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Subject: Letter of motivation for Tonielli Scientific Travel Award

How microbes establish infections and the counter strategies developed by their hosts has a profound impact on the outcome of diseases. I am a fourth year PhD student at the Max Planck institute for the Biology of Ageing dedicated to studying host pathogen interactions. For this purpose, I am investigating the host endoplasmic reticulum (ER) and the human parasite *Toxoplasma gondii* that form contact sites (CSs), or close regions of membrane apposition, during infection. Although these CSs were first described in the 1968, the proteins mediating this contact and its physiological relevance remains a mystery. To investigate this, I have established a novel system to visualize CSs formation between organelles of different species. Utilizing this tool, I performed a genome-wide loss-of-function CRISPR screen and identified the proteins mediating the contact between ER and the *Toxoplasma* vacuole. Our preliminary work suggests a conserved mechanism that *Toxoplasma* and perhaps other pathogens adopt to exploit host organelles.

A crucial way to learn and advance in any scientific project is by discussing and exchanging ideas with peers. Therefore, I am writing this application to seek funding to support my attendance of the Gordon conference titled: Function of Proteins and Lipids at Organelle Membranes in Health and Disease to be held in July, 2022 in Andover, NH, USA. This conference is as an excellent opportunity for young scientists to showcase their work and gain insights into the latest techniques and breakthroughs in the field of interorganellar communication, contact sites and host pathogen interactions.

Pioneers in ER function and contact sites biology such as Dr. Tom Rapport, Dr. Gia Voeltz and Dr. Jennifer Lippincott-Schwartz are amongst the many excellent researchers that will be present at the conference. I will be able to learn from these eminent scientists and interact with them for pursuing future post-doctoral work in their laboratories. Thus, the conference comes at an opportune time as it gives me the chance to present my work, gain valuable feedback to finish my project and network for future research endeavors. Furthermore, given that I have

established a new system to study CSs, I will not only learn at this conference but also share a tool that will benefit many others in the field. I would also like to mention that I started my PhD at the end of 2019 and the pandemic besieged us in early 2020. This resulted in a lack of conferences and travel which, hindered my chances to present my PhD work and network with renowned scientists and young peers internationally, both of which are crucial for a scientist aiming for a career in academia. Access to this scholarship will therefore make it feasible for me to travel to the US and share my work with a broad audience. I would be delighted to receive financial support that will enable me to attend this conference. Thank you for your time and consideration of my application.

Sincerely,

Chahat Mehra

A brief description of the PhD work

Toxoplasma gondii (*Toxoplasma*) is a human parasite that causes a life-long infection in 1/3 of the world's population although this can vary depending on the country; in Germany for example more than 60% of the population over age 60 are estimated to be seropositive for *Toxoplasma*. Therefore, defining the mechanisms by which *Toxoplasma* engages the host cells it infects can deepen our understanding of how this parasite causes disease and lead to the development of better therapeutics.

When entering the host cell, *Toxoplasma* establishes a closed-off niche in which it resides called the parasitophorous vacole (PV). Immediately after infection the *Toxoplasma* PV membrane (PVM) closely associates with several host cell organelles such as the mitochondria and endoplasmic reticulum (ER) (Fig. 1). This association is referred to as contact sites (CSs) that are 12-18nm in distance. CSs in general have been reported to allow transfer of phospholipids, calcium and metabolites thus serving as an ideal way for pathogens to scavenge nutrients and from their hosts. The molecules that mediate *Toxoplasma*-ER tethering and the biological relevance of these contacts sites have remained unknown since its discovery in the 1970s. My PhD work aims to address this unknown, and define the machinery that mediates *Toxoplasma*-ER CSs, as well as the physiological relevance of this CSs during infection.

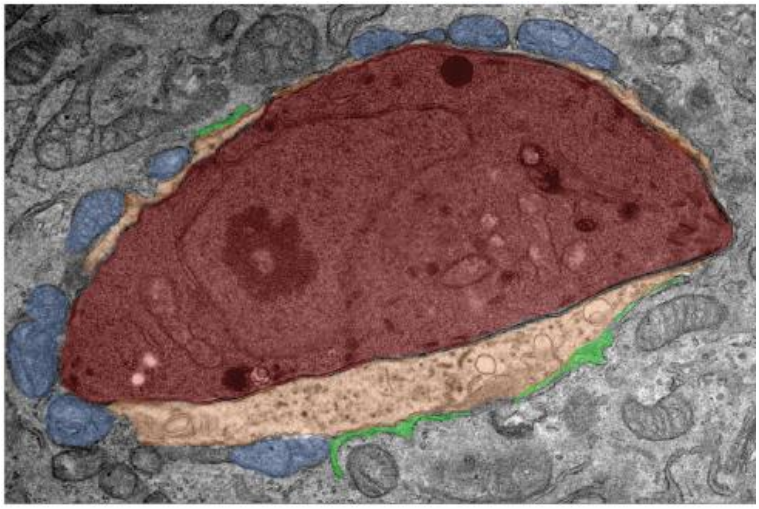

Fig. 1: Representative electron micrograph image depicting host mitochondria (blue) and host endoplasmic reticulum (green) associated with the *Toxoplasma* vacuole. The parasite (dark red) resides in the PV (light red) which is closed off by a membrane that form CSs with the host organelles.

To identify the proteins that mediate these contact sites in an unbiased way, we established a split- green fluorescent protein (split-GFP) based fluorescent sensor for organelle proximity. This was achieved by targeting two non-fluorescent halves of the GFP protein to the ER and the PVM. In this system, the GFP is only reconstituted when the ER and parasite vacuole membrane are within 10 nm. To determine whether our system reported contact sites, we leveraged the well characterized CSs between host mitochondria and the *Toxoplasma*. As expected, in the absence of the proteins mediating *Toxoplasma*-mitochondria CSs, no GFP reconstitution was observed. To identify proteins that tether the endoplasmic reticulum to the *Toxoplasma vacuole* we performed a genome wide loss-of-function CRISPR screen. Our preliminary data suggests a

conserved mechanism by which pathogens tether many host organelles. We are just starting to comprehend the impact of these CSs on host-pathogen interactions, and my work will enhance our understanding of pathogen attacks and host defense, as well as of contact site biology in general.

Chahat Mehra, PhD candidate

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Education

University of Cologne, Ph.D candidate 2019–present

Department of Biology

McGill University, M.Sc. 2017–2019

Department of Cell Biology

McGill University, B.Sc. 2013–2017

Department of Anatomy and Cell Biology

Research

PhD candidate, Max Planck institute for Biology of Ageing 2019-present

Metabolism of Infection with Dr. Lena Pernas. The host endoplasmic reticulum and the human parasite *Toxoplasma gondii* form contact sites, or close regions of membrane apposition, during infection. I am identifying the proteins that mediate this contact and the physiological relevance of this contact site.

Graduate student, M.Sc. 2017–2019

Department of Cell Biology with Dr. Nathalie Lamarche-Vane. I established a role for the Rac1/Cdc42 regulator CdGAP as a positive modulator of prostate tumorigenesis using in vitro and in vivo mouse models.

Honors Research project, B.Sc. 2013–2017

Department of Anatomy and Cell Biology with Dr. Nathalie Lamarche-Vane. I characterized the mRNA levels and protein expression of Cdc42/ Rac1 Regulator CdGAP, in prostate cancer cell lines.

Publications

Li, X., Straub, J., Medeiros, T. C., **Mehra, C**., den Brave, F., Peker, E., ... & Pernas, L. F. (2022). Mitochondria shed their outer membrane in response to infection-induced stress. *Science*, 375(6577), eabi4343.

Medeiros, T. C.*, **Mehra, C**.*, & Pernas, L. (2021). Contact and competition between mitochondria and microbes. *Current Opinion in Microbiology*, *63*, 189-194.
*Equal contribution

Mehra, C.*, Chung, J. H.*, He, Y., Lara-Márquez, M., Goyette, M. A., Boufaied, N., ... & Lamarche-Vane, N. (2021). CdGAP promotes prostate cancer metastasis by regulating epithelial-to-mesenchymal transition, cell cycle progression, and apoptosis. *Communications Biology*, *4*(1), 1-15.
*Equal contribution

Mehra, C., & Pernas, L. (2021). Move it to lose it: Mitocytosis expels damaged mitochondria. *Developmental Cell*, *56*(14), 2014-2015.

Grants, Fellowships, and Awards

NK and Irene Cheung Family Scholar 2022
Won a travel award to attend the keystone symposium conference

PhD fellowship, **International Max Planck Research School fellowship** 2019- 2023
Selected as a member of the Cologne Graduate School of Ageing to receive a multi-year PhD fellowship.

Cellular Stress Responses in Aging-Associated Diseases summer school 2018
Was selected to participate in a fully funded Molecular Mechanisms of Aging-Associated Diseases summer school of CECAD that comprised of comprehensive journal clubs with discussions and presentations based on recent findings in the field of ageing.

Studentship MSc. Award, McGill University 2018
Won the research institute McGill University health center studentship competition Msc. Award, for funding the Masters education

Passport to education, British Columbia ministry of Education 2013
Awarded a scholarship for placing in the top 15% in the province of BC from grades 10 through to 12, to be used towards undergraduate education

Kiwanis Citizenship award, Victoria High School 2013
Awarded to a student displaying leadership, participation and loyalty in the school and community while also displaying outstanding scholarship

Oral Presentation

Presented at the 6th DGZ workshop Membrane Organization and Contact Sites 2022
Presented my PhD work to members of the society of Cellular Biology

Presented at Wissenschaft in Kölner Häusern 2022
Represented my laboratory research topics to a lay audience in the city of Cologne

Scientific Conference

Mitochondrial biochemistry in health and disease (poster) 2022
Keystone symposia, USA. Title of the poster: Identification of host genes that traffic mitochondria to the human parasite *Toxoplasma gondii*

Cell Competition in Development and Disease (poster) 2019
Keystone symposia, USA. Title of the poster: CdGAP/ARHGAP31 is a positive regulator of prostate cancer

The Regulation and Function of Small GTPases Conference (poster) 2019
Federation of American Societies for Experimental Biology (FASEB) conference, USA. Title of the poster: CdGAP/ARHGAP31 is a positive regulator of prostate cancer

Teaching and Mentoring

McGill University, Teaching assistant 2019

Course: ANAT416 Development, Disease and Regeneration
Held review sessions for students before exams, was available during the exam to answer questions, graded exams papers and held post-examination review sessions

Languages

English- Native

Hindi- Native

References

Lena Pernas., Ph.D. (PhD. Mentor)
Max Planck Research Group Leader, Max Planck Institute for Biology of Ageing
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Natalie Lamarche-Vane, PhD. (M.Sc. mentor)
Professor, McGill University
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Cancer Research Program
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