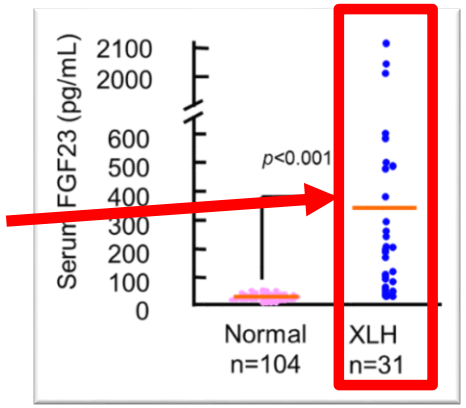
FGF23-related hypophosphatemic rickets and osteomalacia

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

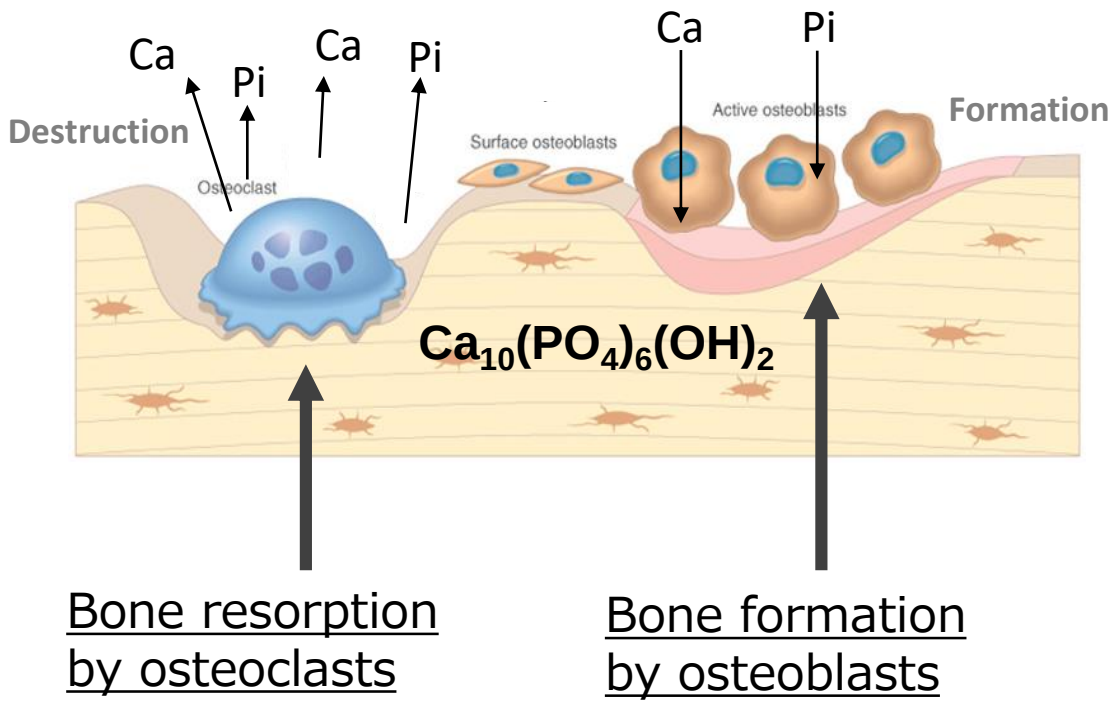
- FGF23-related hypophosphatemic rickets and osteomalacia is a “designated intractable disease in Japan“. Among its causes, the incidence rate of inherited X-linked hypophosphatemia (XLH) is estimated at 1 in 20,000 people.
- In XLH, genetic factors on the X chromosome cause excessive excretion of systemic 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.

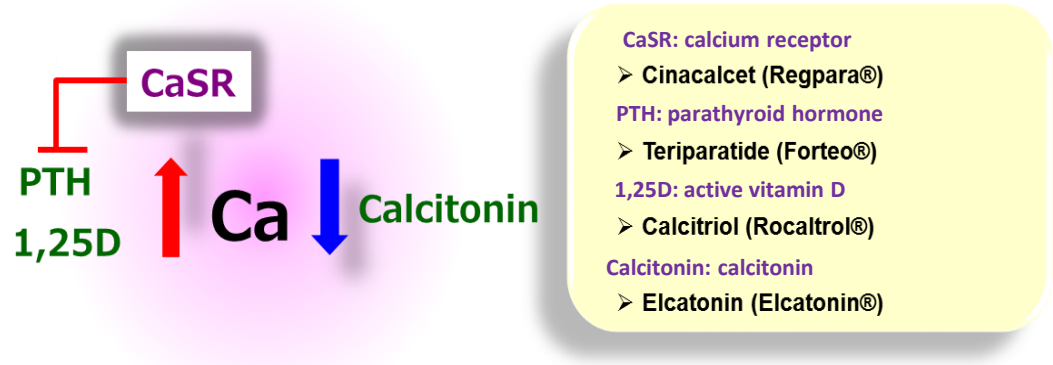
What is bone metabolism?



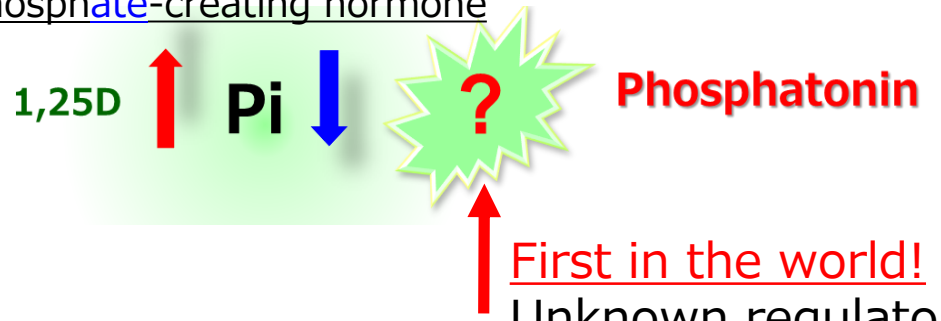
Background of research on anti-FGF23 antibody (2)

- 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

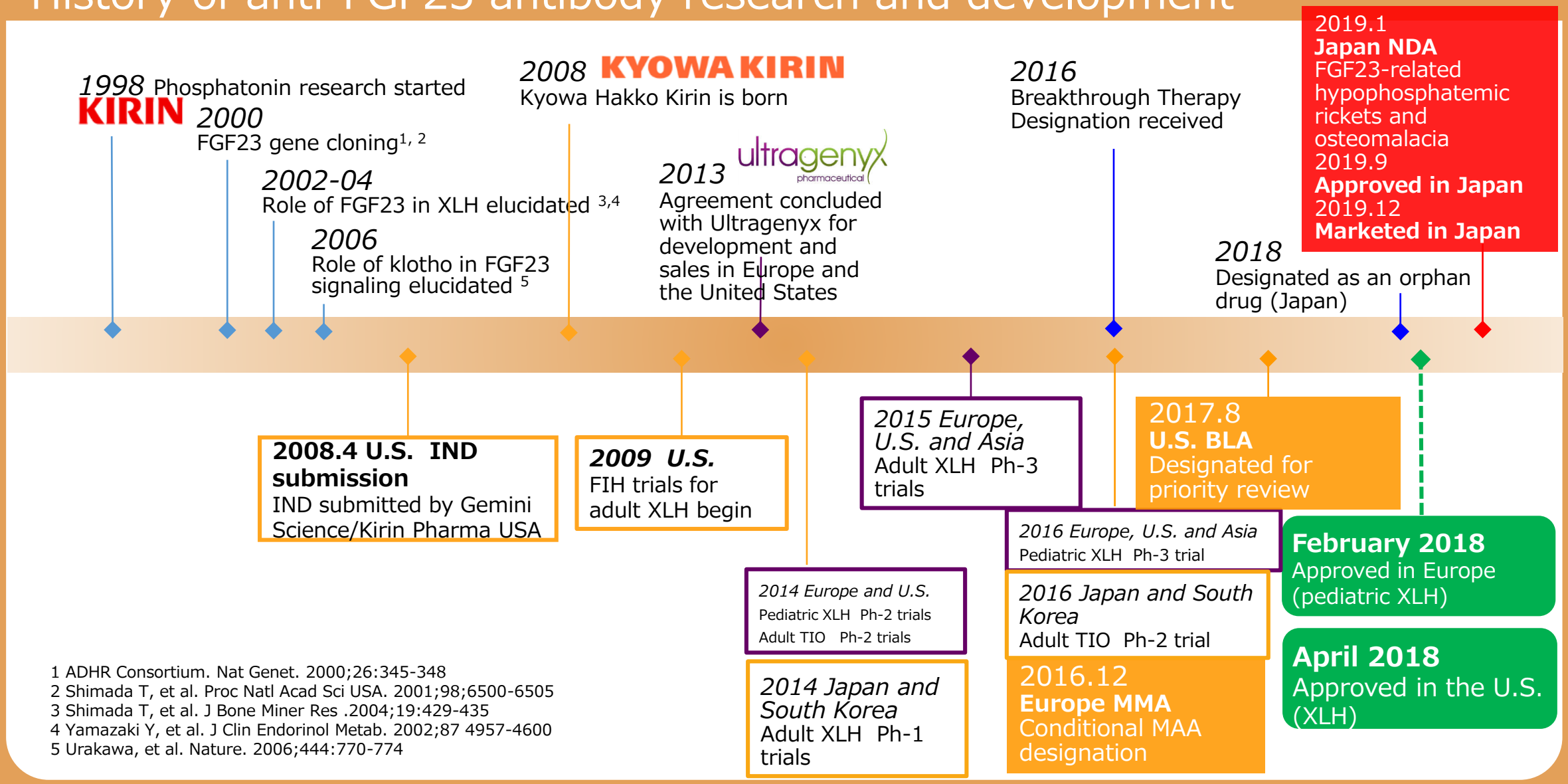


■It was unclear this suggested the presence of a phosphate-creating hormone



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

History of anti-FGF23 antibody research and development

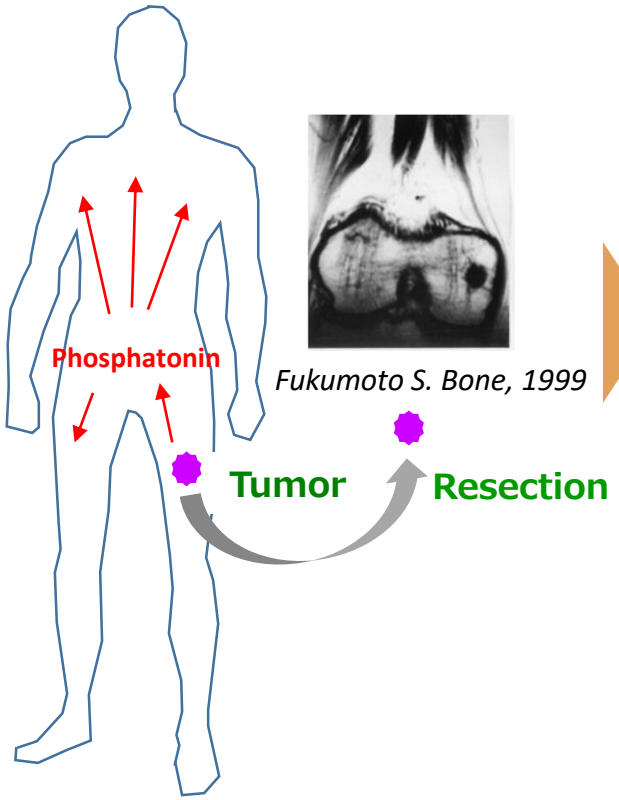


1 ADHR Consortium. Nat Genet. 2000;26:345-348
2 Shimada T, et al. Proc Natl Acad Sci USA. 2001;98;6500-6505
3 Shimada T, et al. J Bone Miner Res .2004;19:429-435
4 Yamazaki Y, et al. J Clin Endorinol Metab. 2002;87 4957-4600
5 Urakawa, et al. Nature. 2006;444:770-774

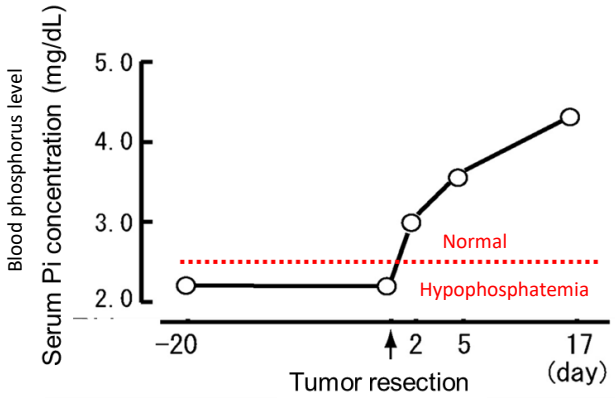
The road to discovery of anti-FGF23 antibodies

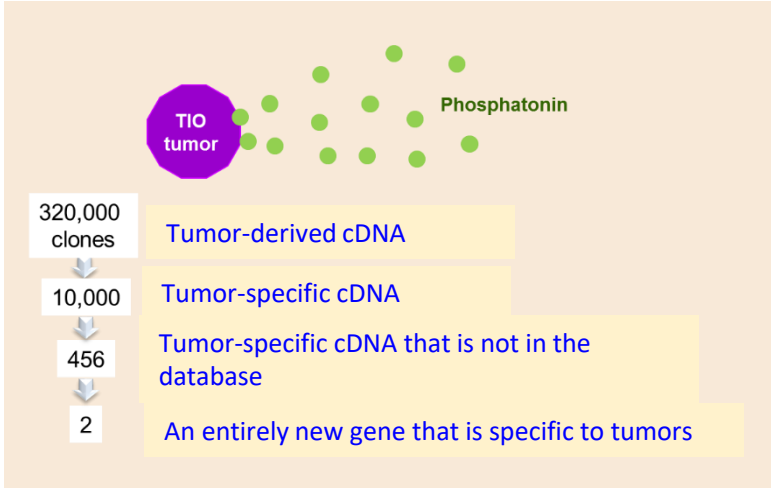
1998 Joint research with Dr. Seiji Fukumoto, University of Tokyo Hospital(at that time)

*Presently Fujii Memorial Institute of Medical Center , Tokushima University



Fukumoto S. Bone, 1999





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)