Nuclear receptors as drug targets

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Q Your focus is on nuclear receptor ligands. Please briefly describe what they are.

A: Nuclear receptors are a family of ligand-regulated transcription factors – proteins that control the transcription of specific genetic information – that are activated by small hydrophobic signaling molecules such as steroid hormones, thyroid hormone and activated vitamin A (retinoid) and D.

Nuclear receptors regulate various biological phenomena, including growth, development, metabolism, the immune system, and homeostasis, and are significant molecular targets for drug discovery in the fields of cancer, metabolic syndromes, autoimmune diseases, and neurodegenerative diseases.

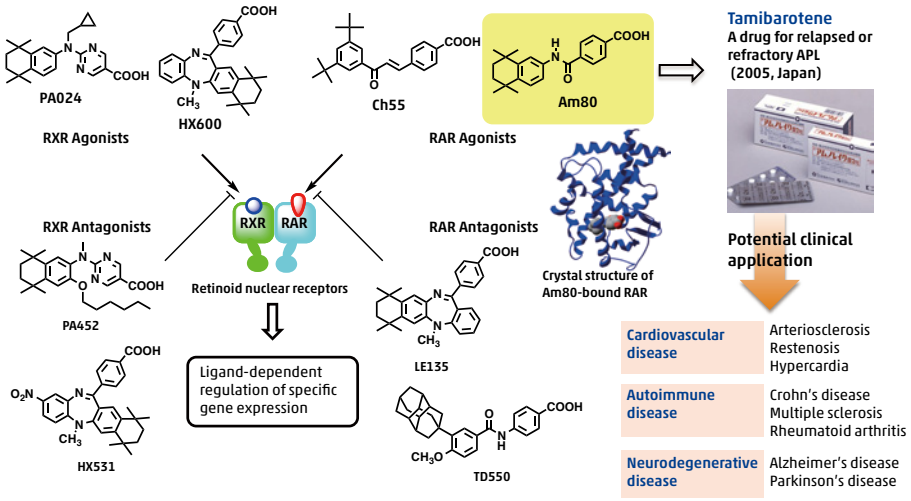
Q Can you give us an overview of your latest findings?

A: We have been extensively studying retinoids (active vitamin A). There are two classes of retinoid nuclear receptors, RARs and RXRs. RXRs play significant roles in nuclear receptor actions by forming heterodimers with various nuclear receptors. We have developed various specific agonists and antagonists for RARs and RXRs. Further, we recently found retinoids with non-classical action mechanisms.

We have also determined the crystal structures of nuclear receptor ligand-binding domains and the ligand-dependent activation mechanism, which enabled us to rationally design selective ligands of nuclear receptors. Further, we have advanced medicinal chemistry of nuclear receptors by successfully developing novel hydrophobic pharmacophores, which have been applied to the development of synthetic steroid hormones and vitamin D analogs with unique structures.

Synthesis of novel nuclear receptor ligands and their clinical application

[Example: Structures of synthetic retinoids and clinical application of Am80 (Tamibarotene)]



Q Please tell us about your other research interests.

A: We have promoted the collaboration with medical and dental researchers. With my colleagues at TMDU, we have recently identified novel bioactive molecules, such as activators of a transcriptional coactivator TAZ involved in the Hippo pathway, the WNK signaling inhibitors as a new class of antihypertensive drugs, and inhibitors of the Nrf2 signaling pathway that plays a critical role in regulating cellular defenses against electrophilic and oxidative stress.

For example, we screened nearly 18,000 molecules in the chemical library of our institute for TAZ activators, and identified one compound that enhanced the myogenesis in mouse C2C12 myoblast cells from 55 hit compounds, which is a promising lead compound for a drug to prevent muscle atrophy and facilitate muscle regeneration after injury.

Q What are the clinical implications of your research?

A: Our synthetic retinoid, Am80 (Tamibarotene) is now clinically used as a drug for acute propyelocytic leukemia (APL). Now, we are trying to use the drug to treat other diseases, including inflammatory bowel disease and Alzheimer's disease.

Dr. Kagechika obtained his PhD from the University of Tokyo in 1989, and was employed as an assistant or associate professor there from 1985-2004. Currently, he is Professor in TMDU's Graduate School of Biomedical Sciences, Institute of Biomaterials and Bioengineering, and has been Vice Dean of the Graduate School since 2012. His major research interest is medicinal chemistry of nuclear receptors.

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