Anti-aging and lifespan extension by protecting mitochondria via enhancing energy:

Simultaneous administration of febuxostat and inosine

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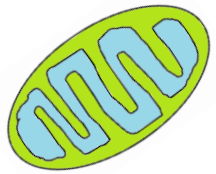
Various mechanisms of aging have been proposed

- Deterioration of mitochondria with age
- Release of reactive oxygen species (ROS)
- Energy (ATP) depletion
- Somatic gene mutation
- Inflammation
- Immune abnormalities
- Telomere shortening
- Calcium abnormalities
- Abnormal protein accumulation (amyloid-β, tau, α-synuclein)

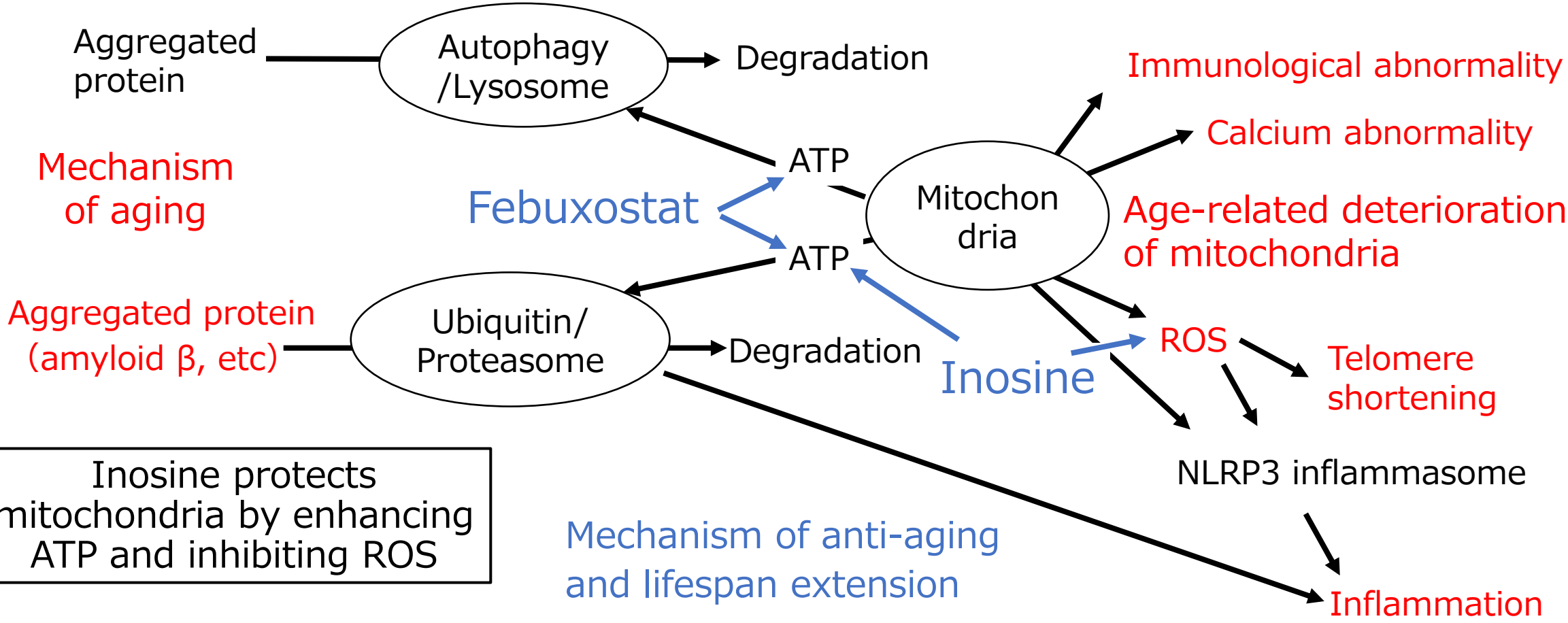
Various theories have been proposed, but all can be explained by mitochondrial deterioration



Mechanisms of aging and how to prevent it

Febuxostat suppresses ATP breakdown and protects mitochondria

Cooperation of febuxostat and inosine to prevent aging and extend lifespan

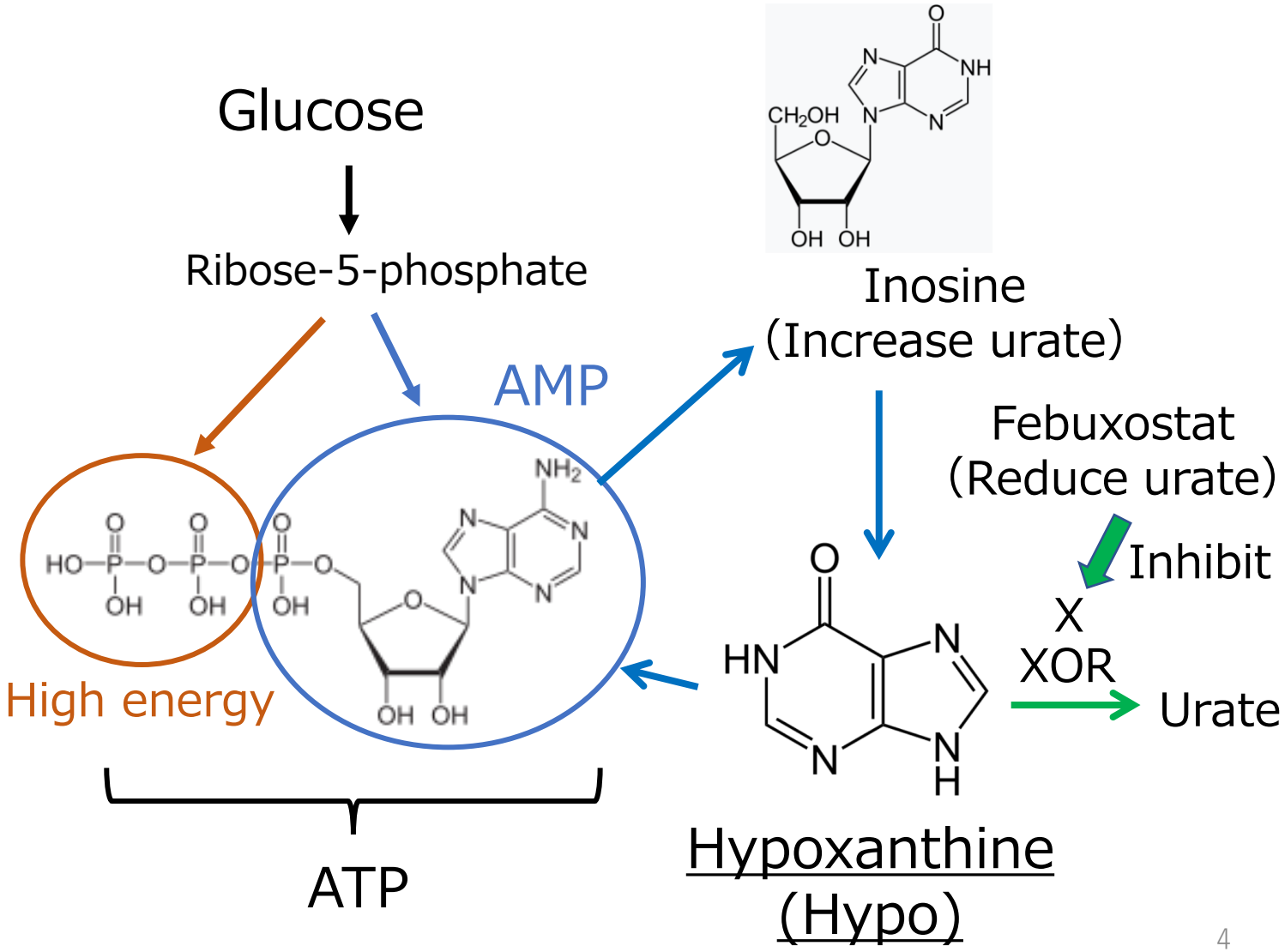


Inosine protects mitochondria by enhancing ATP and inhibiting ROS

Mechanism of anti-aging and lifespan extension

Febuxostat and inosine cooperate to enhance ATP and inosine prevent urate reduction

- ATP is composed of the AMP portion and the high-energy portion.
- Febuxostat and inosine cooperate to increase hypoxanthine which enhances the AMP portion.
- As the AMP portion increases, the high-energy portion, to which glucose is preferentially directed, also increases.
- Febuxostat-induced urate reduction is inhibited by inosine.

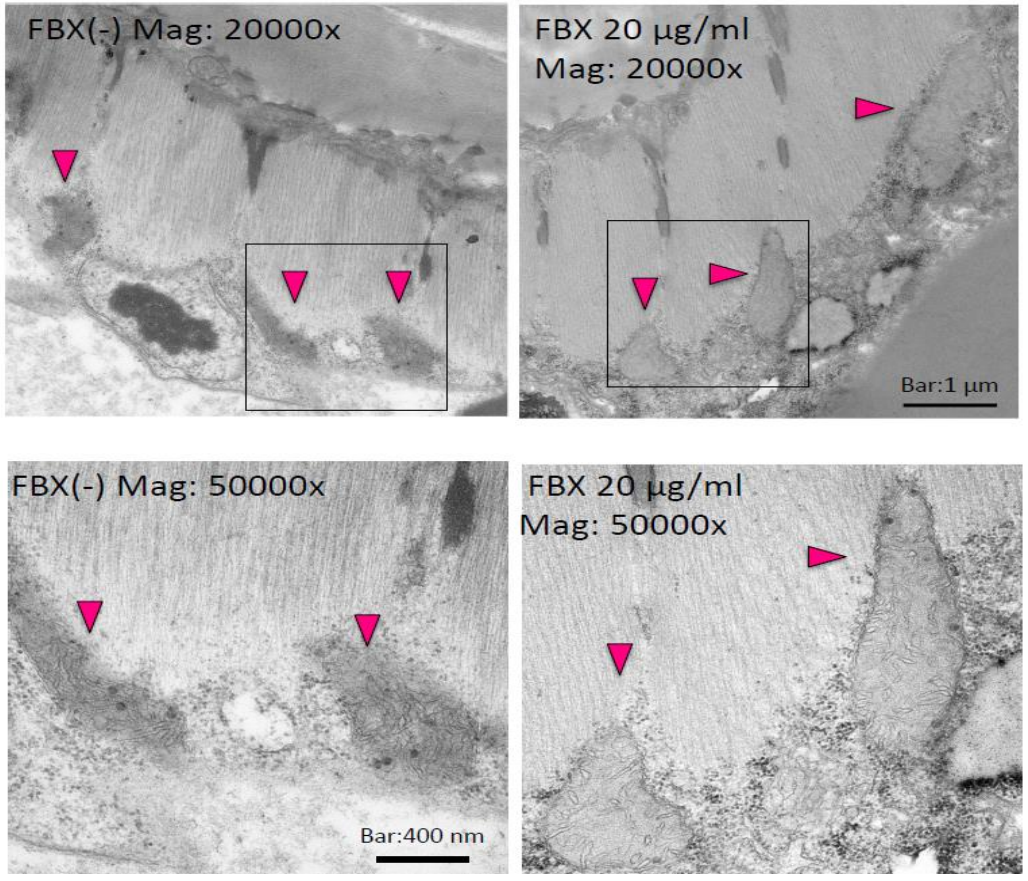


Febuxostat protects mitochondria and extends the nematode's lifespan

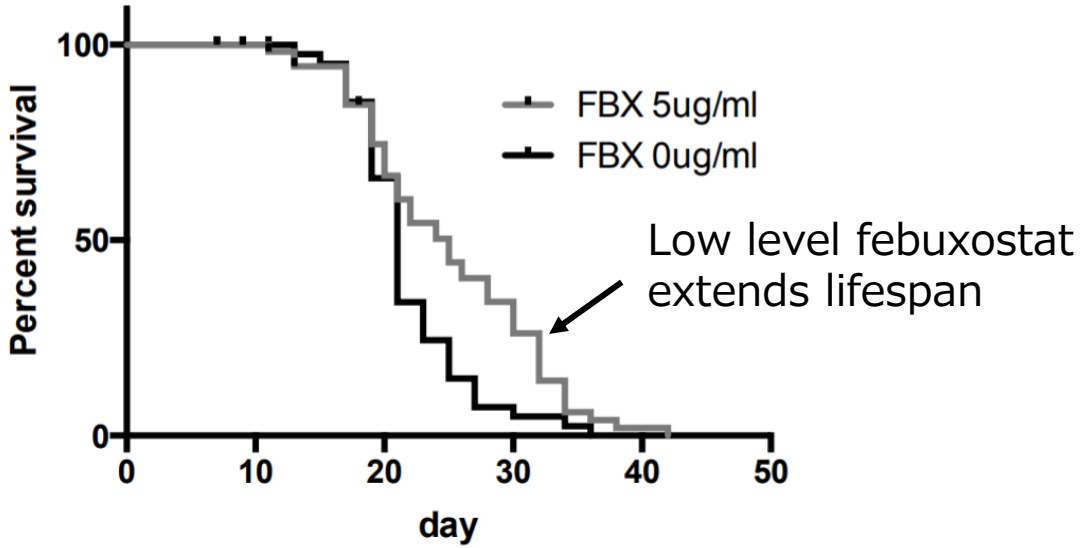
Mitochondria protection by febuxostat (FBX)

Without FBX

With FBX



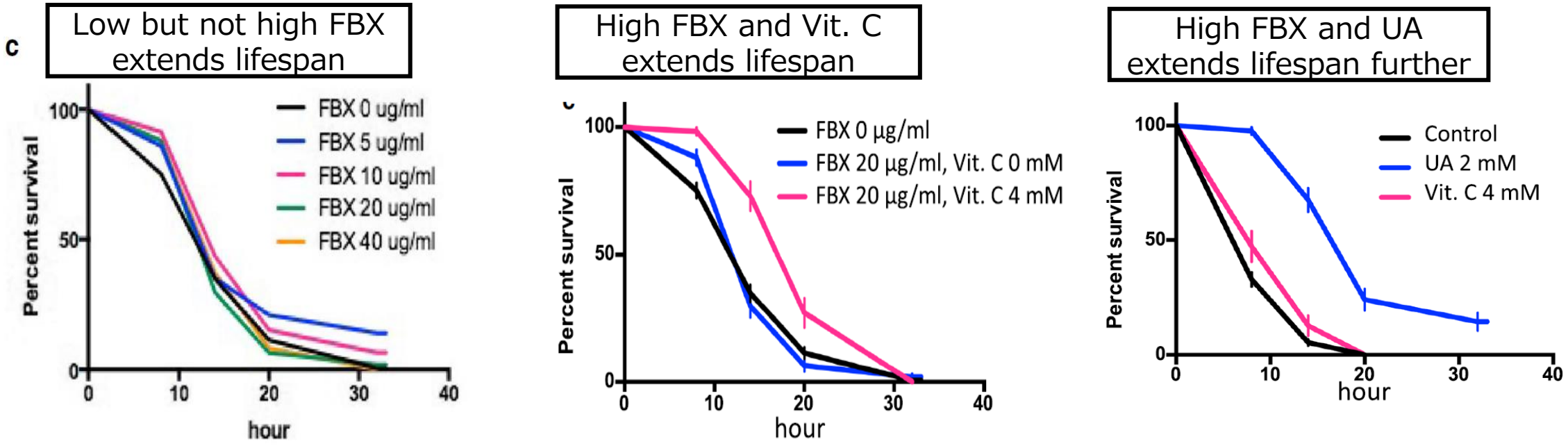
C. elegans



Yoshina S, Izuhara L, Kamatani N, Mitani S. J Physiol Sci. 2022;72:28.

High-dose febuxostat lowers urate too much, and the life-extension effect disappears.

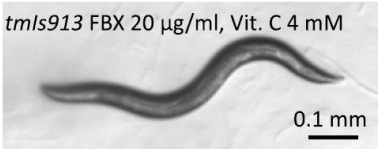
- (A) Low-dose febuxostat increases ATP and extends the lifespan of nematodes, but at high concentrations, the effect disappears.
- (B) The reason is that it lowers urate, a known reactive oxygen scavenger.
- (C) Adding vitamin C or uric acid to high-dose febuxostat restores the life-extension effect.



FBX: febuxostat, Vit. C: vitamin C, UA: urate

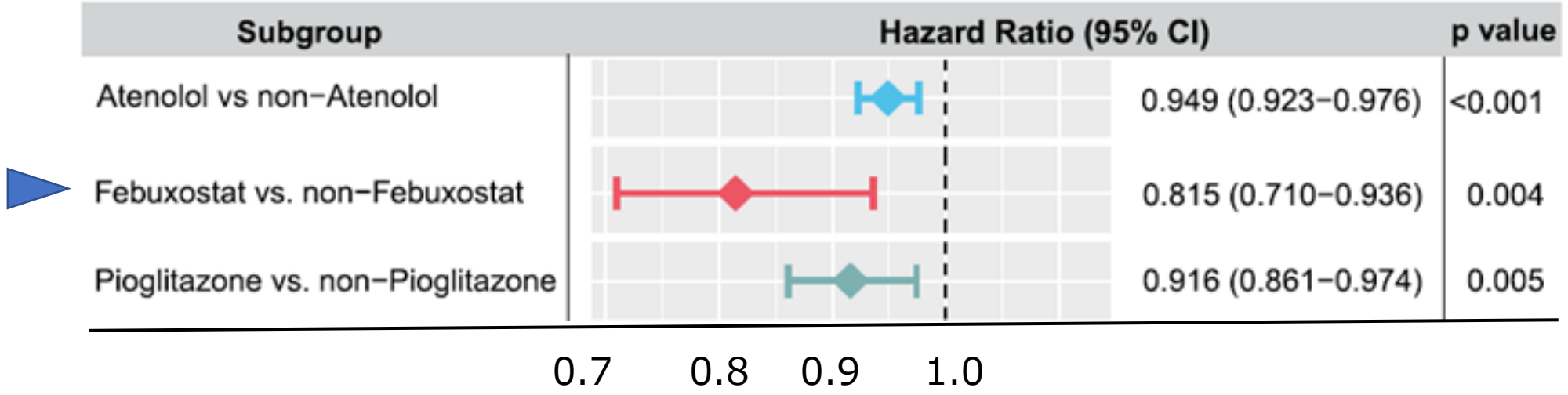
Alzheimer's disease and Parkinson's disease are two of the most common diseases associated with aging.

Febuxostat and anti-oxidant improves Alzheimer's and Parkinson's disease in nematodes.



AI study finds febuxostat to be the most powerful Alzheimer suppressor

- A collaborative study by five U.S. universities using AI (artificial intelligence) found febuxostat to be the most effective drug for Alzheimer's disease.
  - Fang J et al. Artificial intelligence framework identifies candidate targets for drug repurposing in Alzheimer's disease. Alzheimers Res Ther. 2022;14:7.



A large clinical data (7 million patients) confirmed the efficacy.

Clinical big data reveals febuxostat's inhibitory effects on Alzheimer's disease

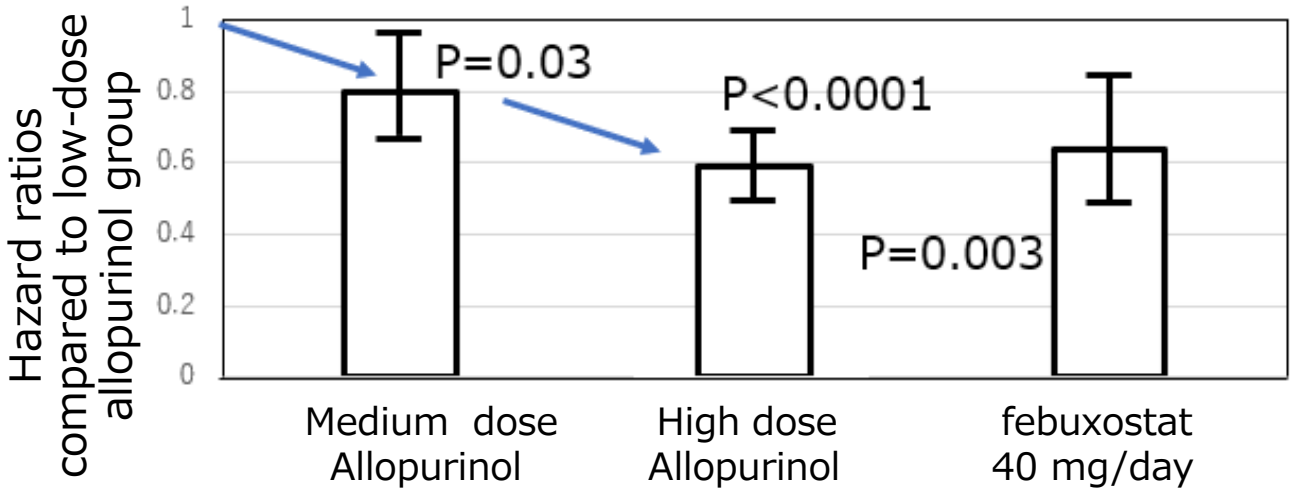
U.S. Medicare data: Allopurinol and febuxostat were found to reduce dementia in a clinical data analysis of 35,030 patients.

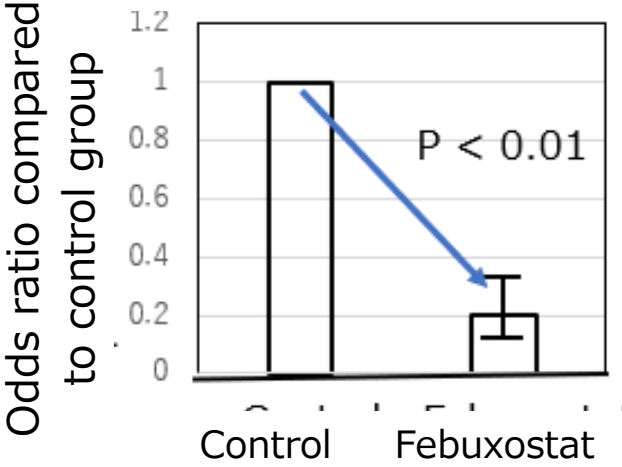
Korean data: Febuxostat suppressed Alzheimer's disease and vascular dementia in 22,178 gout patients and 113,590 controls.

Allopurinol reduced the incidence of dementia in a dose-dependent manner

Febuxostat 40 mg/day reduced the incidence of dementia

Those taking febuxostat had about 80% reduced risk of dementia

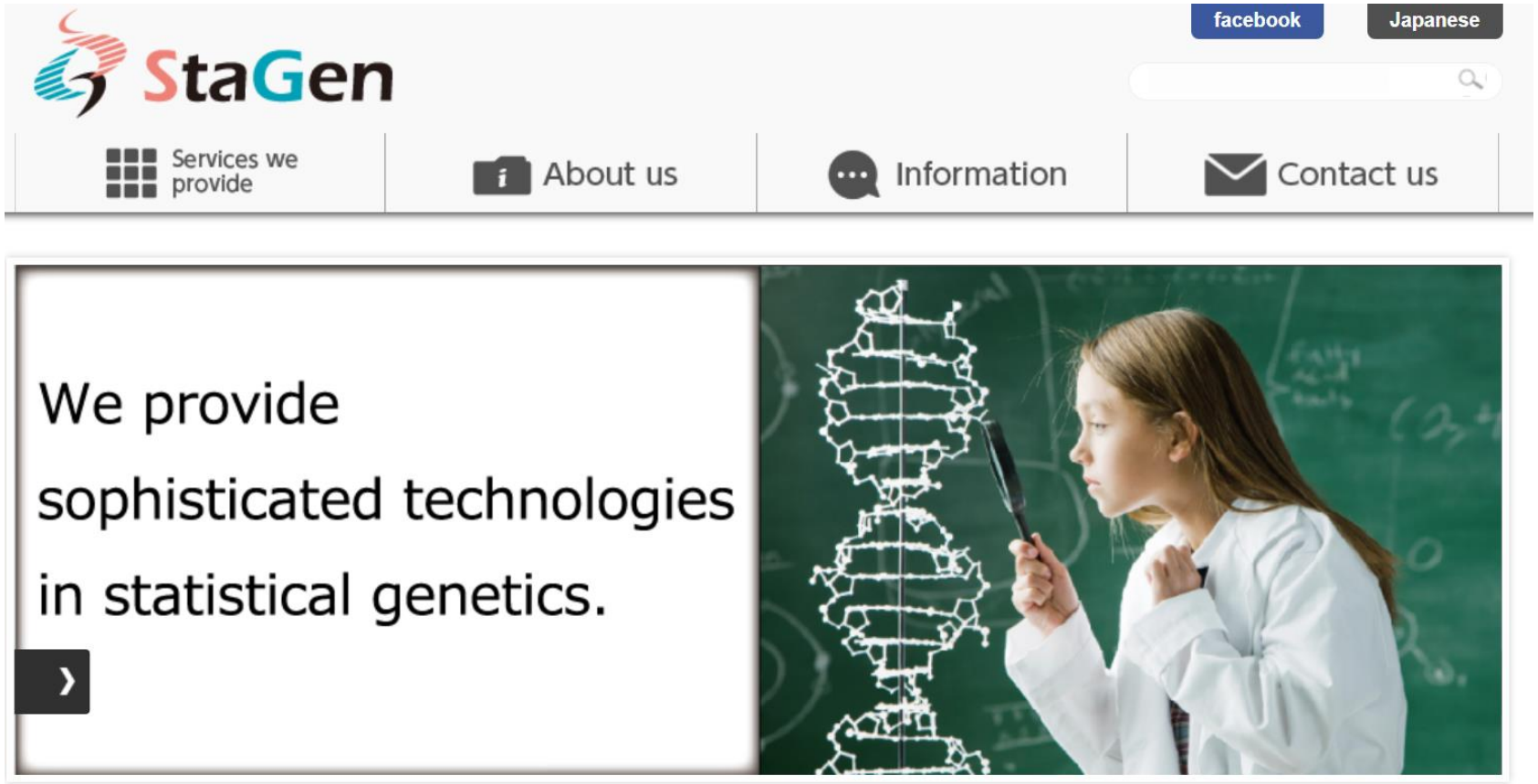




Singh JA et al. Arthritis Res Ther. 2018.

Min KH et al. Am J Geriatr Psychiatry. 2021

Prior to all reports including AI, we applied for patents.



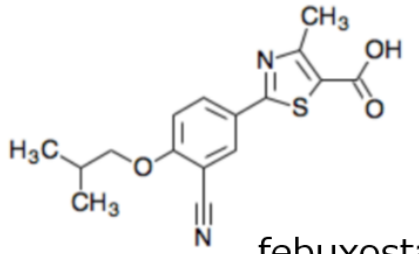
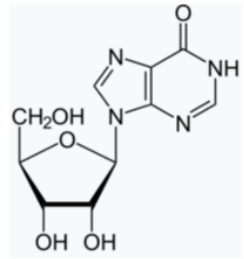
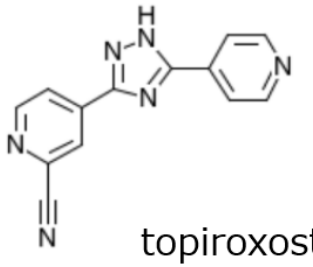
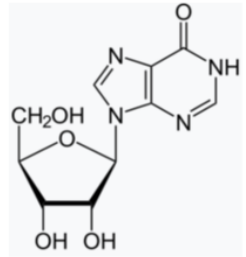
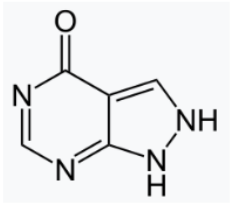
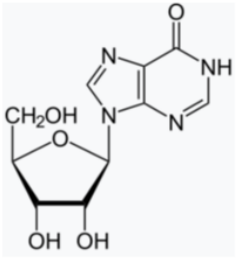
StaGen discovered the disease-improving effects of XOR inhibitors through their ATP-enhancing effects using its proprietary technology (a method to circumvent AI), and applied patents for concomitant administrations or combination drugs of XOR inhibitors (including febuxostat) and inosine.

StaGen's three major patented concomitant administrations and combination drugs

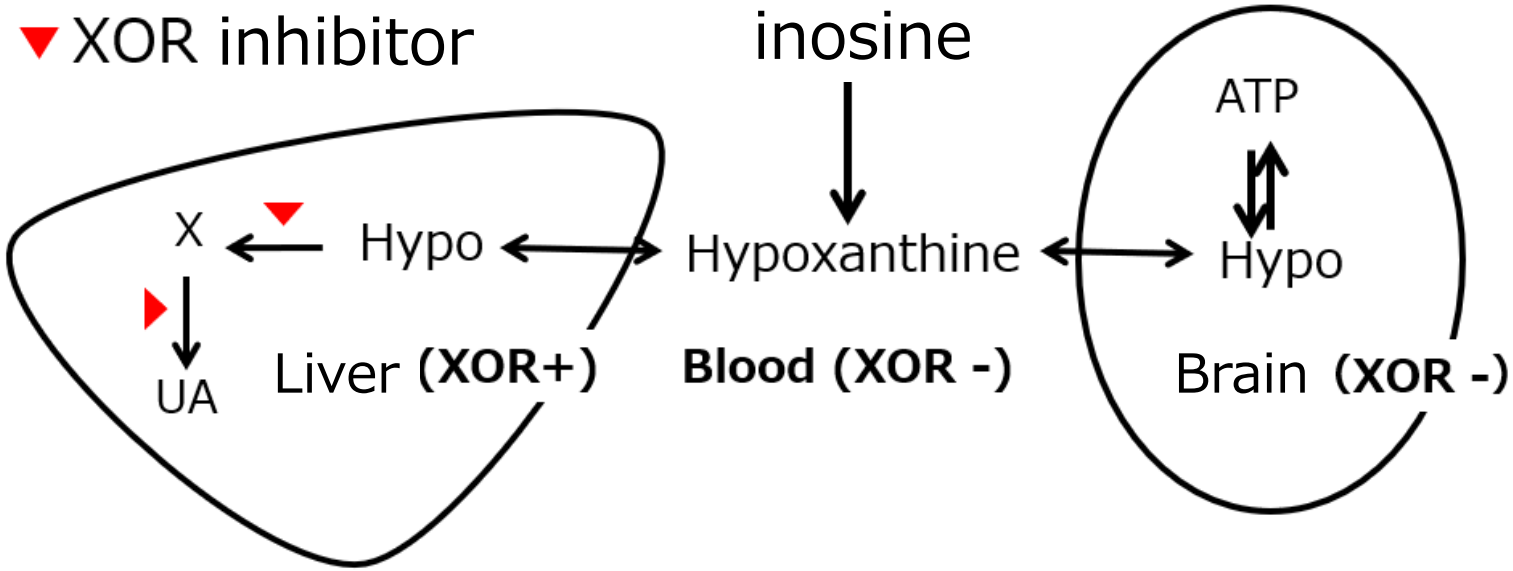
Each of StaGen's treatments is a concomitant administration or a combination drug of an XOR inhibitor and inosine (or hypoxanthine or IMP instead of inosine).

Patented in Japan, US, China, EU, etc.

XOR : xanthine oxidoreductase

	XOR inhibitor	+	inosine
SGD-1	 febuxostat	+	
SGD-2	 topiroxostat	+	
SGD-3	 allopurinol	+	

Mechanism of action of ATP enhancers



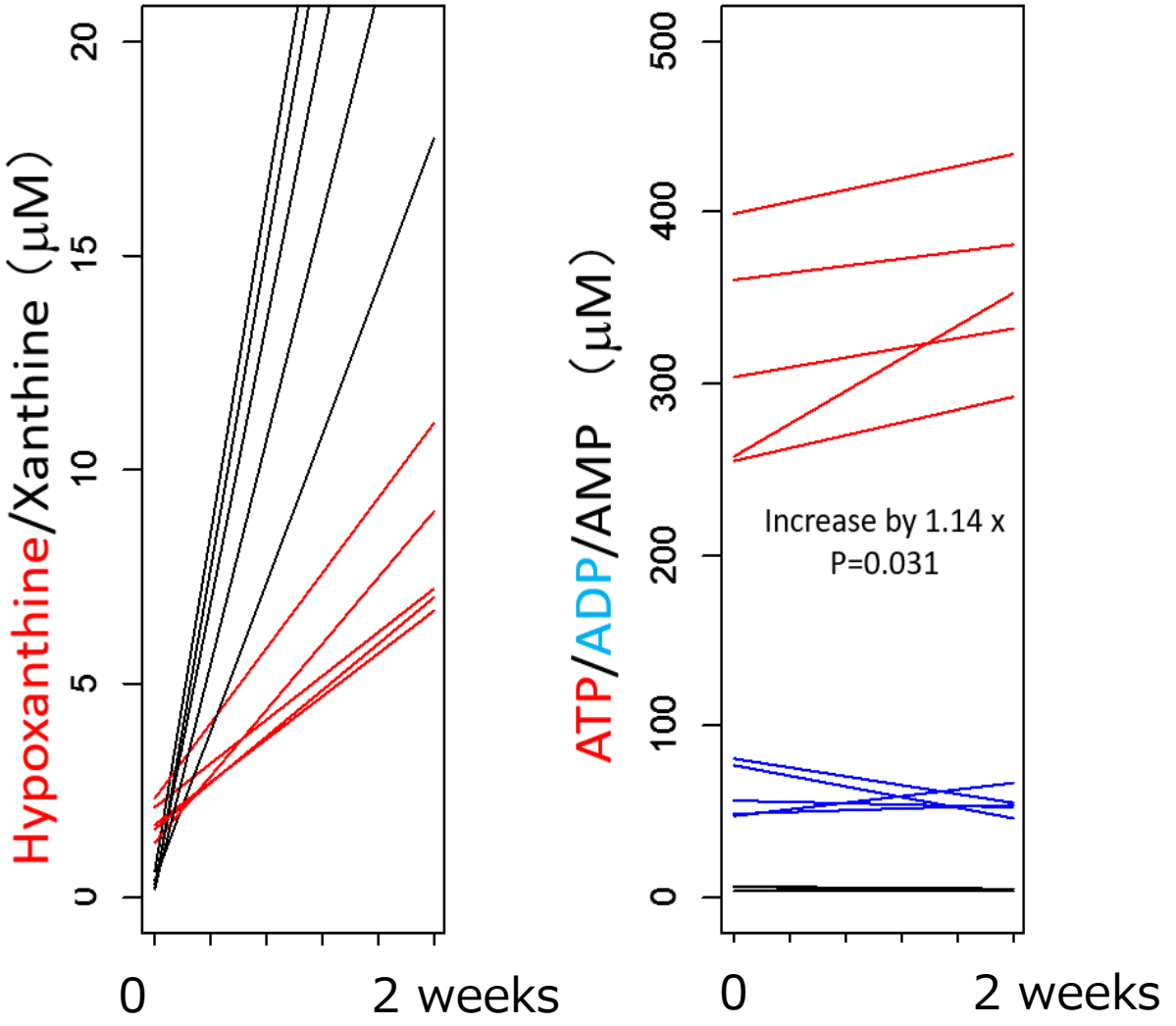
Hypo: Hypoxanthine
XOR : Xanthine oxidoreductase
XOR inhibitor : febuxostat etc

- The brain does not express the target enzyme XOR; XOR inhibitors block XOR in the liver, thereby increasing Hypo in the liver and blood.
- Hypo crosses the blood-brain barrier (BBB) and thus enters the brain to enhance ATP.
- The concomitant administration of febuxostat plus inosine, or a combination drug, is a better drug than febuxostat alone because it further enhances Hypo and inhibits urate reduction.

ATP and Hypo indeed increased in healthy subjects

We administered the XOR inhibitor febuxostat (20 mg) and inosine (0.5 g) twice daily for 2 weeks to healthy subjects.

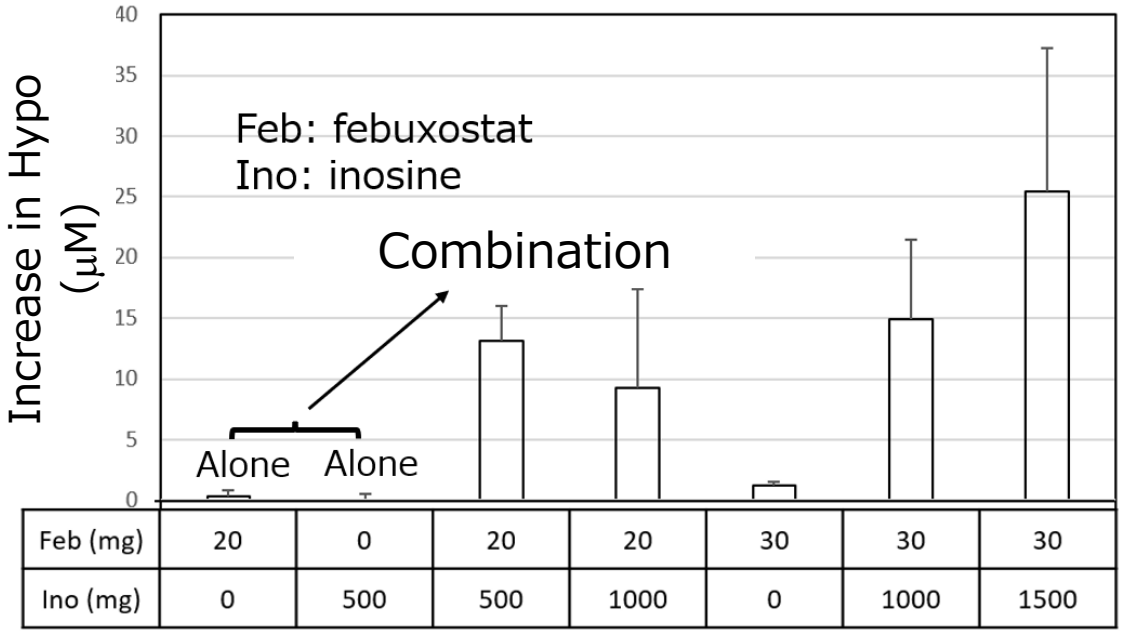
Blood hypoxanthine (Hypo) and ATP were measured.



Kamatani N, et al. Gout and Nucleic Acid Metabolism 41, 171-181, 2017

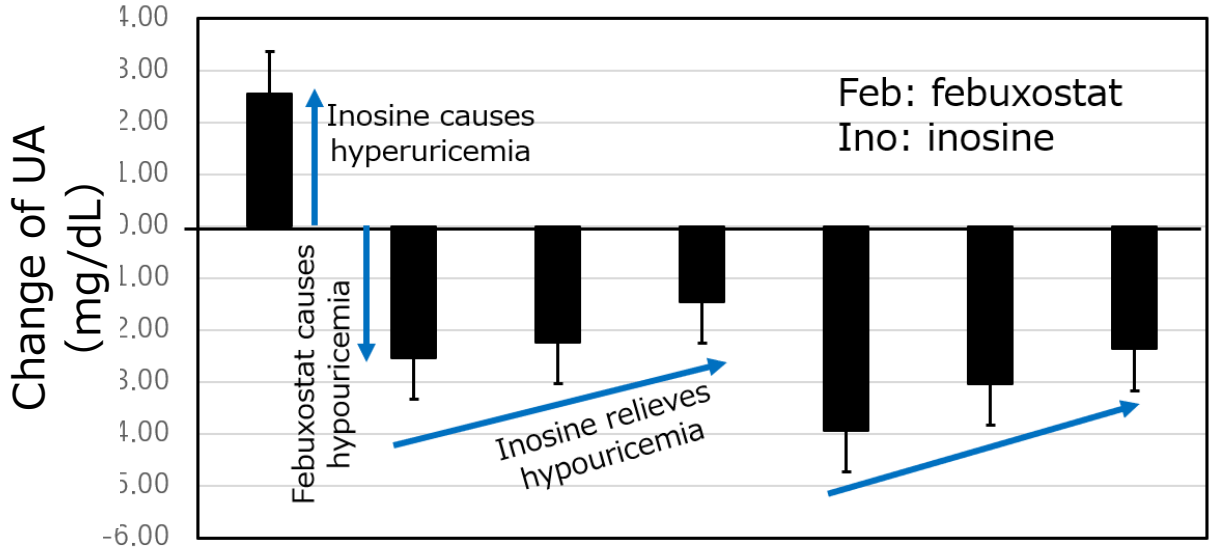
Concomitant administration has a synergistic effect and a reduced side effect of urate reduction

Synergistic effect of simultaneous administration of febuxostat and inosine in healthy subjects on Hypo elevation.



Feb (mg)	20	0	20	20	30	30	30
Ino (mg)	0	500	500	1000	0	1000	1500

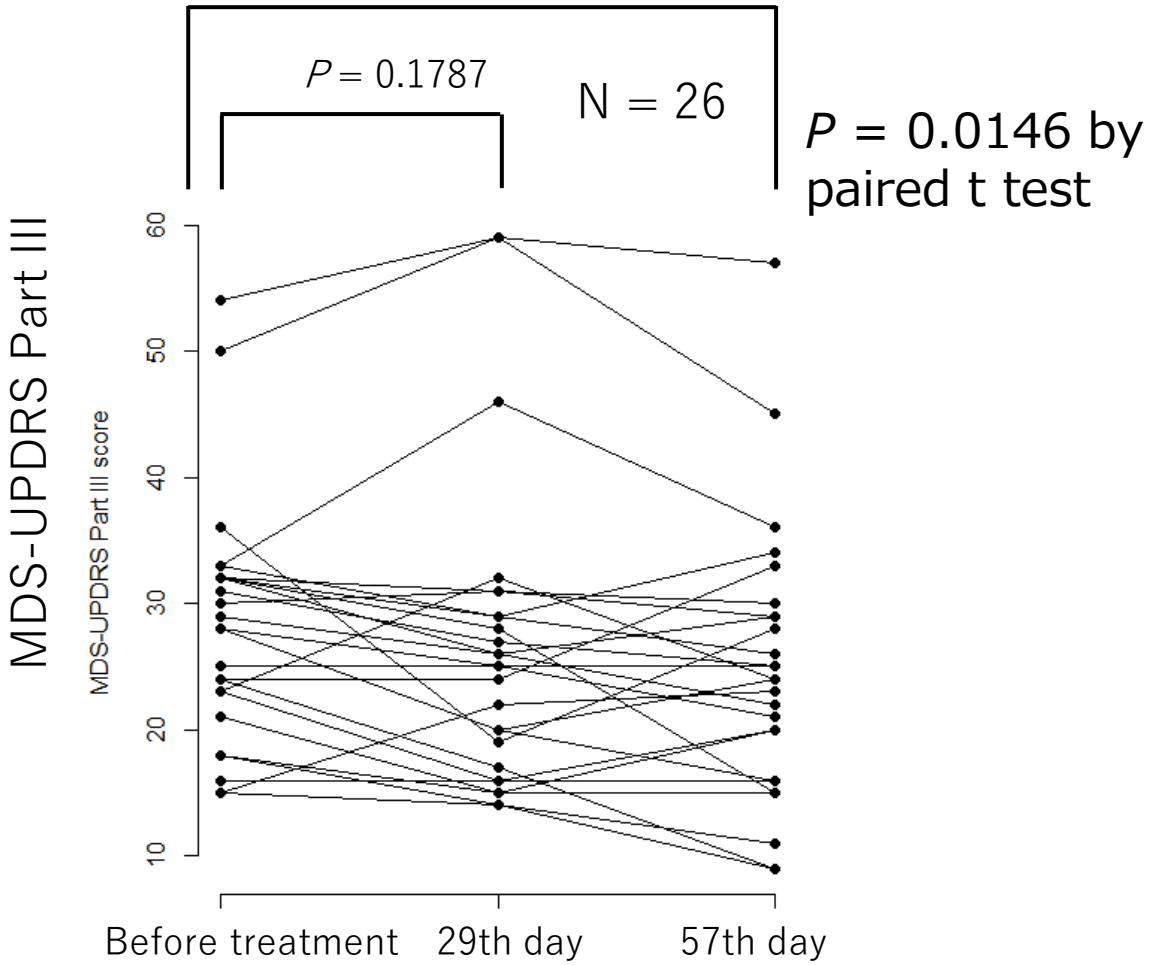
Risks of hyperuricemia and hypouricemia by monotherapies are avoided with concurrent administration



Feb (mg)	0	20	20	20	30	30	30
Ino (mg)	500	0	500	1000	0	1000	1500

Kamatani N, et al. Gout and Nucleic Acid Metabolism 41, 171-181, 2017

Concomitant administration significantly improved the primary endpoint in Parkinson's disease



Concomitant administration of febuxostat and inosine to 26 patients with Parkinson's disease for 2 months significantly improved the primary endpoint (MDS-UPDRS Part III)

Watanabe H et al. Medicine 2020;99:35(e21576).

Management team

Development Director

Naoyuki Kamatani, MD, PhD

Chairman of StaGen Co. Ltd.

(Past career: Professor, Tokyo Women's Medical University; Director, RIKEN Center for Genomic Medicine; Visiting Professor, University of Michigan; Author of over 600 papers, including 34 in Nature & Nat Genet.)

General Manager, Administration Division

Junichi Kaku

President and Representative Director, StaGen Co. Ltd.

Summary

- Aging is caused by age-related deterioration of mitochondria followed by the ATP (energy) shortage and the release of reactive oxygen species (ROS).
- Low febuxostat increases ATP, protects mitochondria and extends the lifespan of C. elegans, but the effects disappears at high-doses since urate, the known ROS scavenger, decreases.
- Adding urate to high-dose febuxostat restores the life-extending effect.
- An AI-based study and large-size clinical studies have shown that febuxostat suppresses the onset of Alzheimer's disease in humans.
- Adding inosine to febuxostat further increases ATP and inhibits urate reduction.
- Simultaneous administration of febuxostat and inosine improved Parkinson's disease.

The concomitant treatment or combination drug of febuxostat and inosine (ATP enhancer) won the FBRI award at the Third Kyoto University Life Science Showcase in San Diego in 2022.