

# Organoprotective effects of a novel natural autophagy inducer

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## Summary

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Supervisor: Prof. Dr. Frank Madeo  
Availability: This position is available.  
Offered by: Medical University of Graz  
Application deadline: Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

## Description

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### Background:

The pharmacological induction of autophagy has emerged as a feasible strategy to mimic at least some of protective effects of fasting against aging (1). Using a screening approach for the systematic identification of potential anti-aging agents, the Madeo laboratory was able to identify a natural polyphenol (4,4-dimethoxychalcone, DMC; flavonoid sub-group) that promotes lifespan and induces autophagy in yeast, worms, flies, and cultivated human cells (manuscript in revision). Polyphenols are a group of plant secondary metabolites that have been associated with several health benefits (2).

### Hypothesis and objective:

Several natural autophagy inducers like spermidine and the polyphenol resveratrol exert beneficial effects during aging, for instance cardioprotection in rodents (3, 4). We thus hypothesize that our newly identified polyphenol, DMC, a natural autophagy inducer with lifespan-extending potential, may also exert protective effects in mice. Therefore, we aim at determining whether DMC has a favorable impact on mouse organs (heart, liver) and if yes, whether this is autophagy-dependent.

### Methodology:

The DK-MCD student will use intraperitoneal injection of DMC or DMSO to assess autophagy induction in the hearts and livers of mice. To assess possible cardioprotection, infarct size after prolonged myocardial ischemia in mice as well as e.g. cardiac hypertrophy and diastolic function in old mice after DMC treatment will be evaluated. In addition, the student will measure the mechano-elastic properties of cardiomyocytes *in vivo* and determine subclinical inflammation rates. Moreover, a rat model for hypertension-induced congestive heart failure will be employed to analyze e.g. systemic blood pressure, cardiac hypertrophy and diastolic function. To assess liver protection, hepatic damage after ethanol intoxication by quantifying alanine aminotransferase activity in DMC-treated and untreated mice will be measured. If positive results are obtained, the student will test (in mice) whether DMC-mediated cardioprotection/hepatoprotection is dependent on autophagy (using Atg5-deficient mice).

This project should lead to the *in vivo* characterization of autophagy-dependent cardio- and/or hepatoprotective effects of our identified polyphenol.

### References:

1. de Cabo R, Carmona-Gutierrez D, Bernier M, Hall MN, Madeo F (2014) The search for antiaging interventions: from elixirs to fasting regimens. *Cell*. 157(7):1515-26. doi: 10.1016/j.cell.2014.05.031
2. Pallauf K, Rimbach G (2013) Autophagy, polyphenols and healthy ageing. *Ageing Res Rev*. 12(1):237-2. doi: 10.1016/j.arr.2012.03.008
3. Eisenberg T, Abdellatif M, Schroeder S *et al.* (2016) Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 22(12):1428-38. doi: 10.1038/nm.4222

4. Raj P, Louis XL, Thandapilly SJ, Movahed A, Zieroth S, Netticadan T (2014) Potential of resveratrol in the treatment of heart failure. *Life Sci.* 95(2):63-71. doi: 10.1016/j.lfs.2013.12.011



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