Mice are Key to Unlocking the Secrets of Life

Mouse experiments on the International Space Station

Experiments running on the Japanese Experiment Module "Kibo" at the International Space Station now!

National Research and Development Agency
Japan Aerospace Exploration Agency
Human Spaceflight Technology Directorate

Mouse Habitat Unit (MHU)
http://iss.jaxa.jp/en/kiboexp/pm/mhu/

JAXA Explore to Realize

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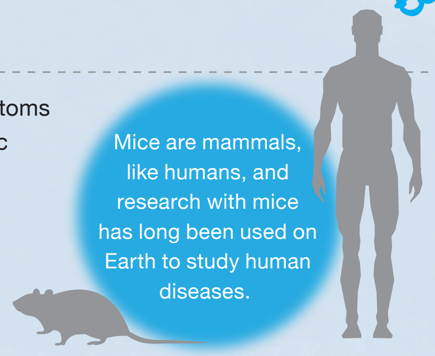
Standardized conditions, comparison, and tissue analysis impossible in humans

Living in space causes a variety of physiological changes, including weakened bones and muscles, lowered immune function, and a worsened sense of balance. Such symptoms are similar to those associated with aging, except that their progression is much faster in space. Mouse studies on the International Space Station (ISS) provide an accelerated platform for aging research, which can help us understand the mechanisms of aging-related symptoms and develop methods for preventing and treating them. Mouse research also gives us valuable information about how humans can operate in space over longer times and distances.

1 Physiological changes in space

After spending a long time in space, even healthy astronauts experience symptoms such as weakened bones and muscles, a worsened sense of balance, optic disc edema (swelling in the area where the optic nerve enters the eye, caused by increasing pressure on the brain and its periphery), and enlargement of the heart. Although we use exercise and other health management measures to address these health issues, we still do not fully understand the mechanisms behind them.



2 Research with mice tells us about disease mechanisms

U.S. and Russian space studies using mice and other small animals have shown that these animals experience physiological changes similar to those in humans. We expect that mouse-based research will help us understand the mechanisms behind such changes at the genetic level.

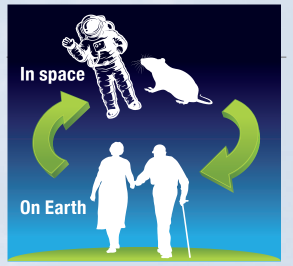
Research into mice raised in space could reveal the mechanism of sarcopenia (loss of muscle mass) and the effect of bone and muscle loss, and also show how the stress of living in a space environment affects the immune system and the central nervous system. By performing mouse research in parallel with measuring the effects on astronauts, we can compare the effects in mice and humans. This will also show how humans can adapt better to the long-term effects of different gravitational environments, such as by investigating how changes in gene expression are passed on to future generations in space environments.

3 A platform for accelerated aging-like phenomena

The physiological changes seen during time spent in space are like an accelerated version of the changes seen in elderly people on Earth. In the absence of sufficient exercise in space, bone density loss occurs around 10-fold faster than in patients with osteoporosis on Earth, and a single day's calf muscle loss in space is equivalent to two days' loss in a bedridden patient, or around six month's loss in an elderly person.

Recently, locomotive syndrome, which involves weakening of bones, muscles, and other organs related to movement, has become an area of increasing interest. Through mouse experiments on Kibo, we plan to identify factors for the early diagnosis of such age-related diseases and to perform pre-clinical studies to investigate the efficacy and safety of prophylactic and therapeutic drug candidates. By helping to prevent and treat locomotive syndrome, these studies are expected to extend health during the lifespan.

4 Standardized conditions, comparison, and tissue analysis impossible in humans



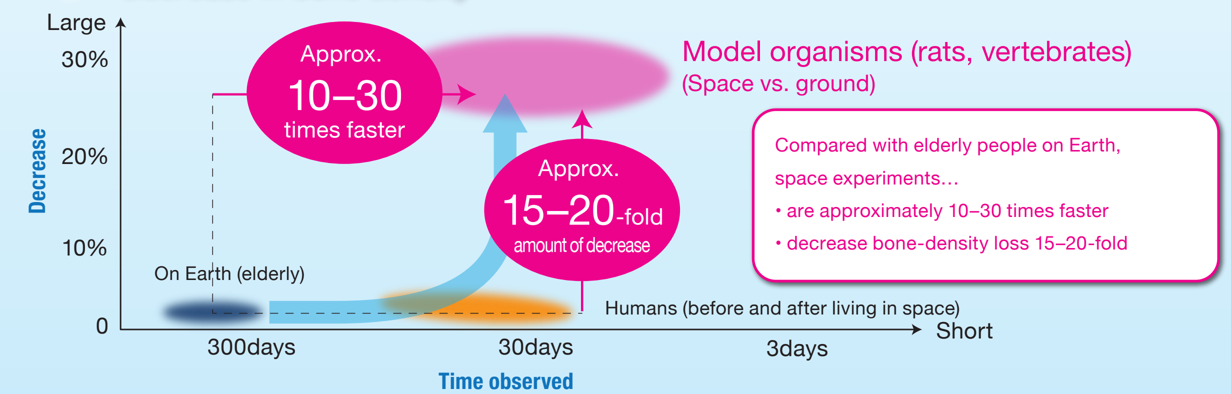
There are many aspects of research that cannot be applied to astronauts, such as standardized experimental conditions for genetics and rearing environments, strict comparison of gravity effects by creating artificial gravity in space, and detailed analysis of tissues and organs. Better results can be obtained for human healthcare on Earth by complementing the data from studies on astronauts with what we learn from mice.

5 Data that cannot be obtained on the ground

The following are some characteristics of space studies:

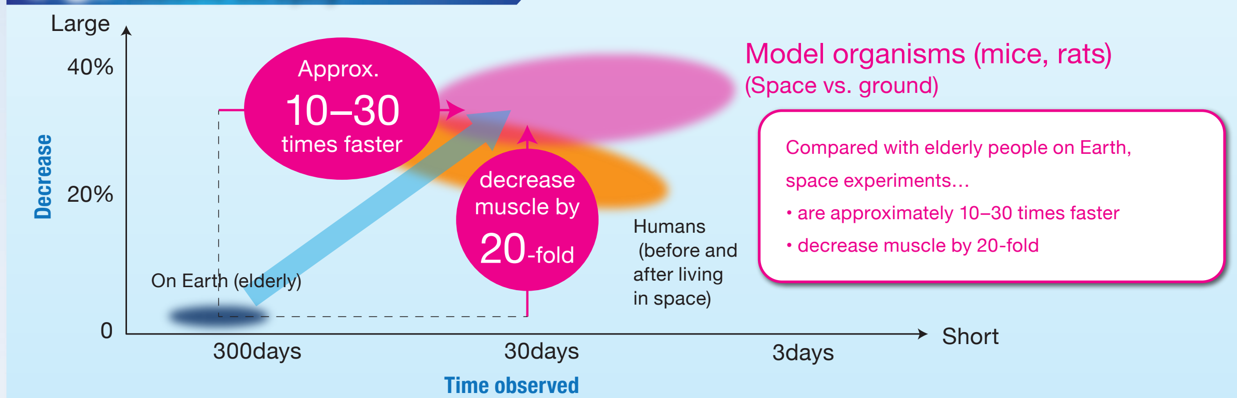
1. Aging-like phenomena occur 10 to 30 times faster in space than on Earth. In comparison with astronauts, who must exercise every day for health maintenance, model organisms that do not perform daily exercise allow for observations of bone density and muscle area losses that are fifteen- to twenty-fold the severity.
2. Changes can be measured over time in response to only gravitational changes within individual mice. After returning those mice to Earth, it is also possible to observe recovery from symptoms similar to aging.
3. Whole-body effects can be observed without unnatural conditions such as altered genetics or partial paralysis. These features that are impossible to reproduce on Earth can be used to discover new phenomena. The results may identify genes related to diseases in which aging and environment are factors.

Decrease in bone density



Studies related to bone density loss in space: L. Vico et al. (2003) *Lancet* (human); A. LeBlanc et al. (2007) *Journal of Musculoskeletal and Neuronal Interactions* (human); E. Morey-Holton et al. (2000) *Journal of Applied Physiology* (rats); M. Chatani et al. (2015) *Scientific Reports (Oryzias latipes)*, etc.

Muscle atrophy



Studies related to reduction of muscle cross-sectional area in space: R. Fitts et al. (2010) *Journal of Physiology* (human); T. Nikawa et al. (2004) *The FASEB Journal* (rats); B. Harrison (2003) *Journal of Physiology* (mice); D. Sandona et al. (2012) *PLOS One* (mice); M. Sung et al. (2013) *Journal of Muscular and Skeletal Neurology* (mice), etc.

Project Flow

Project Start

Announcements of opportunity for space experiments
Proposals for experiments are solicited from universities, research organizations, and companies.

Experiment selection
Experiments are selected based on their contents and expected outcomes.

Study of experimental conditions
The details of experimental conditions, such as number of samples, scheduling on Earth and in space, and equipment, are studied collaboratively by JAXA and the researchers.

Preparatory experiments
Gravitational effects can be evaluated before space experiments by using a centrifugal habitat that produces a hyper-gravity environment on the ground.

Committees
All experimental plans, including preparatory experiments, are subject to approval by institutional animal careand use committees and ethics review boards in related organizations in Japan and overseas.

Launching to the ISS
Mice are transported to the ISS.

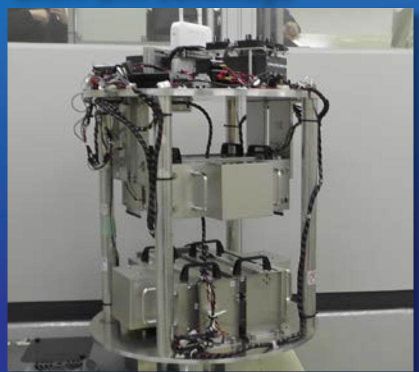
Performing experiments on Kibo
Experiments are conducted on Kibo.

Transport to Earth and handover to researchers
Mice raised in space are transported to Earth and returned to their respective researchers.

Kibo is a laboratory that allows for unique experiments in space. JAXA has accumulated technology and know-how related to crewed space missions to support new ideas for R&D using the space environment.

Example results from preparatory experiments

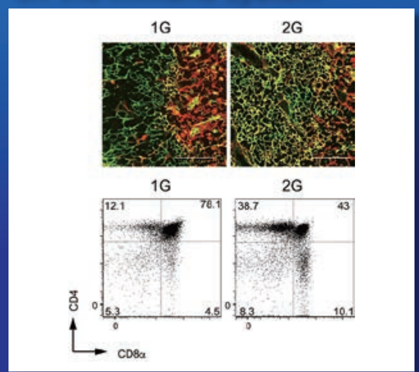
Mouse habitat using a short-arm centrifuge



A study examining whether mice can be raised under the influence of artificial gravity produced by a short-arm centrifuge of the same radius as that in space was published in the journal *PLOS One*.

H. Morita et al. (2015) *PLOS One* (collaborative research with Gifu University)

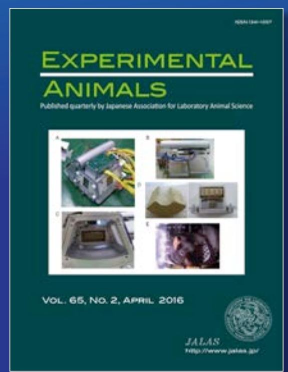
Effects of hyper-gravity (2G) on the immune system



A study examining the effects of hyper-gravity (2G) on the immune system was published in the journal *PLOS One.*

R. Tateishi et al. (2015) *PLOS One* (in cooperation with T. Akiyama, University of Tokyo)

A new habitat cage for mice



A paper describing the results of evaluation testing of a prototype mouse cage for use in space was published in the journal *Experimental Animals*, and featured on the cover.

M. Shimbo et al. (2016) *Experimental Animals* (in cooperation with S. Takahashi, University of Tsukuba)

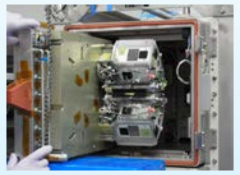
The ISS and Kibo

The ISS is a massive crewed research facility that was constructed approximately 400 km above the Earth. Fifteen nations, including the U.S., Japan, Canada, Russia, and various European countries, are project participants, and have conducted various experiments and research in space. JAXA developed and operates Kibo.

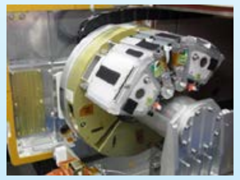
Experiment Facility

Biological experiment facility

These photos show the environment control device for biological experiments with a centrifuge to produce artificial gravity in Kibo. Habitat cages are divided into upper (microgravity) and lower (artificial gravity) sections, which can house six mice each, to compare gravitational effects.



Microgravity section



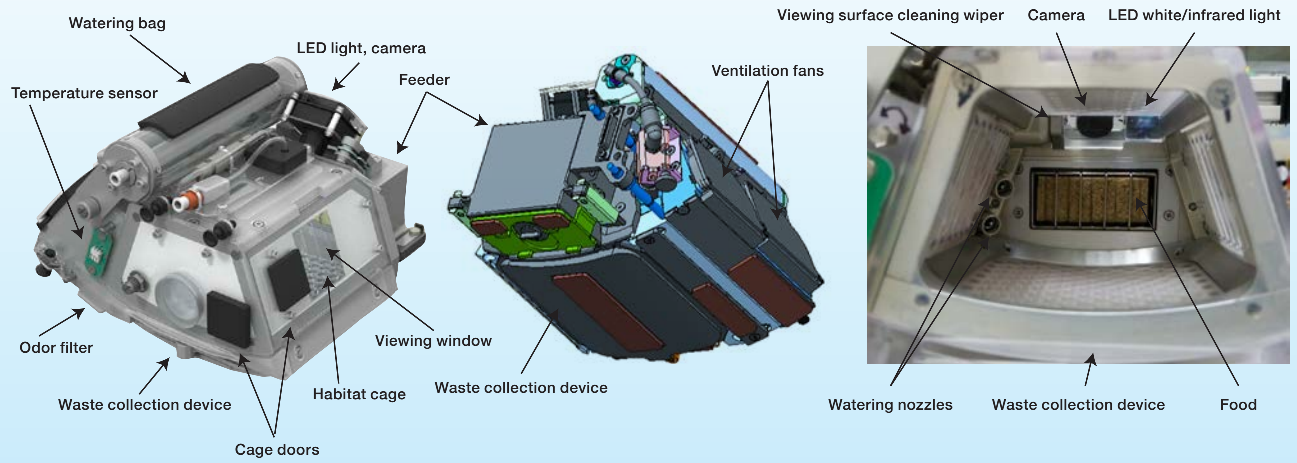
Artificial gravity section

Mouse experiment glove box

Used for exchanging and maintaining habitat cages and taking samples

Mouse habitat cages

Mice can be kept in cages for approximately 30 days, or for longer with cage exchanges. Cages are equipped with feeding and watering devices, LED white and infrared illumination, waste collection ability, odor filters, and two ventilation fans. The cages also have video cameras with night-vision capability, viewing surface cleaning wipers, and temperature sensors.



Future Research Using the Mouse Habitat Unit

Strategic domains

A platform for supporting research into aging

Bioinformatics research

In space

An accelerated model for aging-like phenomena (bone and muscle loss, lowered immunity)

- Analysis of epigenomic changes characteristic of space environments
- Correlation with age-related disease on Earth

On Earth (universities, laboratories, etc.)

Constructing a life information database and correlation analysis with space

- Searching for and identifying biomarkers* for age-related disease

*Indices for evaluating illness and physical condition

Drug discovery for age-related diseases

In space

Pre-clinical testing of new drug candidates

- Verification of the effects of preventative medicine and therapeutic agents for disease factors in mice raised in microgravity

On Earth (pharmaceuticals manufacturers, laboratories, etc.)

Drug discovery for age-related diseases

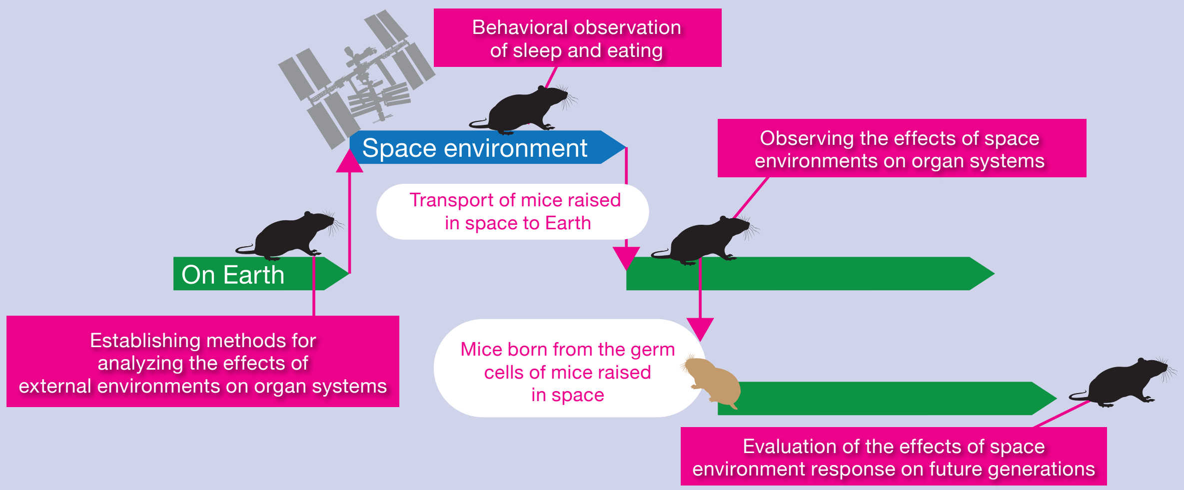
- Designing suitable compounds for regulating the activity of targets of underlying disease

Search and selection	Development and verification (bioinformatics)	Deepening and expansion (drug discovery for age-related disease)
Present	5 years	10 years
	Technologies for early disease detection	Innovative preventive and therapeutic drugs

Note: Research based on new ideas is possible

Comprehensive evaluation of mouse response to space environments (University of Tsukuba)

Investigating changes in gene expression, chemical changes in DNA, and their effects on future generations will help elucidate the factors and mechanisms behind biological responses to space environments.



Effects Basic data and knowledge obtained from studies of long-term rearing of mice in space contribute to various studies relevant to human health and disease, including space studies for drug discovery using model mice with diseases featuring similar symptoms, anti-aging measures related to the mechanisms of bone density loss and muscle atrophy, and environmental adaptation studies on Earth

Q Can rats or other animals besides mice be used?

A Currently, we can only accommodate experiments using mice. There is the other equipment aboard Kibo available for use as a habitat for *Oryzias latipes* (Medaka fish) or other small freshwater fish.

Q Can transgenic mice be used?

A Yes. However, experiments requiring transport of mice to the U.S. require time for applications and reproduction, so the feasibility of such studies will require consideration based on experimental requirements.

Q Are there limits on the age of mice at the time of launch?

A There are some. Mice in the cages in space are assumed to be capable of using a water nozzle and eating solid food, and so will require being raised on Earth to some extent. The launch of very young mice may require special handling.

Q Is group rearing possible?

A The current equipment does not allow this.

Q Are experiments on mice (blood and other samples, data acquisition, observation) in orbit possible?

A Yes, these are possible, as long as the astronauts can perform them in a glove box. The feasibility will be considered based on the experimental requirements.

Q Are experiments by private organizations allowed?

A Yes, they are. Please contact us for details.

Preliminary analysis report on the first rearing in space for 35 days

Twelve mice were reared in Kibo for 35 days in July-August 2016. All mice were successfully returned to the Earth alive.

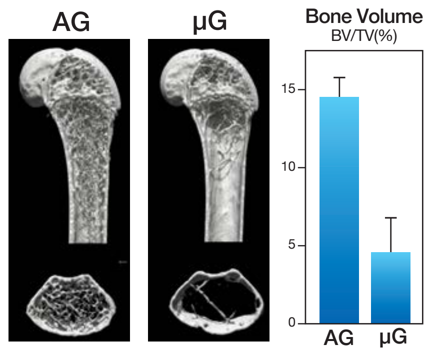
Microgravity (μG)

Artificial gravity (AG: 1G in space)

Fifth day of on-board rearing (July 25, 2016)
http://iss.jaxa.jp/kiboexp/news/20161013_mouse.html

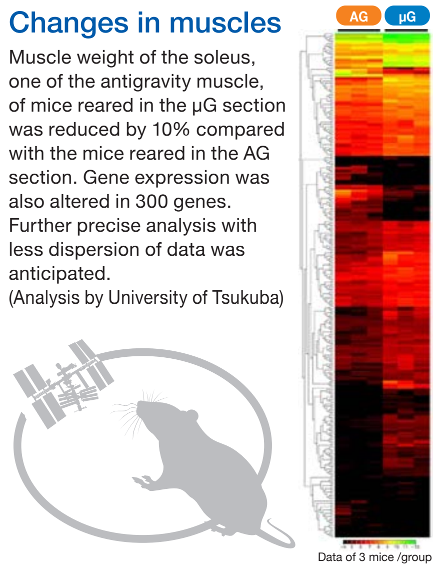
Changes in bones

It was found that cancellous bones in the femur of the returned mice had dramatically decreased among mice reared in the μG section compared with those reared in the AG section. Symptom similar to severe osteoporosis was observed by rearing in space for only 35 days.
(Analysis by Tokyo Medical and Dental University)



Changes in muscles

Muscle weight of the soleus, one of the antigravity muscle, of mice reared in the μG section was reduced by 10% compared with the mice reared in the AG section. Gene expression was also altered in 300 genes. Further precise analysis with less dispersion of data was anticipated.
(Analysis by University of Tsukuba)



Check! Mouse studies in Kibo can contribute to research on age-related symptoms such as osteoporosis and sarcopenia.