

# Shining Light on the Cytosolic Surface of the Mitochondrial Outer Membrane, a Central Hub of Cancer Cell Metabolism

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## Summary

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Supervisor: Prof. Dr. Roland Malli  
Availability: This position is available.  
Offered by: Medical University of Graz  
Application deadline: Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

## Description

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**Background:** Most cancer cells exhibit specific metabolic settings and flexibilities in order to efficiently cope with constantly high demands of building blocks and energy for fast cell proliferation and growth<sup>1</sup>. We recently developed and applied genetically encoded fluorescent probes and respective imaging protocols to visualize cancer cell type specific ion signaling<sup>2</sup>, mitochondrial protein import<sup>3</sup>, and metabolic activities<sup>4</sup> with high spatial and temporal resolution using high- and super-resolution microscopy<sup>5,6</sup>. Our recent data confirm strong and stable interactions between hexokinase-1 (HK-1) and hexokinase-2 (HK-2) with the most important porine of the mitochondrial outer membrane, the voltage dependent anion channel 1 (VDAC1), in cancer cells. Specific disturbances of the HK-1/HK2 VDAC1 interactions and/or the activities of the mitochondrial located HKs might have detrimental effects on cancer cells<sup>7</sup>.

**Hypothesis and Objectives:** We hypothesize that a better understanding of those cellular processes that regulate the expression, activities, and subcellular location of mitochondrial HKs in cancer cells has a high potency to develop novel strategies in the personalized diagnosis and therapy of most human cancers.

We aim to develop sophisticated fluorescent protein based probes, tools, and imaging protocols to study and manipulate the subcellular distribution and activities of mitochondrial HKs in various human cancer cells. We will correlate how different stimuli and stresses impact the subcellular ion homeostasis and metabolic activities and correlate respective signals with the mitochondrial location and activity of HK-1 and HK-2.

**Methodology:** In addition to classical biochemical and molecular biology approaches including Western Blotting, PCR, cloning, cell culture, virus preparation, infection, and transfection, we will mainly use state-of-the-art fluorescence microscopy techniques to investigate cancer cell signaling and metabolism *in vitro*. The PhD candidate will be well trained in both conventional wide-field fluorescence microscopy, short- and long-term live cell imaging as well as high-resolution array confocal laser scanning microscopy and respective image and data analysis. If meaningful, cancer/immune cells organoids as well as xenograft animal models might be exploited during the last semesters, in order to transfer and confirm the *in vitro* findings *in vivo*.

## References:

<sup>1</sup> Natalya N. Pavlova and Craig B. Thompson The Emerging Hallmarks of Cancer Metabolism Cell Metabolism 23, January 12, 2016 DOI: 10.1016/j.cmet.2015.12.006

<sup>2</sup> Bischof, H; Rehberg, M; Stryeck, S; Artinger, K; Eroglu, E; Waldeck-Weiermair, M; Gottschalk, B; Rost, R; Deak, AT; Niedrist, T; Vujic, N; Lindermuth, H; Prassl, R; Pelzmann, B; Groschner, K; Kratky, D; Eller, K; Rosenkranz, AR; Madl, T; Plesnila, N; Graier, WF; Malli, R

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<sup>3</sup> Ramadani-Muja J, Gottschalk B, Pfeil K, Burgstaller S, Rauter T, Bischof H, Waldeck-Weiermair M, Bugger H, Graier WF, Malli R. Visualization of Sirtuin 4 Distribution between Mitochondria and the Nucleus, Based on Bimolecular Fluorescence Self-Complementation. *Cells*. 2019 Dec 6;8(12). pii: E1583. doi: 10.3390/cells8121583.

<sup>4</sup> Depaoli MR, Karsten F, Madreiter-Sokolowski CT, Klec C, Gottschalk B, Bischof H, Eroglu E, Waldeck-Weiermair M, Simmen T, Graier WF, Malli R. Real-Time Imaging of Mitochondrial ATP Dynamics Reveals the Metabolic Setting of Single Cells. *Cell Rep*. 2018 Oct 9;25(2):501-512.e3. doi: 10.1016/j.celrep.2018.09.027.

<sup>5</sup> Depaoli MR, Bischof H, Eroglu E, Burgstaller S, Ramadani-Muja J, Rauter T, Schinagl M, Waldeck-Weiermair M, Hay JC, Graier WF, Malli R. Live cell imaging of signaling and metabolic activities. *Pharmacol Ther*. 2019 Oct; 202:98-119. doi: 10.1016/j.pharmthera.2019.06.003. Epub 2019 Jun 7. Review.

<sup>6</sup> Gottschalk B, Klec C, Leitinger G, Bernhart E, Rost R, Bischof H, Madreiter-Sokolowski CT, Radulović S, Eroglu E, Sattler W, Waldeck-Weiermair M, Malli R, Graier WF. MICU1 controls cristae junction and spatially anchors mitochondrial Ca<sup>2+</sup> uniporter complex. *Nat Commun*. 2019 Aug 19;10(1):3732. doi: 10.1038/s41467-019-11692-x.

<sup>7</sup> Mathupala SP, Ko YH, Pedersen PL. Hexokinase II: cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria. *Oncogene*. 2006 Aug 7;25(34):4777-86. DOI: 10.1038/sj.onc.1209603



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