

## 【Grant-in-Aid for Specially Promoted Research】

### Biological Sciences



**Title of Project:** Comprehensive and expansive research of the universal metabolic regulation mechanisms for healthspan

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Research Area: Metabolism

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#### 【Purpose and Background of the Research】

Evolution of all organisms on earth reflects a history of their attempts to adapt to famine or malnutrition which determined the life span of each organism including humans. In fact, until recently, malnutrition, compromised immunity associated with malnutrition, and infections, had been the major causes of human deaths. However, from the latter half of the 20th century, humankind has entered an era of unprecedented hypernutrition, which is triggering diseases that have come to be termed “lifestyle-related diseases” and reducing the life spans of affected individuals. To fundamentally solve all the problems brought about by these drastic changes in nutrition and the environment that have occurred in a short time, it is essential to gain a panoramic view of universal life phenomena occurring in organisms in a variety of nutritional and environmental conditions, and gain an understanding of the mechanisms of their disruption. This research aims at elucidating universal metabolic pathways for healthy longevity, and establishing the methods for its realization.

#### 【Research Methods】

The applicants aim to identify biologic responses as well as mechanisms of their regulation in various types and degrees of nutritional environments by utilizing the metabolome, epigenetic and transcriptome analytical methods. Using the information gained, the applicants attempt to gain a panoramic view of the biological responses, which are determined by nutritional and other environmental conditions, and expressed as aging and lifespan in individual living organisms, as a consequence of each organ’s different responses and coordination among the organs. In this regard, the applicants recently clarified that the anti-diabetic hormone adiponectin(Ad) /AdipoR signals are newly implicated in determining lifespan, and succeeded in obtaining Ad/AdipoR signal-activating small-molecular compound: AdipoRon (Fig.1). Thus, the applicants propose to identify novel universal metabolic pathways involved in healthy longevity, other than Ad or known longevity-associated genes.

Ultimately, the aims are to identify the universal metabolic pathways related to healthy longevity, and build scientific evidences to allow the advancement to the stage of clinical research of AdipoR-activating drug as a healthy longevity medication.

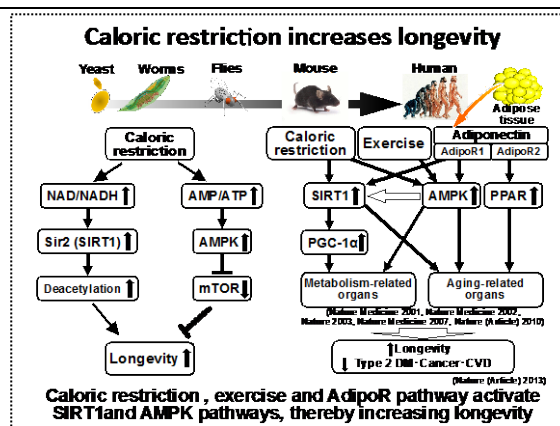


Figure 1

#### 【Expected Research Achievements and Scientific Significance】

This proposed research aimed at clarifying the universal mechanisms of metabolic regulation should allow the applicants to provide evidence-based answers to the questions, “What is an optimal diet?” and “What steps need to be taken to achieve health longevity?” Acquisition of evidence for optimizing AdipoR signal-activating small-molecular compounds for human applications will help realize clinical research and drug discovery, and contribute greatly to realizing the treatment of diabetes and lifestyle-related diseases, and ultimately, to making healthy longevity a reality. The applicants feel that this is a highly significant, all-encompassing research endeavor which leads to the conquest of lifestyle-related diseases and the creation of a lively aging society, as well as to the realization of pre-emptive medicine.

#### 【Publications Relevant to the Project】

- Okada-Iwabu M, Yamauchi T, Iwabu M, (13 authors), and Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature* 503, 493-499 (2013).
- Iwabu M, Yamauchi T, Okada-Iwabu M, (22 authors), and Kadowaki T. Adiponectin and AdipoR1 regulate PGC-1 alpha and mitochondria by Ca<sup>2+</sup> and AMPK/SIRT1. *Nature* 464, 1313-1319 (2010).

【Term of Project】 FY2014-2018

【Budget Allocation】 394,800 Thousand Yen

【Homepage Address and Other Contact Information】 <http://dm301k.umin.jp>