



# COULD IMMUNE PROTEINS HAVE ANTI-AGEING BENEFITS?

Researchers in Japan are investigating whether an **IMMUNE-BOOSTING PROTEIN MIGHT HAVE USES IN SLOWING AGE-RELATED DECLINE** and improving cognition as societies around the world are rapidly ageing.

**Trained as an oncologist, ageing and death are never far from Toshio Inui's mind.** He lives in Japan, which has one of the most aged societies in the world, where nearly one in three people are aged 65 or over. While growing old can bring the joy of grandchildren and greater wisdom, it can also herald a slew of problems such as physical frailty, mental decline and higher disease risks.

Pondering whether science could slow, or even reverse, the natural process of ageing, led Inui — a clinician with four decades of experience — to co-found Saisei Pharma, a biotech and nutritional supplement company, the name of which means 'rejuvenation' or 'regeneration' in Japanese.

"In Japan and other countries, the number of

elderly people is increasing," he says. In Japan today 30% of the population are 60 or older — and the World Health Organization estimates that by 2050 this demographic will account for 22% of the global population, with two thirds of them living in low- and middle-income countries. This will lead to an increased burden on health and social systems due to age-related diseases and conditions.

"But with healthy ageing, we can reduce the incidences of many diseases such as cancer, heart disease, diabetes, and neurodegenerative diseases," Inui adds.

Inui leads a team at Saisei Pharma, a research-led company established in 2014 in Osaka, Japan. They are investigating the properties of an immune-boosting

protein called macrophage activating factor (MAF). Specifically, whether it could help people age more slowly, thus increasing healthspan — defined as the number of years a person lives in good health — and whether the benefits can be achieved if the protein is taken orally.

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## A SURPRISING FIND

MAF plays an important role in the immune system. Produced by the body in response to infections or tumours, its primary task is to activate and enhance the defensive power of macrophages — white blood

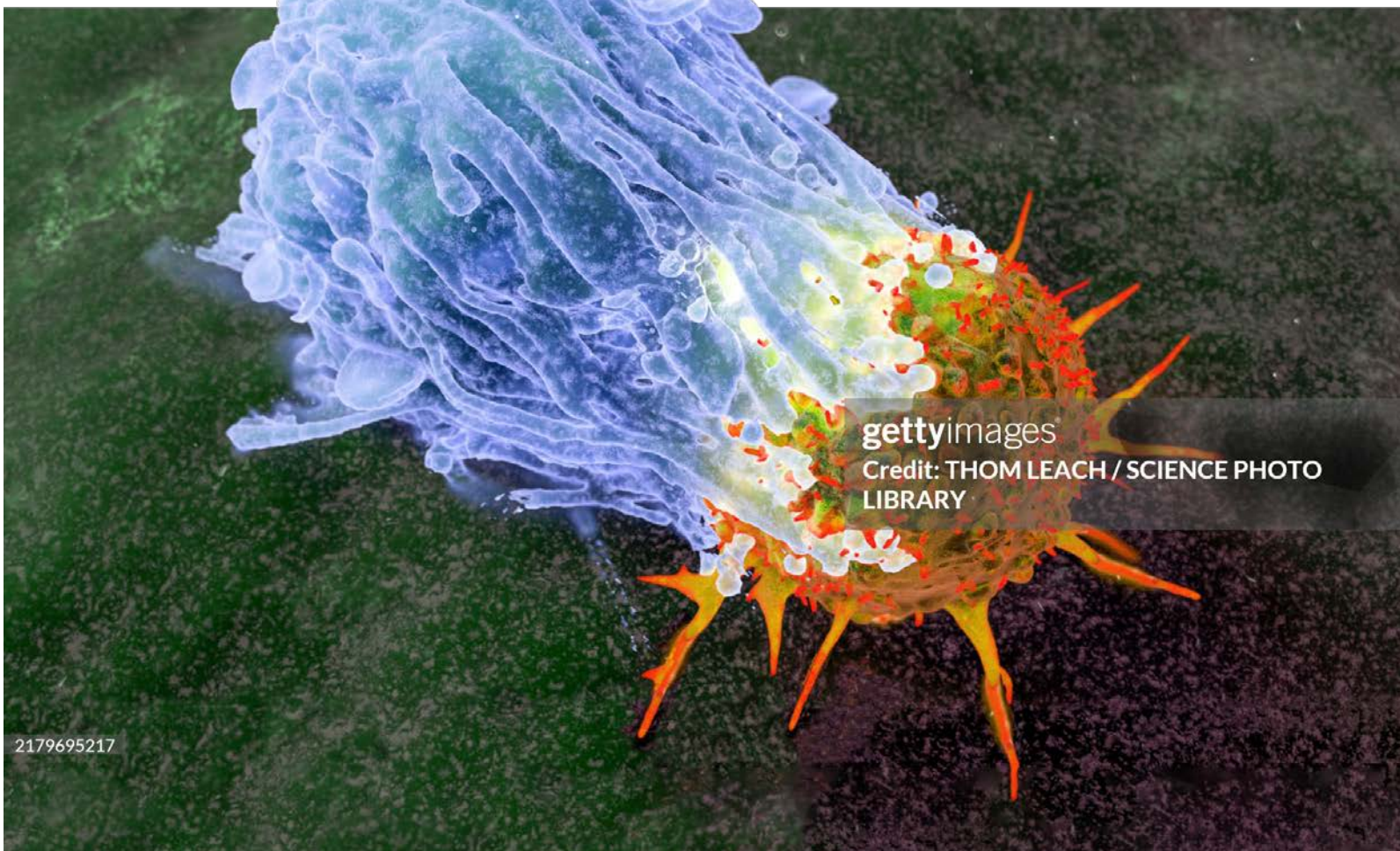
cells that engulf and destroy damaged cells, cancerous cells, and pathogens such as viruses and bacteria. Inui and other researchers are looking into whether they might have potential for treating various health conditions through improved immune responses.

Inui's first experience of cancer came in the late 1980s, after his father's struggle with and eventual death from the disease. "It brought home the limitations of conventional therapies for cancer, including surgery, chemotherapy and radiation," he says.

Striving to understand the capacity of different kinds of therapies, Inui established a cancer immunotherapy clinic in Osaka in 1987, and Saisei Mirai in 2009, focusing on emerging immunotherapies. In 2010



▲ Researchers at Saisei Pharma are investigating whether macrophage activating factor has an impact on the length of telomeres (left). Toshio Inui is the co-founder of Saisei Pharma, based in Osaka, Japan (right).



▲ A false-coloured scanning electron micrograph shows an immune macrophage (blue) attacking a cancerous cell (orange).

THOM LEACH/Science Photo Library/Getty

he began collaborating with researchers from Tokushima University, Japan, to study MAF-based therapies aimed at cancer, infectious diseases, and slowing ageing, which later led to the formation of Saisei Pharma as a spinoff company in 2014. The Saisei Mirai Group now has several branches around the world.

## TELOMERES AND KLOTHO

Inui's research in mice suggested that MAF works in two ways: by extending telomere length and overexpressing Klotho, both factors that have been shown in numerous studies to "slow biological ageing and promote longevity," he says<sup>1</sup>.

Discovered in the 1930s, telomeres, named from the combination of the Greek words for 'end' and 'part', are structures found on the tips of chromosomes. They have sometimes been likened to the protective plastic tips on the ends of shoelaces. Telomeres help prevent chromosomes from fraying or sticking together during DNA replication, preventing genetic information from getting lost.

Telomeres naturally shorten every time a cell divides, but beyond a certain threshold, the truncated caps lead to genomic instability, a decline in tissue function, and increased susceptibility to

various age-related diseases, such as diabetes, cancer, and osteoarthritis.

"Ageing biomarkers, like telomere length, can estimate an organism's biological age and predict how long you'll live," explains Inui.

In a series of experiments, the Saisei team have demonstrated that oral administration of MAF to mice, extends their telomere length. They also showed that the expression of both telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) was increased in the peripheral blood of mice following oral intake for 4 weeks<sup>2</sup>. The significance of this finding

is that longer telomere length protects against cellular senescence.

The researchers are conducting studies on the effects of oral MAF administration in individuals aged 40 and older. In Japan, a clinical trial with 161 participants measured telomere length and the Klotho gene. And a trial in Indonesia is assessing telomere length, telomerase, and Klotho in 60 participants, with completion expected in 2025.

The researchers are measuring the Klotho gene to test another hypothesis — that MAF causes an over-expression of Klotho. Named after the Greek goddess who spins the



thread of life, Klotho codes for a hormone that plays a significant role in regulating various physiological processes related to ageing.

Klotho expression decreases with age, and low levels are associated with cardiovascular disease, sarcopenia, cognitive decline and other age-related disorders.

Previous experiments by other research groups have demonstrated how mice with mutated or deficient Klotho genes exhibit signs of accelerated ageing, including muscle atrophy, thinning skin, and reduced fertility; with their lifespans reduced by as much as 80%. Conversely, an over-expression of the gene in some studies seemed to extend longevity by 20% to 30%<sup>1</sup>, compared to normal mice.

Inui's team has been studying whether oral administration of MAF has an impact on Klotho expression in animals. Saisei Pharma are now conducting human trials in

Japan to see whether MAF has a similar effect in people.

The research in mice shows that MAF can extend telomere length and increase Klotho gene expression. "This represents a significant advancement in anti-ageing research," explains Inui.

**"AGEING BIOMARKERS LIKE TELOMERE LENGTH CAN ESTIMATE AN ORGANISM'S BIOLOGICAL AGE AND PREDICT HOW LONG YOU'LL LIVE."**

#### COGNITIVE FUNCTION

More recently, the team has also sought to study the impact of MAF in a real-world setting, by conducting a study of 43 elderly dementia patients at a daycare rehabilitation facility in the Japanese city of Okayama<sup>3</sup>. One group received MAF alongside dietary guidance, another was

given dietary guidance alone, while the control group was administered a placebo.

#### BOOSTING IMMUNITY

When the COVID-19 pandemic hit in 2020, the Saisei Pharma researchers also set out to study if MAF might have an effect on immunity in elderly patients in response to the virus. As the pandemic progressed, scientists began to suspect that a reason why the SARS-CoV-2 virus progressed more rapidly in some people was because immune cells, such as macrophages and monocytes, were dysregulating the body's immune response.

To study this, the Saisei researchers launched two clinical studies, one in Italy<sup>4</sup> and another in Ukraine<sup>5</sup>. The aim of these trials — conducted in more than 300 adults hospitalized with non-critical COVID-19 — was to find out whether MAF would benefit patients and might be useful in treatment regimes. The researchers looked at

blood oxygen levels, white blood cell count, need for intensive care, and overall mortality rates.

The research built on an earlier experiment conducted in mice, where the researchers found that oral administration of MAF can help suppress inflammatory responses to gram-negative bacteria<sup>6</sup>, helping to prevent tissue damage caused by overactive immune responses.

The researchers found that MAF, with its galactose sugar groups removed, gets converted to an active form, which reduces levels of pro-inflammatory cytokines, including the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) in vitro<sup>7</sup>, leading to less damage from inflammation.

The Saisei Pharma researchers now plan to undertake clinical trials to investigate whether MAF may also have uses in treating other diseases and conditions, such as dengue fever, and if it might promote wound healing. ■

#### REFERENCES

1. Kurosu, H. et al., *Science* **309**, 1829 (2005).
2. Inui, T., et al., *Sci. Rep.* **14**, 30859 (2024).
3. Uchiyama-Tanaka, Y. et al., *Nutrients* **16**, 2078 (2024).
4. Spadera, L., et al., *Biomed. Pharmacother.* **169**, 115894 (2023).
5. Inui, T. et al., *BMC Infect. Dis.* **24**, 519 (2024).
6. Inui, T. et al., *Front. Nutr.* **9**, 852355 (2022).
7. Uto, T., et al., *Anticancer Research* **35**, 4487-4492 (2015).



▲ A researcher examines samples at the Saisei Pharma lab in Osaka, Japan.



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