

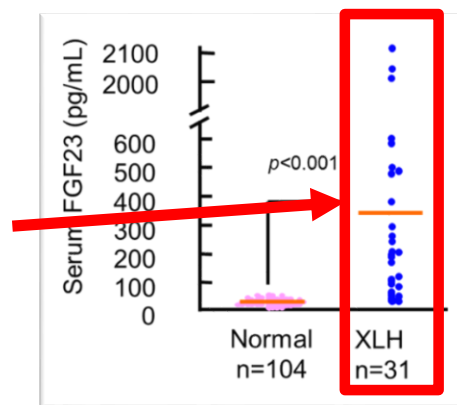
What is FGF23-related hypophosphatemic rickets and osteomalacia?

FGF23-related hypophosphatemic rickets and osteomalacia

Disease characteristics

- A type of rickets/osteomalacia caused by excessive actions of the hormone FGF23, which lowers blood phosphate levels and inhibits bone calcification.
- A rare and intractable disease, it is associated with growth impairment and bone deformity in children; in adults, symptoms include bone pain, proneness to fracture and muscle weakness leading to lack of strength.

Healthy subjects and XLH patients have different FGF23 levels



Yamazaki, et al. JCEM 2002

Causes and potential patient population

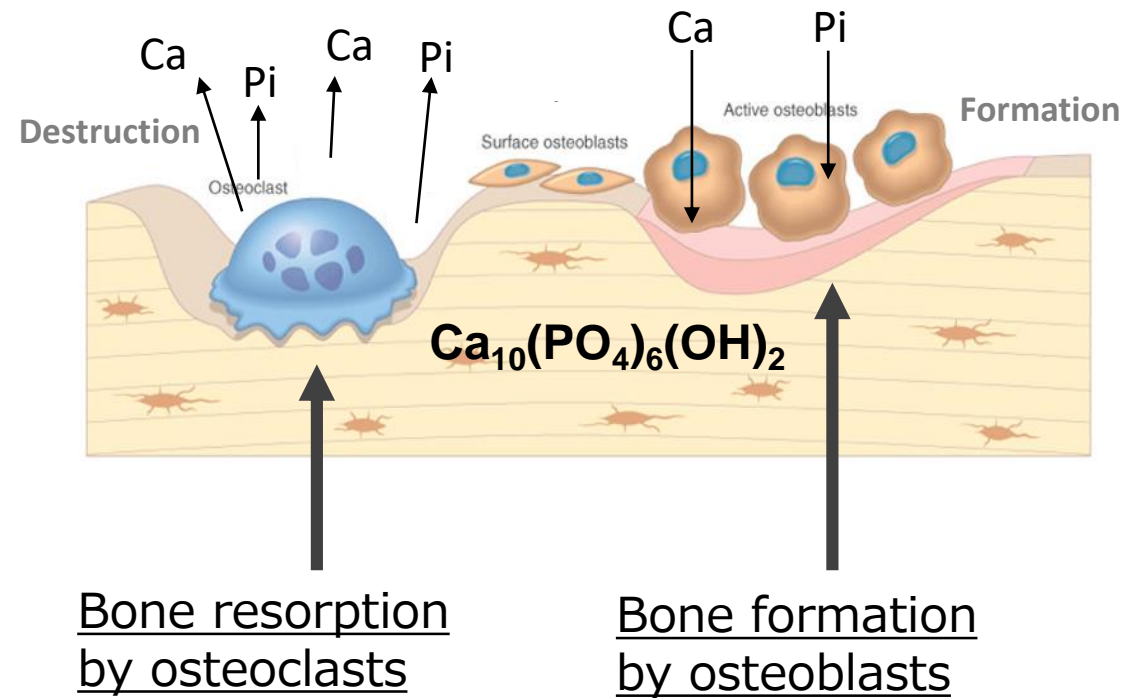
- FGF23-related hypophosphatemic rickets and osteomalacia is a “designated intractable disease in Japan”. Among its causes, the incidence rate of inherited X-linked hypophosphatemia (XLH) is estimated at **1 in 20,000 people**.
- In XLH, genetic factors on the X chromosome cause excessive excretion of systemic phosphate in the urine, resulting in **chronically low blood phosphate levels**.
- Phosphate is a mineral required for forming healthy bones and teeth as well as for maintaining the body's energy levels and muscle function and is essential to human life.

Background of research on anti-FGF23 antibody (1)

Our goal was to elucidate the biological factors involved in the regulation of bone metabolism and apply them to drug discovery

- Kirin Brewery's former Pharmaceutical Development Laboratory (at that time) was researching **bone metabolism**.
- Development was prompted by a focus on phosphate due to concurrent research in the key area of nephrology.
- **Phosphate** is the second most abundant mineral in the body after calcium, and is a major component of bones and teeth.
- Compared to calcium, however, research into phosphate regulation mechanisms lagged behind globally at the time. Kirin's researchers saw an **opportunity to help patients suffering from related diseases** and began their studies.

What is bone metabolism?

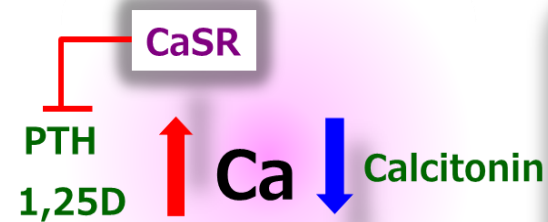


Anti-FGF23 antibody research and development

Background of research on anti-FGF23 antibody (2)

- In 2000, based on research into the pathogenesis of hypophosphatemia, we made the **unprecedented discovery** that FGF (fibroblast growth factor) 23 plays a central role in regulating blood phosphate levels.
- FGF23 is a humoral factor (hormone) that lowers blood phosphate produced by osteocytes. Suppression of FGF23 raises vitamin D and reduces phosphate excretion from the kidneys. We hypothesized that this may help treat XLH, and continued our research.
- The problem was how to suppress FGF23. By utilizing Kirin's **human antibody production technology**, we were able to create KRN23, an anti-FGF23 antibody suitable for the therapeutic purpose of suppressing FGF23.

■ Blood calcium homeostasis is controlled by systemic hormones



CaSR: calcium receptor
➢ Cinacalcet (Regpara®)
PTH: parathyroid hormone
➢ Teriparatide (Forteo®)
1,25D: active vitamin D
➢ Calcitriol (Rocaltrol®)
Calcitonin: calcitonin
➢ Elcatonin (Elcatonin®)

■ It was unclear this suggested the presence of a phosphate-creating hormone



First in the world!
Unknown regulatory hormone was found to be FGF23

History of anti-FGF23 antibody research and development

1998 Phosphatonin research started
KIRIN

2000 FGF23 gene cloning^{1, 2}

2002-04 Role of FGF23 in XLH elucidated^{3,4}

2006 Role of klotho in FGF23 signaling elucidated⁵

2008 **KYOWA KIRIN**
Kyowa Hakko Kirin is born

2013 **ultragenyx**
pharmaceutical
Agreement concluded with Ultragenyx for development and sales in Europe and the United States

2016 Breakthrough Therapy Designation received

2018 Designated as an orphan drug (Japan)

2019.1 Japan NDA
FGF23-related hypophosphatemic rickets and osteomalacia
2019.9 Approved in Japan
2019.12 Marketed in Japan

2008.4 U.S. IND submission
IND submitted by Gemini Science/Kirin Pharma USA

2009 U.S. FIH trials for adult XLH begin

2015 Europe, U.S. and Asia Adult XLH Ph-3 trials

2017.8 U.S. BLA Designated for priority review

2016 Europe, U.S. and Asia Pediatric XLH Ph-3 trial

February 2018 Approved in Europe (pediatric XLH)

2014 Europe and U.S. Pediatric XLH Ph-2 trials
Adult TIO Ph-2 trials

2016 Japan and South Korea Adult TIO Ph-2 trial

April 2018 Approved in the U.S. (XLH)

2014 Japan and South Korea Adult XLH Ph-1 trials

2016.12 Europe MMA Conditional MAA designation

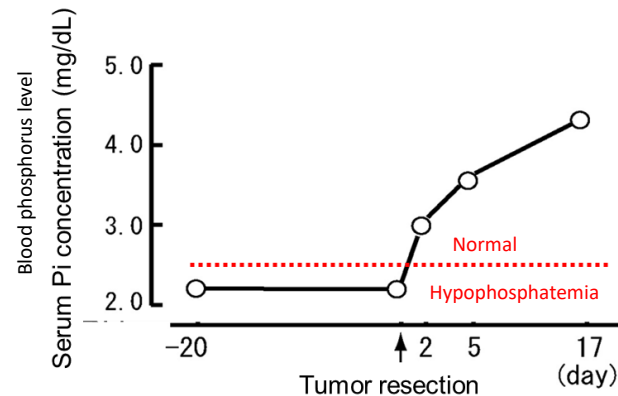
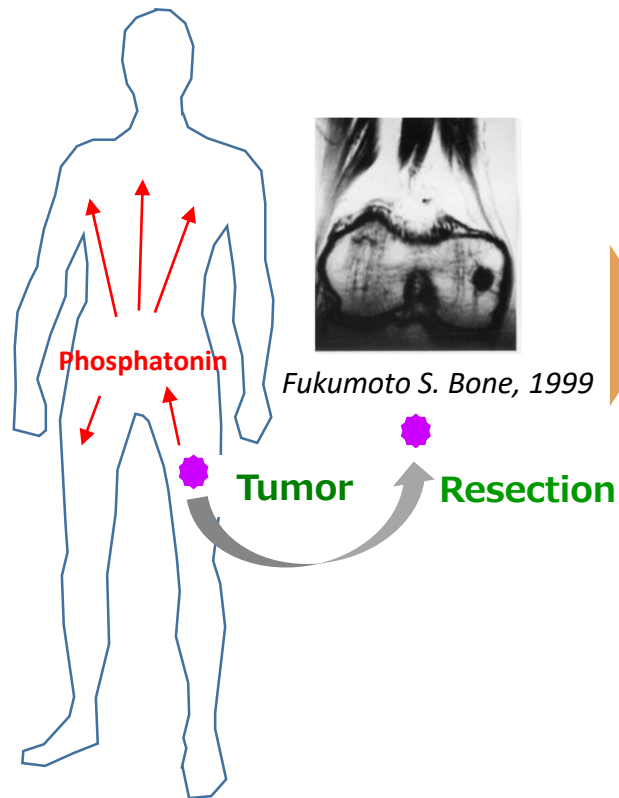
1 ADHR Consortium. Nat Genet. 2000;26:345-348
2 Shimada T, et al. Proc Natl Acad Sci USA. 2001;98:6500-6505
3 Shimada T, et al. J Bone Miner Res. 2004;19:429-435
4 Yamazaki Y, et al. J Clin Endocrinol Metab. 2002;87:4957-4600
5 Urakawa, et al. Nature. 2006;444:770-774

Discovery of anti-FGF23 antibodies

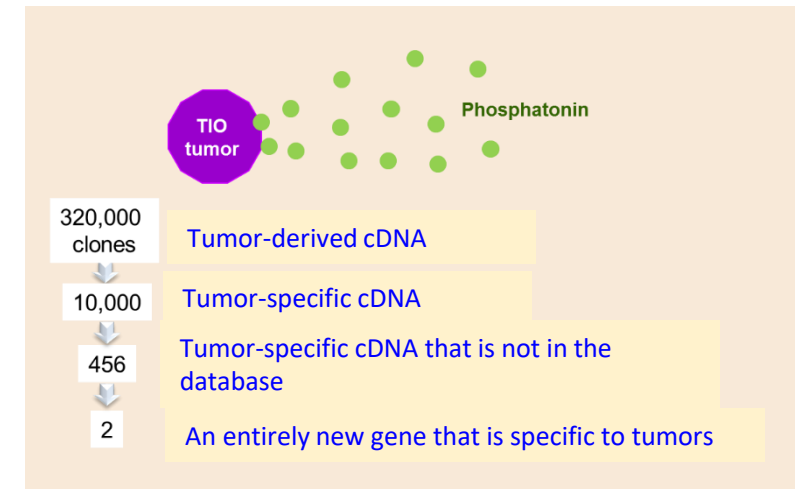
The road to discovery of anti-FGF23 antibodies

1998 Joint research with Dr. Seiji Fukumoto, University of Tokyo Hospital(at that time)

*Presently Fujii Memorial Institute of Medical Center , Tokushima University



Resected tumors were found to be overproducing an unknown phosphate-lowering hormone



➔ Unknown phosphate-lowering hormone identified from resected tumors — toward discovery

Expanding the use of anti-FGF23 antibody

To contribute patients around the world



Launched	Japan, USA, Canada, UK, eight EU countries*, Israel, UAE, Norway, Bahrain, Oman
Approved	18 EU countries other than the above, Iceland, Liechtenstein, Switzerland and Hong Kong
Under Review	China, Taiwan, Singapore, Kuwait and Saudi Arabia

As of June 30, 2020*Germany, Netherlands, Luxembourg, Slovakia, Sweden, Czech Republic, Denmark, Italy

Net sales	2018	7.7 billion yen (overseas)
	2019	32.5 billion yen (overseas)
	2020 forecast	51.1 billion yen (overseas) 3.5 yen (in Japan)