

HEALTHY LONGEVITY GLOBAL COMPETITION

2022 Catalyst Awardees

Sponsor: Agency for Medical Research and Development of Japan

Elucidation of reprogramming mechanism of senescent cells to establish advanced technology for extending healthy life expectancy

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Co-Investigator(s)	None

PROJECT DESCRIPTION

The accumulation of senescent cells plays a crucial role in aging and age-related diseases. Indeed, removal of senescent cells, "Senolysis", can ameliorate various age-related diseases. However, senescent cells also include non-regenerative cell types such as neurons and cardiomyocytes, and there are growing concerns about the side effects of senolysis. To develop an innovative approach as an alternative to senolysis, this study will examine the possibility of the rejuvenation of senescent cells, "senescence reprogramming", by transiently expressing Yamanaka factors specifically in senescent cells. Furthermore, we will establish the molecular basis underlying "senescence reprogramming" without using Yamanaka factors to make it possible to return senescent cells to a normal state without impairing brain or heart function. This study has a potential impact because it will lead to the development of advanced healthy life extension medicine without concern for side effects. Moreover, along with the construction of a social system in which elderly people can enjoy their lives without health concerns even after the age of 100, it is expected to be a drastic solution to the problem of a super-aging society, which is an urgent worldwide issue.

Elucidation of the cause of why heart failure is an incurable disease

Principal Investigator	FUJII Katsuhito
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Co-Investigator(s)	NAKAYAMA Yukiteru; SUGITA Junichi; OSHIMA Tsukasa;

PROJECT DESCRIPTION

Heart failure is currently an incurable disease. I will try to clarify why it is not curable.

So far, I have found that macrophages in the heart have cardioprotective effects, and their deficiency results in heart failure death (Nat Med 2017) and sudden cardiac death (Nat Commun 2021). We also found that the cardioprotective effect of cardiac macrophages is maintained by the inter-organ network among the heart, brain, and kidney via the immune and nervous system networks (Nat Med 2017). Based on the previous findings, we will examine how the cardiac homeostasis mechanism is disrupted and find new therapeutic targets for heart failure.

I hypothesized that "cardiovascular stress and aging accumulate somewhere as stress memory. Our preliminary data demonstrated new inter-organ coordination between heart-brain-several organs via the vagal afferent,

brain, and sympathetic efferent provoke innate immune memory. Then, the stress memory impaired the differentiation of tissue macrophages in the heart and other organs. We believe that this mechanism is the cause of repeated heart failure once it develops.

In particular, we focus on the activation of afferent neurons. The neurons directly sense changes in the heart and integrate them within the neurons. Our findings suggest cardiovascular stress may be perceived as a specific substance. This project will identify molecular switches of heart failure as particular substances and their receptors by analyzing selectively activated afferent neurons.

These experiments should provide a new heart failure-associated interorgan communication and find new heart failure-specific substances and receptors that provoke heart failure recurrence and comorbidities.

Novel development of pain evaluation devices and nerve regeneration tools using nerve organoids derived from human iPS cells

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Co-Investigator(s)	HAYATSU Manabu; KIMURA Hiroo; KAWADA Jiro; OKUYAMA Kentaro

PROJECT DESCRIPTION

To achieve healthy longevity in the aging society that the world is now facing, it is of utmost importance to maintain higher quality of life until the end of life. By utilizing our technology of patented special culture system development and the technology of human nerve organoids derived from iPS cells, a life with abundant quality of life without any pain for whole lifetime and enhanced regeneration of neural circuit can be achieved by our active collaboration between medical and engineering specialists.

We seek to establish a novel system that can unbiasedly quantify and visualize "pain" in vitro by using human iPS-derived sensory neurons. No one was achieved yet, because "pain" evaluation was always relied on human subjective sensations, or on experimental animals. By applying it to drug discovery screening, our new system has the potential to contribute to the discovery of analgesics that surpass morphine.

We are also working on the development of safe artificial nerves that promote nerve regeneration by using the axonal bundles originated from human iPS derived nerve organoids, in which cell bodies and axon bundles are separately cultured with the special patented culture devices. It is suggested that our new artificial nerve leads to the novel nerve regeneration technology that tends to promote the recovery of motor function rather than pain. We believe that if our development is completed, it will be key innovative technologies that lead to happy healthy longevity.