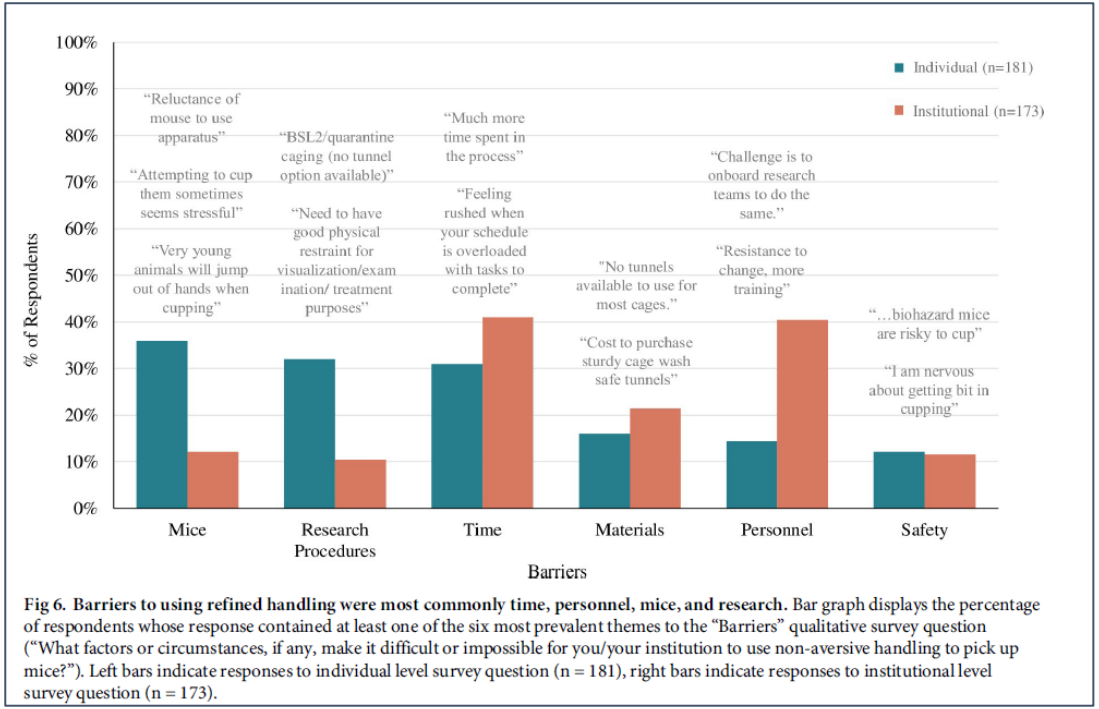


Fig 6. Barriers to using refined handling were most commonly time, personnel, mice, and research. Bar graph displays the percentage of respondents whose response contained at least one of the six most prevalent themes to the “Barriers” qualitative survey question (“What factors or circumstances, if any, make it difficult or impossible for you/your institution to use non-aversive handling to pick up mice?”). Left bars indicate responses to individual level survey question (n = 181), right bars indicate responses to institutional level survey question (n = 173).

Full paper available here

Young et al., 2023

Resources, outreach and education

Resources

Prevalence & Barriers longitudinal survey (ongoing)

Resource Hub

Certification Course

Outreach/Education

Presentations

Workshops

3RsC's Refined Handling Hub.

https://www.na3rsc.org/refined-mouse-handling-overview/

Overview | How To | Operations and Tunnels | Institutional Change | Presentations | Publications

Workshops | Time and Other Concerns | e-Learning Course | FAQs

How to conduct refined mouse handling

Tunnel handling vs. cupping

Tunnel handling simply involves guiding mice into a tunnel to pick them up out of their cage. They can then be tipped out of the tube backward and scruffed for procedures, as needed. The benefits of tunnel handling remain even if mice are subsequently given injections, have blood drawn, or undergo gas anesthesia.

Cupping involves picking mice up with cupped hands. It does not require any new equipment but does require a bit more training of mice.

See **How to conduct refined handling** for more information on tunnel and cupping methods.

Tunnel handling

Cupping

Choosing a Tunnel

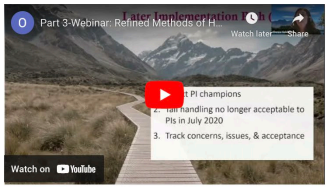
Tunnel	Source	Material
	Bio-Serv	high temp polycarbonate
	Scanbur	high temp polycarbonate
	LBS Biotechnology	polycarbonate
	Bio-Serv	recycled pulp paper
	Datesand	high temp polycarbonate

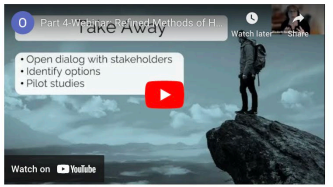
Creating Institutional Change for Refined Mouse Handling

It takes time and dedicated effort to switch an entire institution to refined mouse handling. Below are the steps we recommend taking for the best success.

Success Stories

Below are success stories from AstraZeneca and University of Florida that detail their processes, challenges, and solutions in transitioning their institutions to refined mouse handling.





Workshops

- Overview, training plan, and logistics available to download on website
- **June:** CALAS National Meeting in Saskatoon
- **November:** National AALAS Meeting in Nashville
- Is your institution hosting a symposium, conference or meeting where you think a refined handling workshop could be incorporated? Reach out to laurenyoung@3rc.org to discuss collaboration with the 3RsC

Certification Course

- Developed in conjunction with NC3Rs
- Free, open-access
- The course includes 5 different sections
  - Background
  - Evidence
  - Tunnel Handling
  - Cup Handling
  - Next Steps
- Each section contains lessons, video demonstrations, knowledge checks and quizzes
- The course will take approximately 45 minutes to complete from start to finish

Takeaway: refined handling is advantageous to animals, science, & people.

Improves animal welfare

Increases scientific quality

Improves ease of handling

Citations

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14. Nakamura, Y., & Suzuki, K. (2018). Tunnel use facilitates handling of ICR mice and decreases experimental variation. Journal of veterinary medical science, 18-0044.
15. Reynolds, P. S. (2022). Introducing non-aversive mouse handling with 'squnnels' in a mouse breeding facility. Animal Technology and Welfare 21(1), 42-45.
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For full list of studies: https://www.nc3rs.org.uk/3rs-resources/mouse-handling/mouse-handling-research-papers

Thank you!
Questions?

Sarah.Thurston@crl.com

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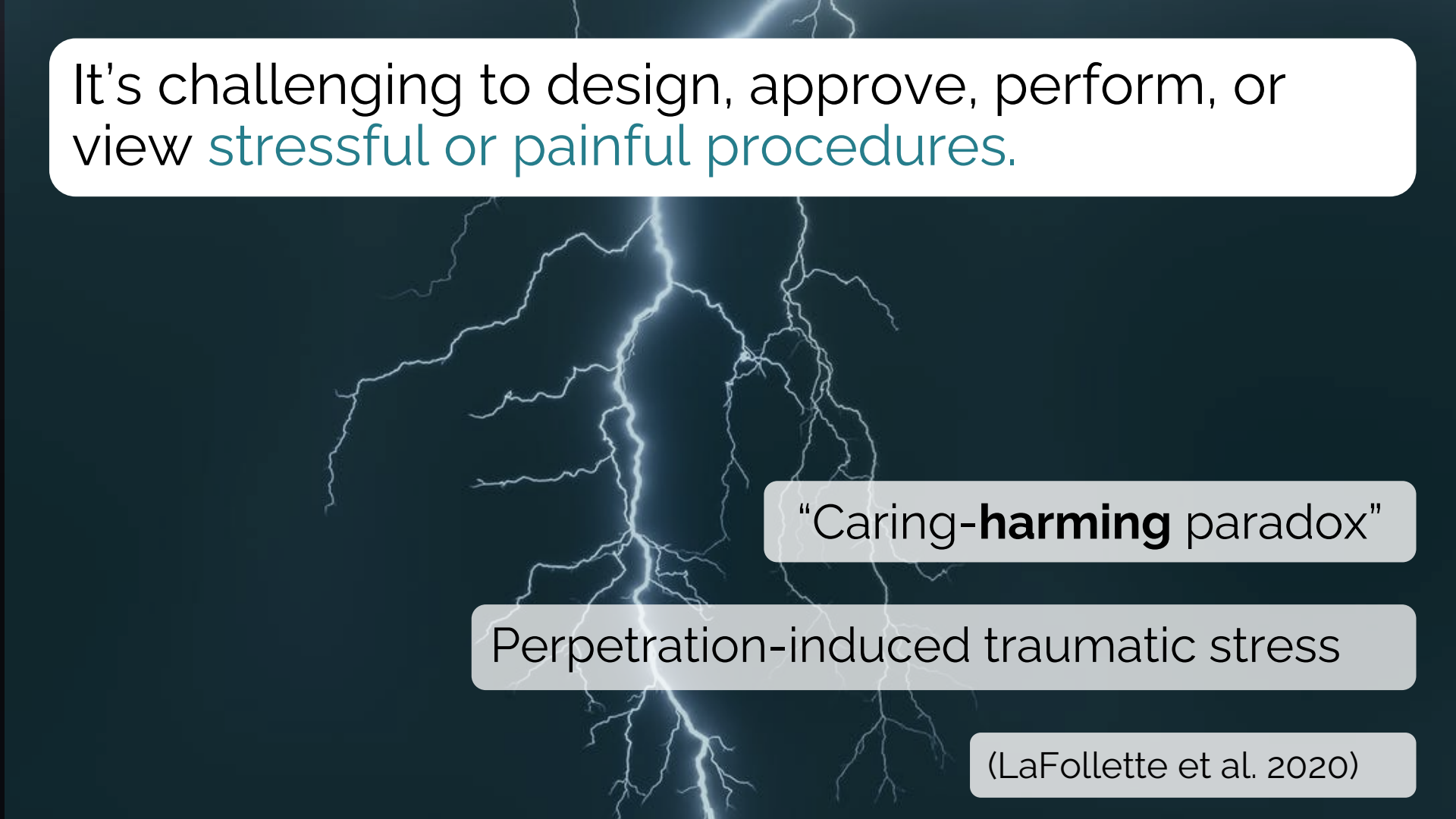
Compassion Fatigue, Resiliency & Culture of Care


Working in animal research is uniquely rewarding & challenging.

It can be deeply meaningful & rewarding to promote animal welfare & good science.

Working with research animals can be challenging.



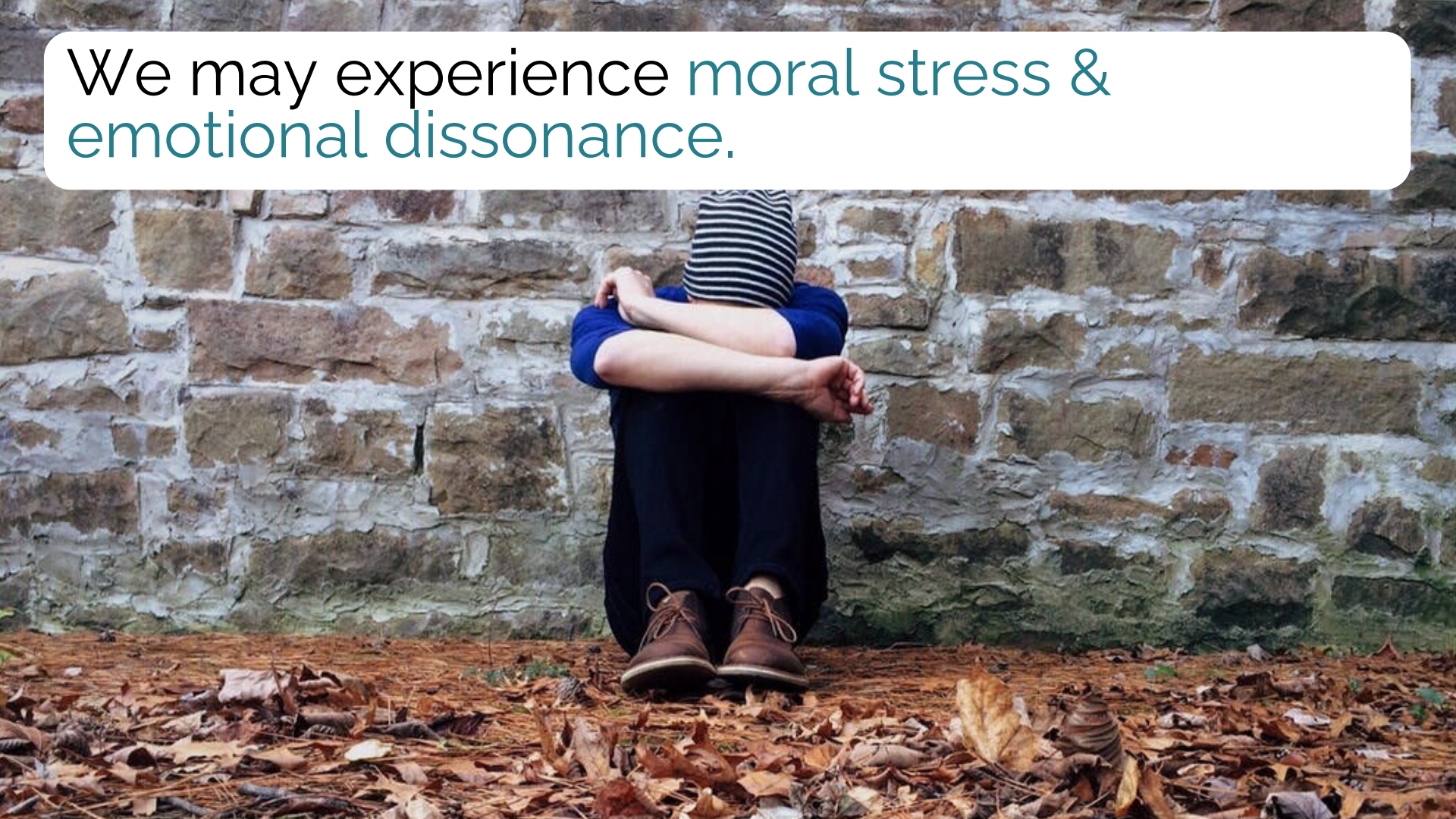
It's challenging to design, approve, perform, or view stressful or painful procedures.

"Caring-**harming** paradox"

Perpetration-induced traumatic stress

(LaFollette et al. 2020)

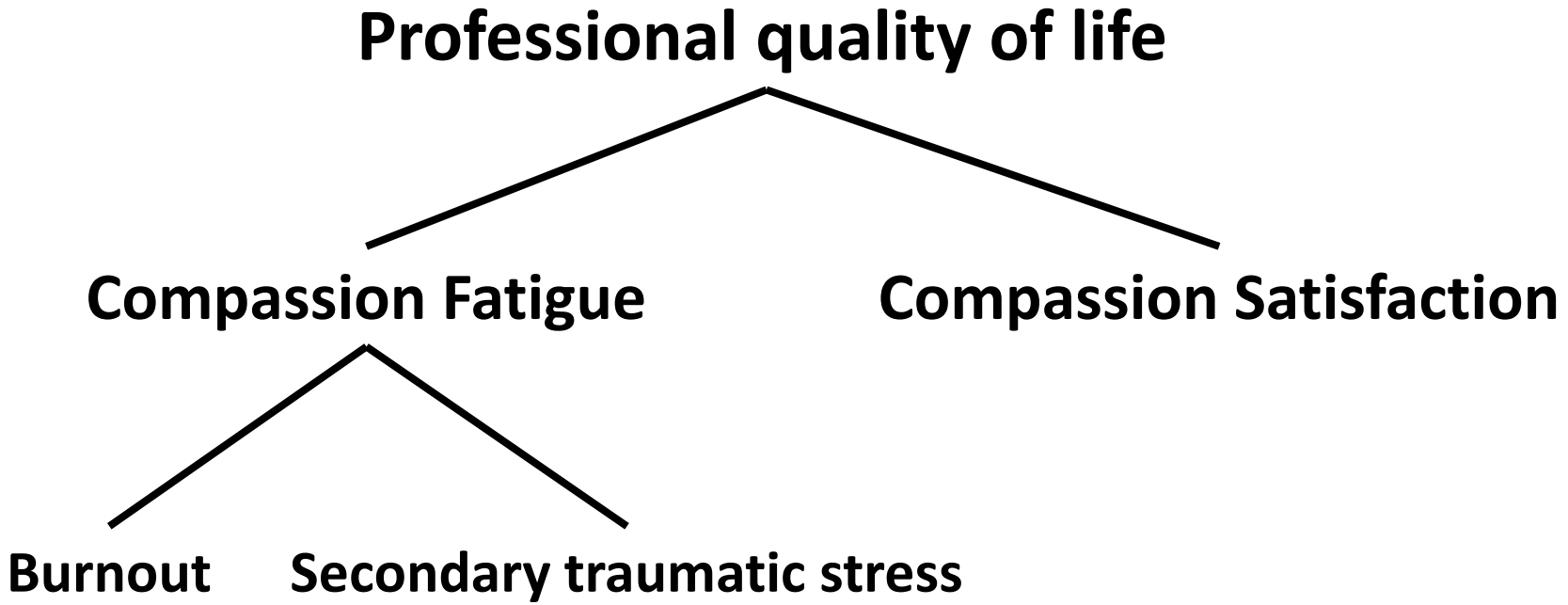
We may experience moral stress & emotional dissonance.

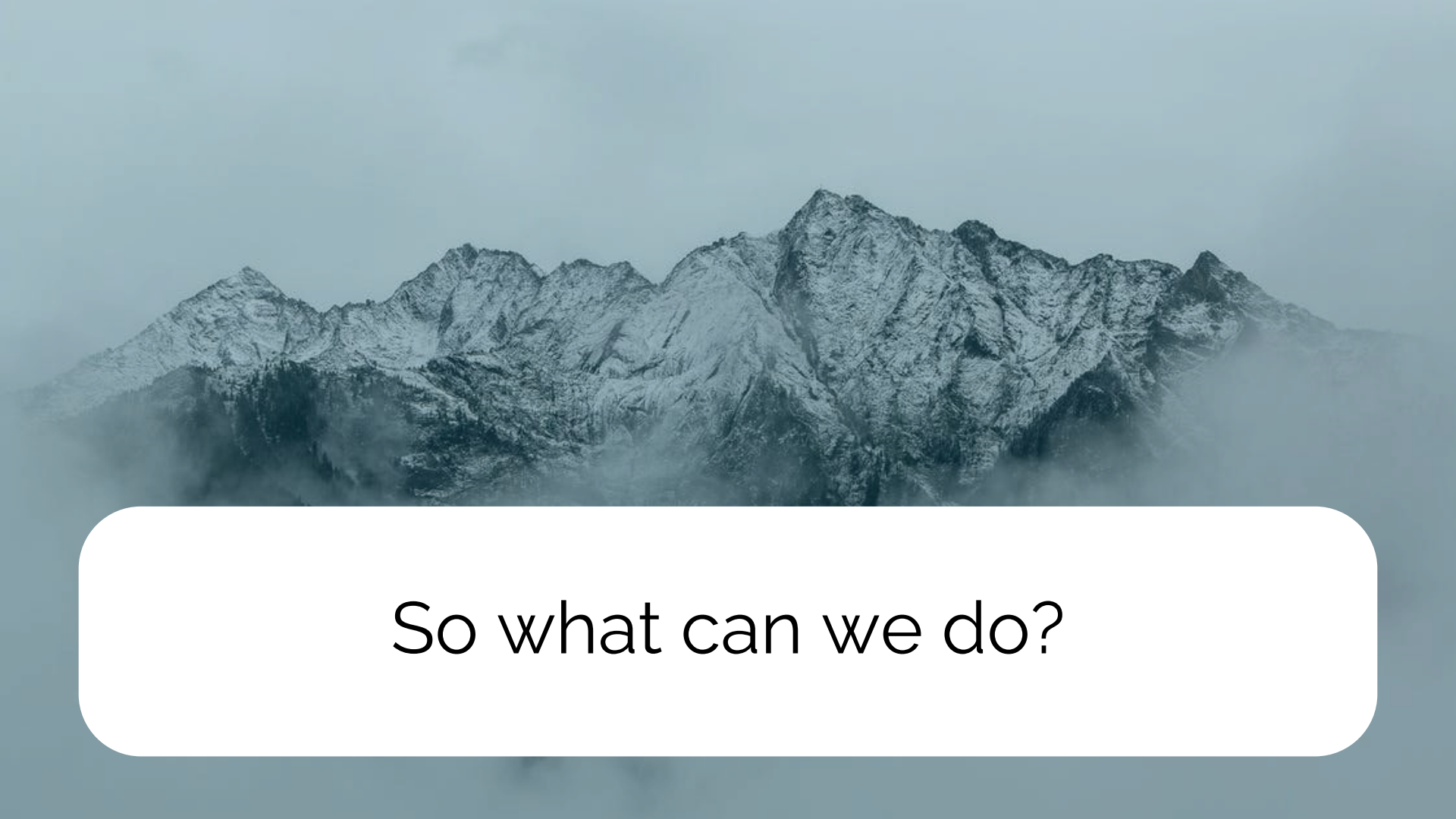


We may not feel supported or valued by family, friends, or society in our work.

(LaFollette et al. 2020, Goñi-Balentziaga et al. 2021, Schlanser et al. 2021)

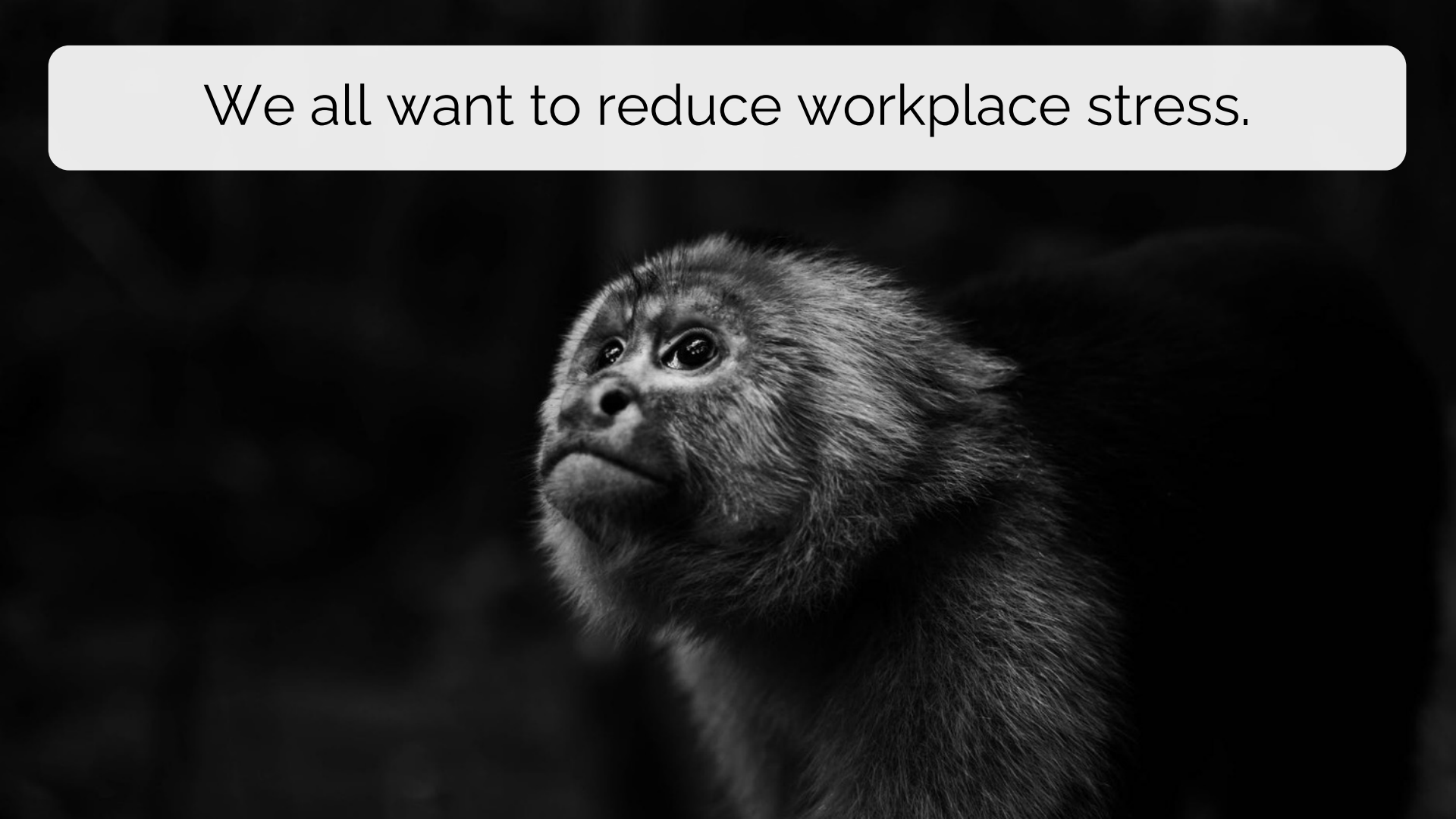
Caring for staff is about promoting a good professional quality of life:



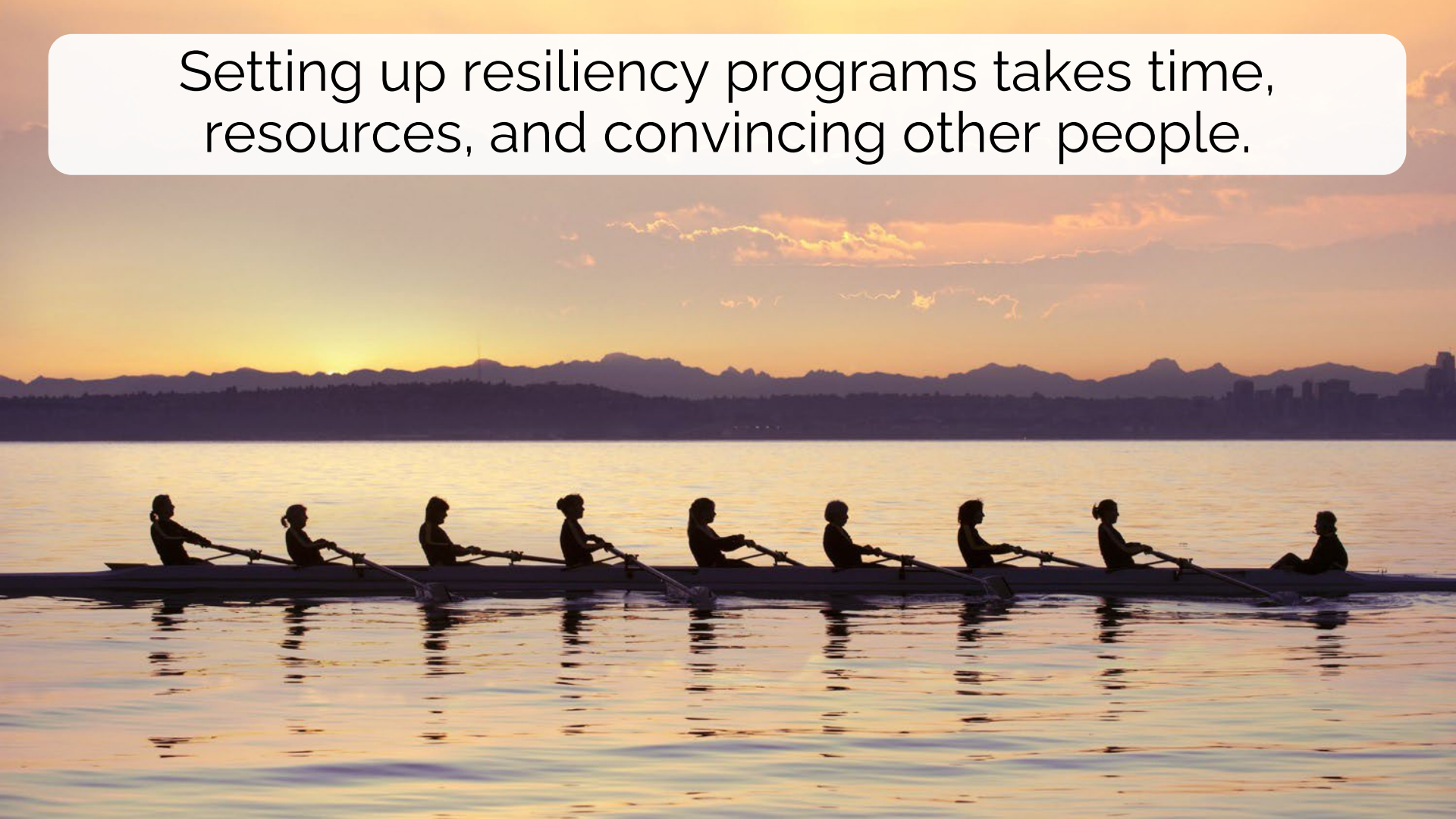


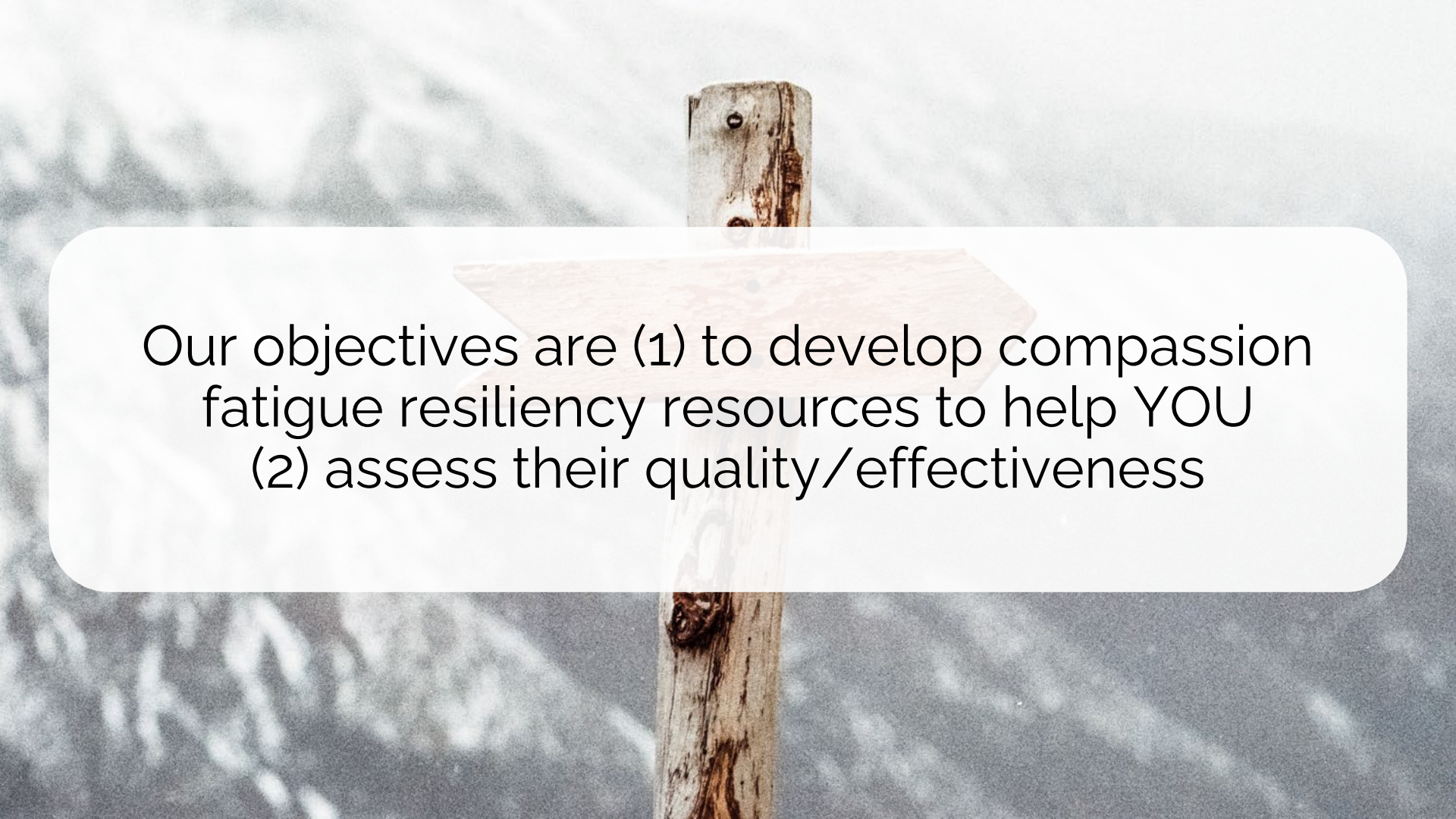
So what can we do?

We all want to reduce workplace stress.



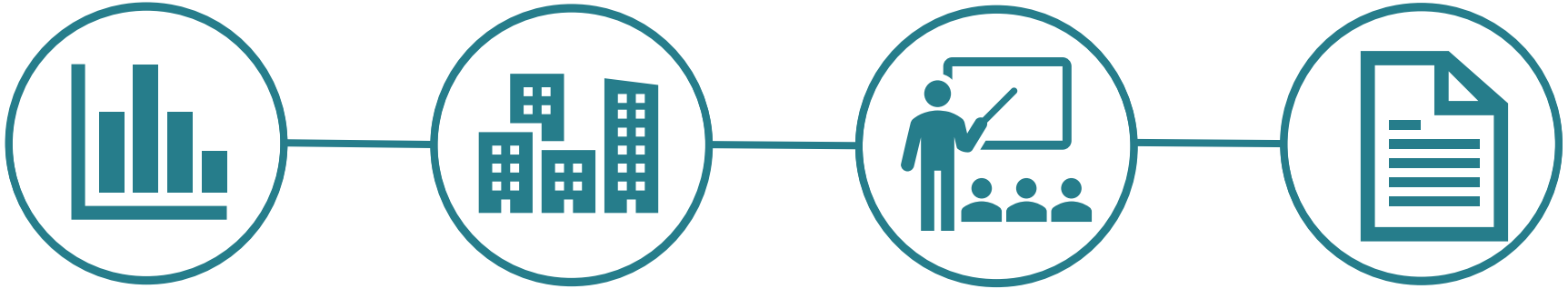
Setting up resiliency programs takes time, resources, and convincing other people.





Our objectives are (1) to develop compassion fatigue resiliency resources to help YOU (2) assess their quality/effectiveness

We created institutional resources, are formally evaluating them, & made them freely accessible.



Longitudinal Survey

Starter Pack & Resources

Interactive Webinars

Poster

https://bit.ly/3RC_CFR_Institutions

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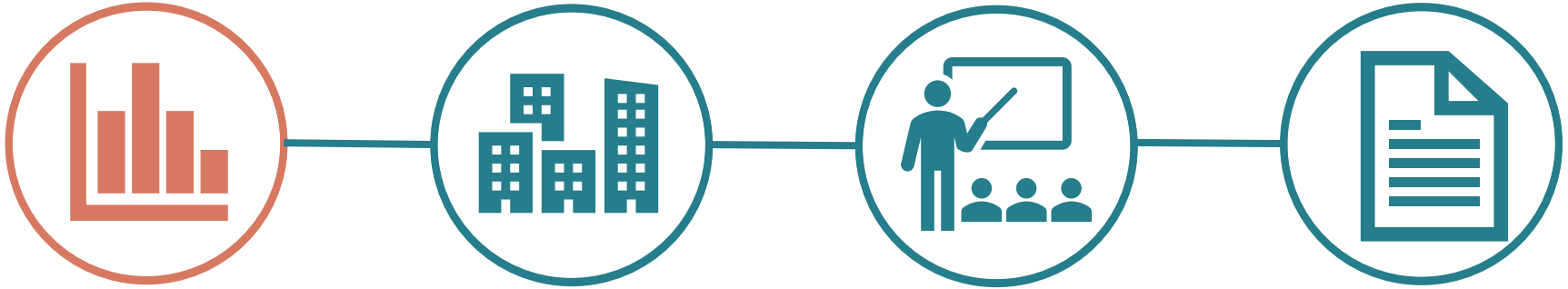

Longitudinal Survey

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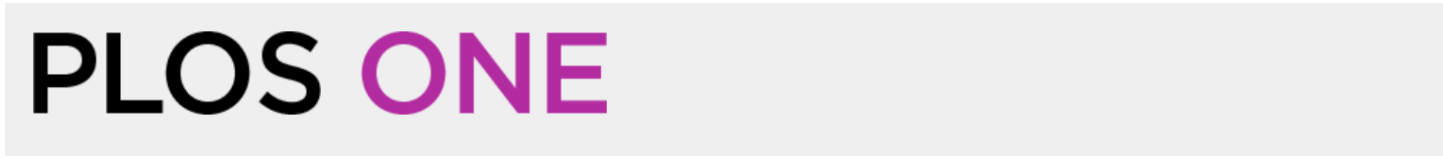
Results of baseline publication:



OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

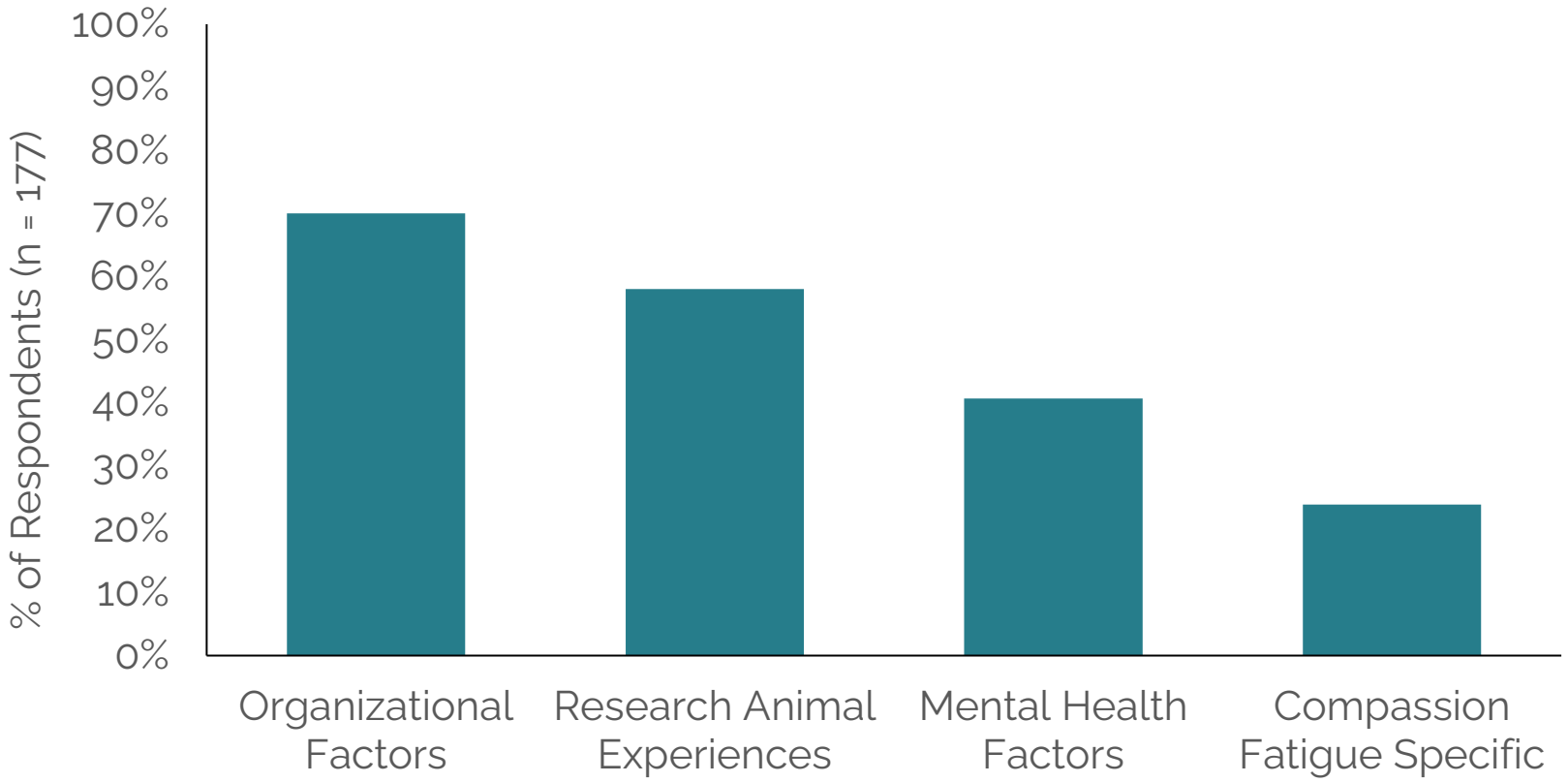
Professional quality of life in animal research personnel is linked to retention & job satisfaction: A mixed-methods cross-sectional survey on compassion fatigue in the USA

Lauren Young, Fabienne Ferrara, Lisa Kelly, Tara Martin, Sally Thompson-Iritani, Megan R. LaFollette

Professional quality of life is linked to job satisfaction & retention

- Increased compassion satisfaction = Increased job satisfaction & Increased retention
- Increased burnout = decreased job satisfaction

Participants indicated that their compassion fatigue was most impacted by Organizational Culture & Research Animal Experiences.



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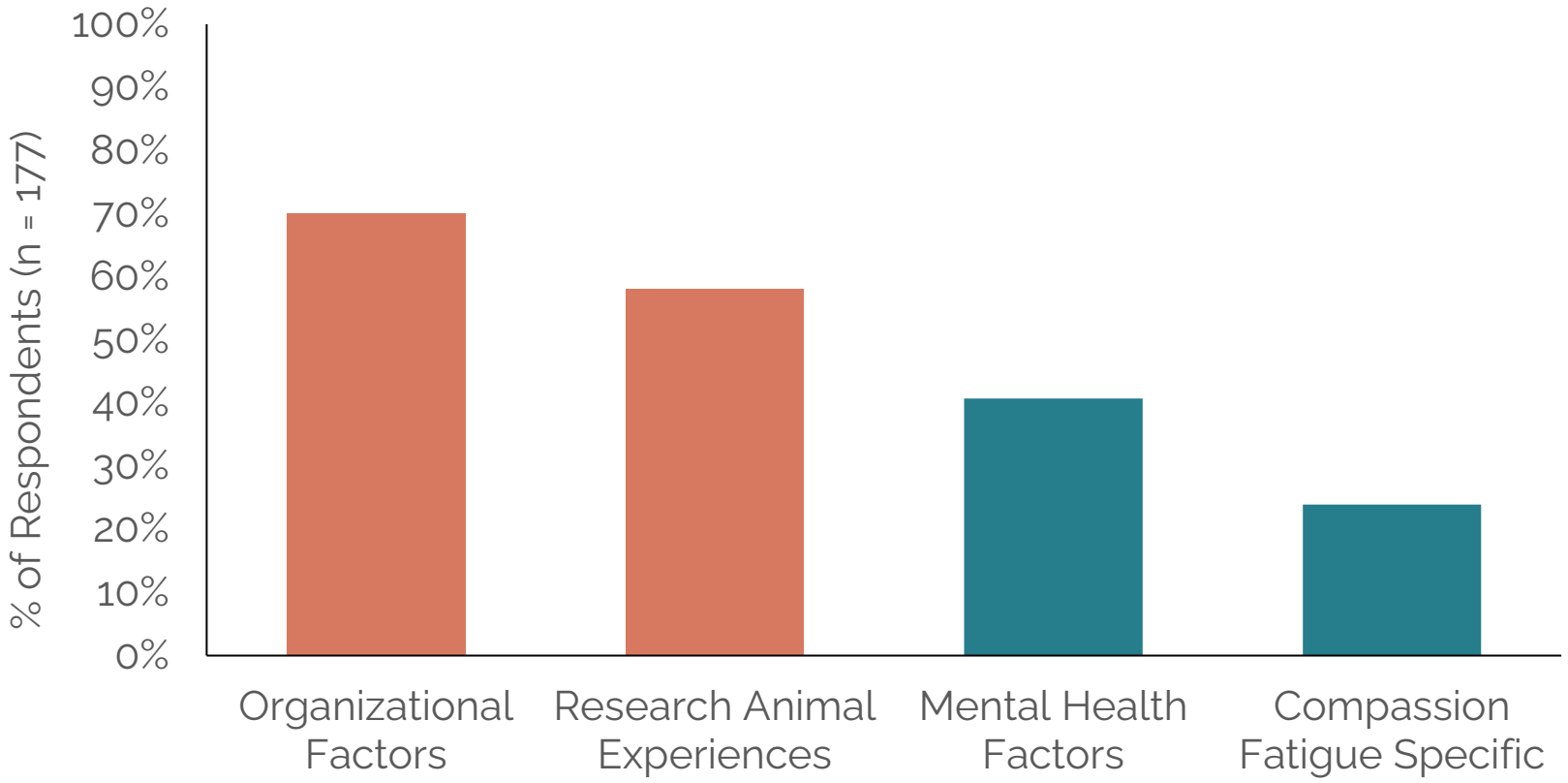
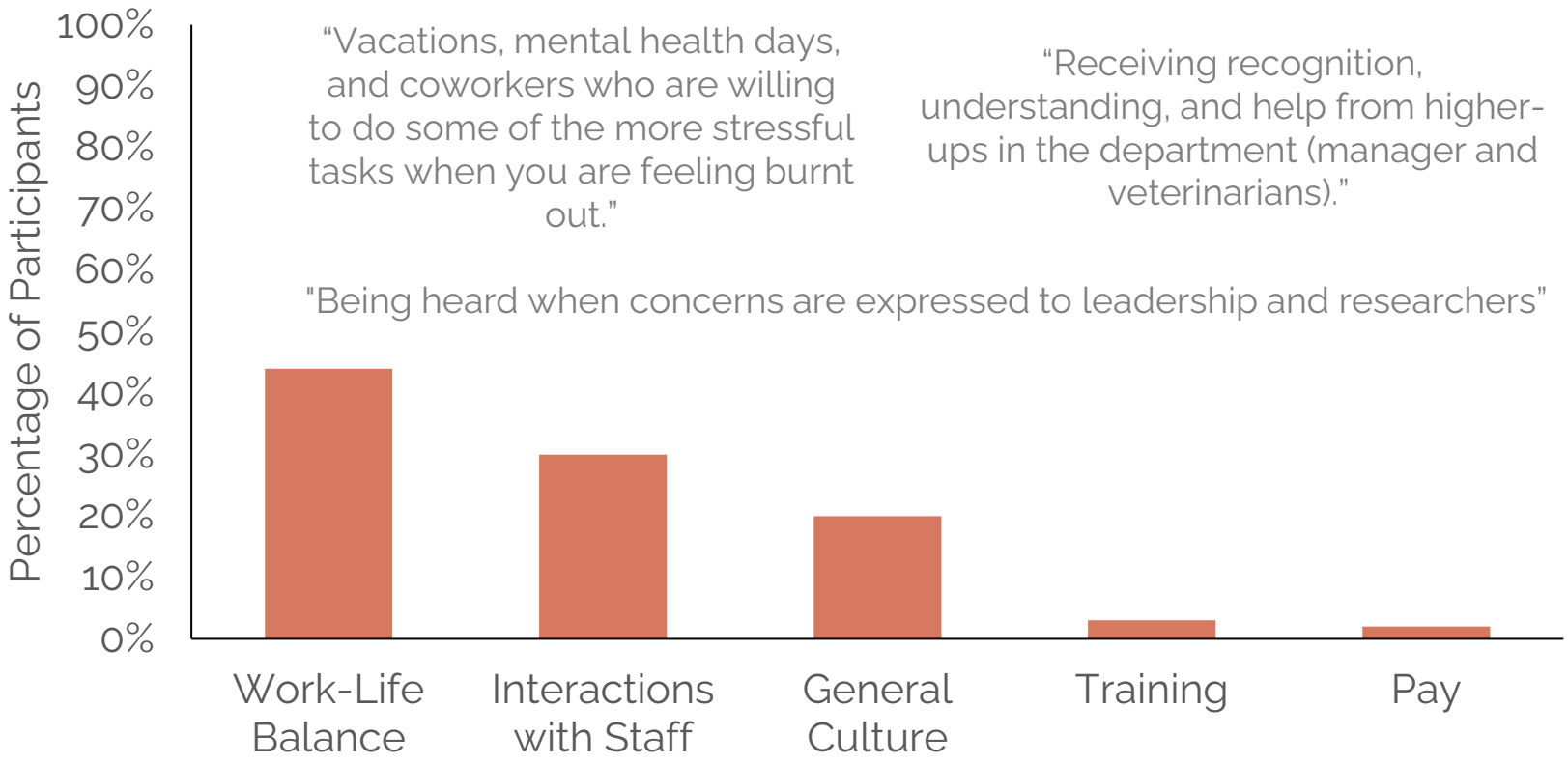


Theme 1

"The **culture of my institution** impacts my compassion fatigue"

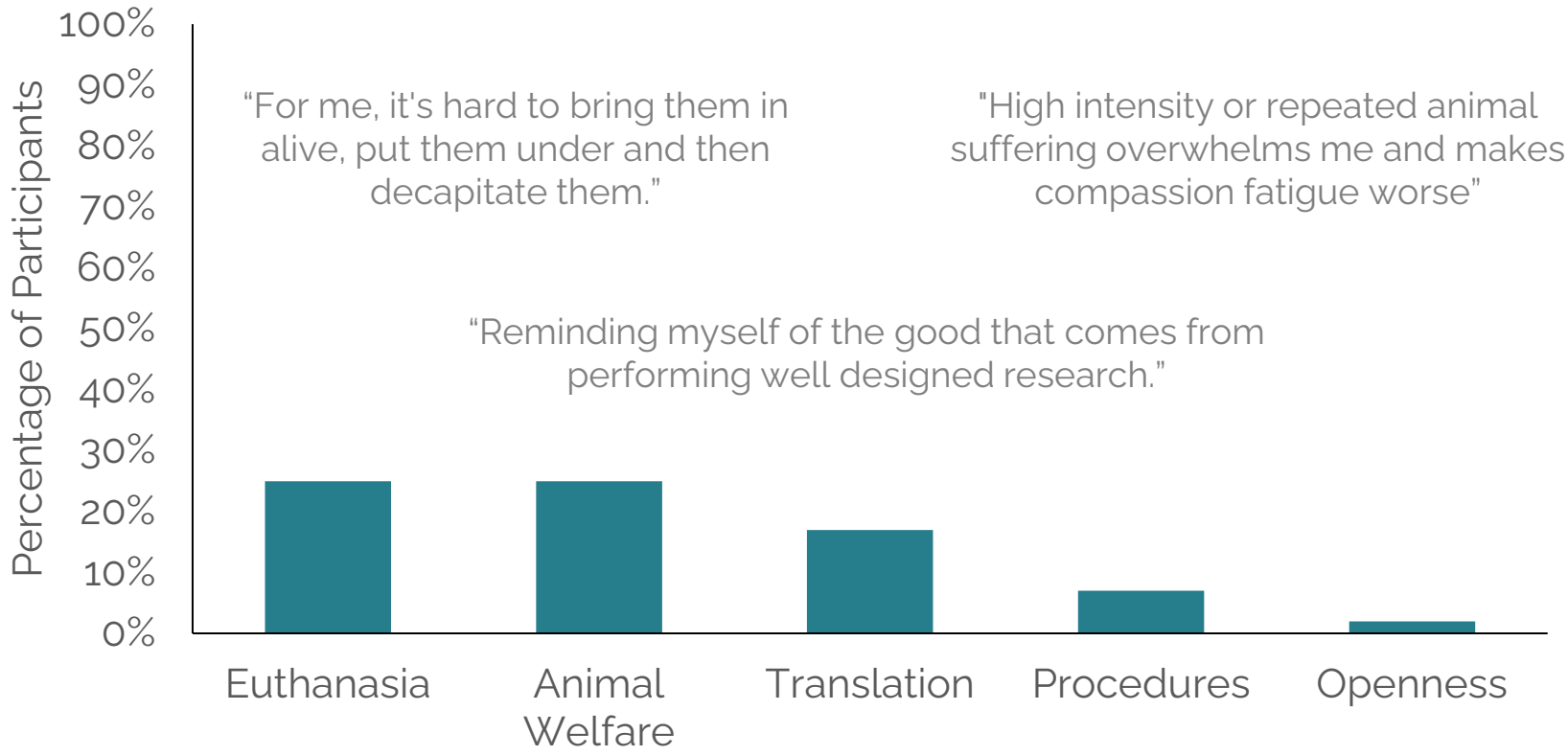
Work-life balance & interactions with staff impact my compassion fatigue



Theme 2

"Working with research animals can be **challenging or rewarding**"

Euthanasia, animal welfare, & translational research impact my compassion fatigue



Main Takeaways

Personnel impacted by:

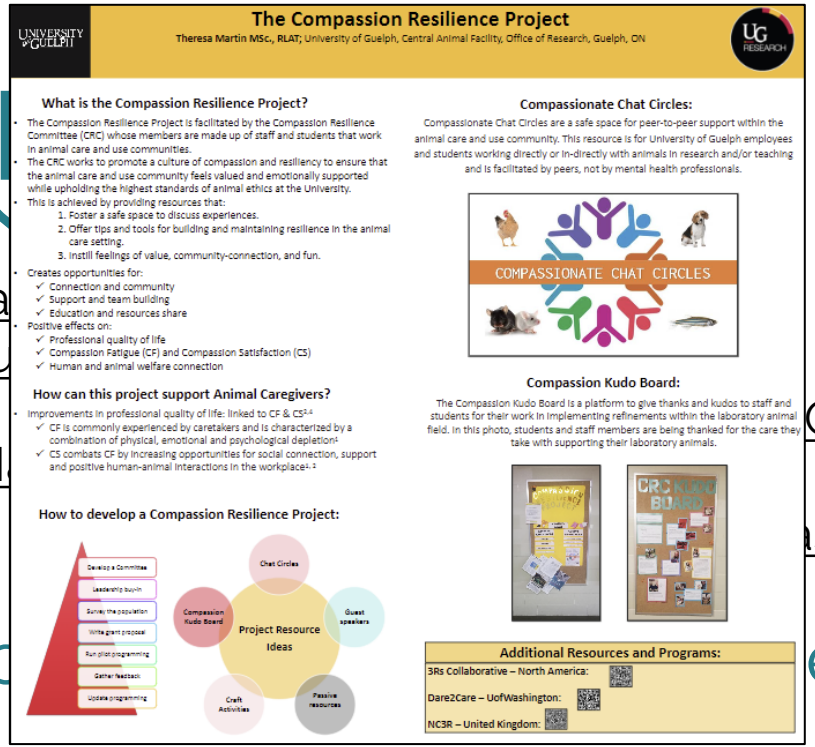
- Organizational culture
- Research animal work

Professional Quality of Life Linked to:

- Job Satisfaction
- Retention

We've created an institutional compassion fatigue resiliency starter pack:

Poster: Theresa Martin, University of Guelph



The Compassion Resilience Project

Theresa Martin MSc., RLAT, University of Guelph, Central Animal Facility, Office of Research, Guelph, ON

What is the Compassion Resilience Project?

- The Compassion Resilience Project is facilitated by the Compassion Resilience Committee (CRC) whose members are made up of staff and students that work in animal care and use communities.
- The CRC works to promote a culture of compassion and resiliency to ensure that the animal care and use community feels valued and emotionally supported while upholding the highest standards of animal ethics at the University.
- This is achieved by providing resources that:
  1. Foster a safe space to discuss experiences.
  2. Offer tips and tools for building and maintaining resilience in the animal care setting.
  3. Instill feelings of value, community-connection, and fun.
- Creates opportunities for:
  - ✓ Connection and community
  - ✓ Support and team building
  - ✓ Education and resources share
- Positive effects on:
  - ✓ Professional quality of life
  - ✓ Compassion Fatigue (CF) and Compassion Satisfaction (CS)
  - ✓ Human and animal welfare connection

How can this project support Animal Caregivers?

- Improvements in professional quality of life: linked to CF & CS[2,4]
  - ✓ CF is commonly experienced by caretakers and is characterized by a combination of physical, emotional and psychological depletion[1]
  - ✓ CS combats CF by increasing opportunities for social connection, support and positive human-animal interactions in the workplace[1, 2]

How to develop a Compassion Resilience Project:

Develop a Committee
Leadership buy-in
Survey the population
Write grant proposal
Run pilot programming
Gather feedback
Update programming

Project Resource Ideas
Chat Circles
Guest speakers
Passive resources
Craft Activities
Compassion Kudo Board

Compassionate Chat Circles:

Compassionate Chat Circles are a safe space for peer-to-peer support within the animal care and use community. This resource is for University of Guelph employees and students working directly or in-directly with animals in research and/or teaching and is facilitated by peers, not by mental health professionals.

COMPASSIONATE CHAT CIRCLES

Compassion Kudo Board:

The Compassion Kudo Board is a platform to give thanks and kudos to staff and students for their work in implementing refinements within the laboratory animal field. In this photo, students and staff members are being thanked for the care they take with supporting their laboratory animals.

CRC KUDO BOARD

Additional Resources and Programs:

3Rs Collaborative – North America:
Dare2Care – UofWashington:
NC3R – United Kingdom:

La
Institu

A M

Webinar Series

Survey

Group Activity Ideas

assive Learning Packet

Co er resources

Together, we can promote a culture of care to improve all aspects of our work.

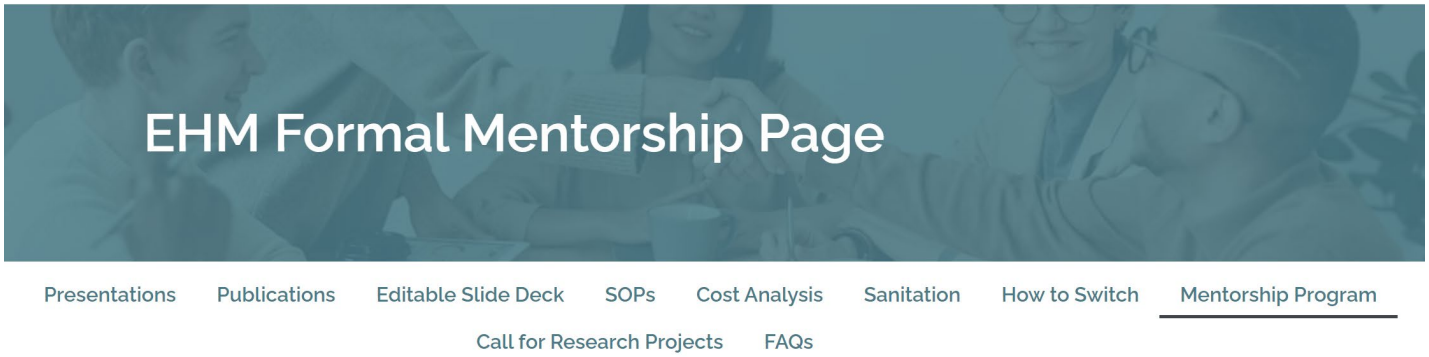
Thank you to our Compassion Fatigue Team = 29 individuals from 22 institutions

Aleeza Stephens, 3RsC
Alison Hayward, MIT
Beth Greenhough, Keble College, Oxford
Crystal Johnson, Georgetown University
Elizabeth Clemmons, Southwest NPRC
Fabienne Ferrara, Consultant
Francesca Perrotta, University of Washington
Genevieve Andrews-Kelly, LabCorp
Jennifer McMillan, Emory University
Judy Murray, Charles River Laboratories
Kirsten Bell, AstraZeneca
Lauren Healy, Bristol Myers Squib
Lauren Young, University of Guelph
Lisa Kelly, University of Georgia
Lisa Stanislawcyzk, Bristol Myers Squib
Megan LaFollette, 3RsC
Pat Frost, Texas Biomedical Research Institute
Preston Van Hooser, University of Washington
Rhonda MacAllister, Oregon NPRC
Rita Bellanca, University of Washington
Sally Robinson, AstraZeneca
Sally Thompson-Iritani, University of Washington
Sarah Thurston, Charles River Laboratories
Stephanie Oldham, AstraZeneca
Tara Martin, University of Michigan
Taylor Carroll, Mass General
Temeri Wilder-Kofie, NIH/NIAID/CMB
Theresa Martin, University of Guelph
Vanessa Lee, Emory

Visit 3RC.org to learn more &
join us to further the 3Rs.

Additional questions? Email us!
Lauren Young: laurenyoung@3rc.org
Sarah Thurston: sarah.thurston@crl.com

EHM Formal Mentorship Program



Fill out our mentee survey to match you with one of our mentors!

3RC Environmental Health Monitoring Mentorship Program: Mentee Survey

Subscribe to The 3Rs Collaborative's newsletter for a copy of these slides & practical 3Rs Resources

https://bit.ly/3RC_Newsletter

Questions?