Developing Diagnostic Tools and Drug Candidates against Diseases Thought to be Intractable

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Contributing to Healthcare through the Power of Synthetic Small Molecules

Mission

Nurturing future leaders in medicinal chemistry

Discovering seed compounds for future drugs

Developing new strategies for drug discovery

Serving as a critical complement to the efforts of the pharmaceutical industry

Vision

Addressing the challenge of developing new drugs and better versions of orphan drugs

- Developing better drugs for the treatment of type 1 and type 2 diabetes
- Generating alternatives to steroids for the treatment of Crohn's disease, rheumatoid arthritis and atopic dermatitis
- Developing drugs against cancers including leukemia and breast cancer
- Creating drugs to alleviate chronic pain

Approach

Performing not only organic syntheses but also biological evaluation (including in vivo tests) by us

Kakuta Lab.

Showing the power of molecules

Selection of target diseases and molecular target molecules → Seed compound selection

Molecular design・Organic syntheses・Bioactivity evaluation → Collaboration with Companies or labs

Animal experiments also performed

"Revival drug discovery"

This strategy is to revive abandoned drug targets by research for avoiding their side effects and so on. If we can eliminate the side effects, the target will become revived as a new drug target. It is promising because the targets are already researched in detail, the problems are only the generation of side effects.

Our current target: Retinoid X receptors

Why do we focus on Retinoid X receptors (RXRs)?

RXR agonists show anti-diabetes, anti-obesity, anti-inflammation, and so on.

However, **the past RXR agonists show several side effects** such as plasma triglyceride elevation, hepatomegaly, and hypothyroidism. (**abandoned drugs**)

We succeeded in creating novel RXR partial agonists without the side effects.

Generating *screening or diagnostic tools・drug seeds targeting RXRs*

Principle of FP assay

Fluorescent RXR ligand

RXR + *High FP* *Analyte*

RXR + *Low FP*

Screening tools

RXR ligand screening assay kit based on fluorescence polarization(FP)

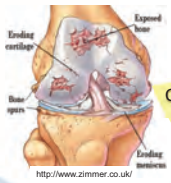
Accomplished by creation of fluorescent RXR ligands

Yamada S, *et al.* *Bioorg. Med. Chem. Lett.* 2010, *20*, 5143–6. etc.

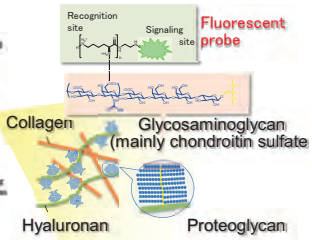
Drug seeds

Developing RXR ligands

Knee Arthritis



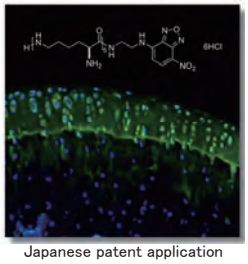
http://www.zimmer.co.uk/



Diagnostic tools

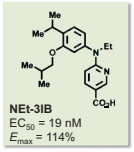
Cartilage selective probes

Collaborated with Dr. Oohashi



Japanese patent application No. 2012–055511.

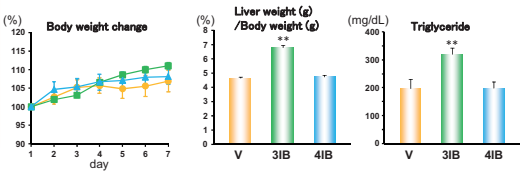
RXR full agonist



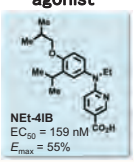
Side effect evaluation by 7 days administration

ICR mice ♂, 6 weeks, n = 7 – 8, 30 mg/kg/day *p.o.*

* p<0.05, ** p<0.01 vs vehicle

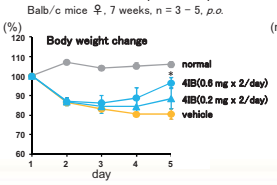


RXR partial agonist



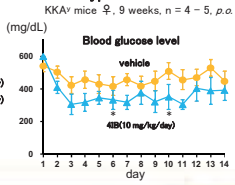
Anti-IBD effect (NBD-Cl)

Balb/c mice ♀, 7 weeks, n = 3 – 5, *p.o.*



Anti-type 2 diabetes

KKAʸ mice ♀, 9 weeks, n = 4 – 5, *p.o.*



RXR partial agonist CBt-PMN exerting therapeutic effects on type 2 diabetes without the side effects of RXR full agonists
Kakuta H, *et al. ACS. Med. Chem. Lett.* 2012, *3*, 427–432.

RXR partial agonists showing anti-diabetes and anti-autoimmune disease such as Crohn's disease and so on.
Japanese patent application No. 2012-041353.
Japanese Patent No. 4691619.

Promise as anti-Alzheimer's effect

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