Okayama University Medical Research Updates （OU-MRU） 2019.11 Vol.72

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Okayama University research: Synthetic compound provides fast screening for potential drugs

(Okayama, 4 November) **A simple assay may benefit drug discovery for treating diabetes, Parkinson's, and Alzheimers disease, as well as studies of functional food and endocrine disruptor report researchers at Okayama University in the *Journal of Medicinal Chemistry*. The assay hinges on a synthetic compound that allows faster screening with fewer hardware resource requirements than existing methods.**

Retinoid X receptors (RXRs) are a type of nuclear receptor - proteins that regulate an organism's development, homeostasis and metabolism. They usually operate as heterodimers alongside other proteins and receptors, so the ligands targeting them are key to controlling their activity. RXR activators have attracted particular interest recently because of their potential to treat diabetes, Alzheimers and Parkinsons disease. They are also associated with functional foods and processes by which environmental pollutants damage health. However, methods for screening compounds for their potential RXR targeting ligand activity have so far proved slow and awkward. Associate Professor KAKUTA Hiroki at University of Okayama Graduate School of Medicine and Shogo Nakano at the University of Shizuoka in Japan, and their colleagues have now demonstrated an assay based on a synthetic compound CU-6PMN - referred to as **10** - that can screen for RXR targeting ligand activity in hours instead of days with no complex equipment or radioactive isotopes needed.

The researchers based the chemical structure of synthetic compound **10**, on the RXR activator CD3254, referred to as compound **9**. "Because **9** has a cinnamic acid structure, we anticipated that this structure could be developed toward an umbelliferone structure," they explain in their report of the work. The significance of umbelliferone is its fluorescence. Not only is the fluorescence of umbelliferone relatively easy to detect - widely available filter sets can detect it - but the compound can also be modified so that its fluorescence intensity increases in aqueous environments. This means that if a compositely binding RXR ligand displaces the receptor bound compound, the fluorophore will be exposed to a more aqueous environment, its fluorescence will increase, and the activity of the ligand can be detected.

With compound **10** the researchers showed they could detect RXR targeting ligand activity in just a few hours with standard fluorescence microplate readers and no need for complicated processes. In their report they conclude, "We believe it will be useful not only for identifying RXR binders in drug discovery studies but also for studies of functional foods and endocrine disruptors, though it should be noted that fluorescence-based assays often suffer from interference when used to screen natural products."

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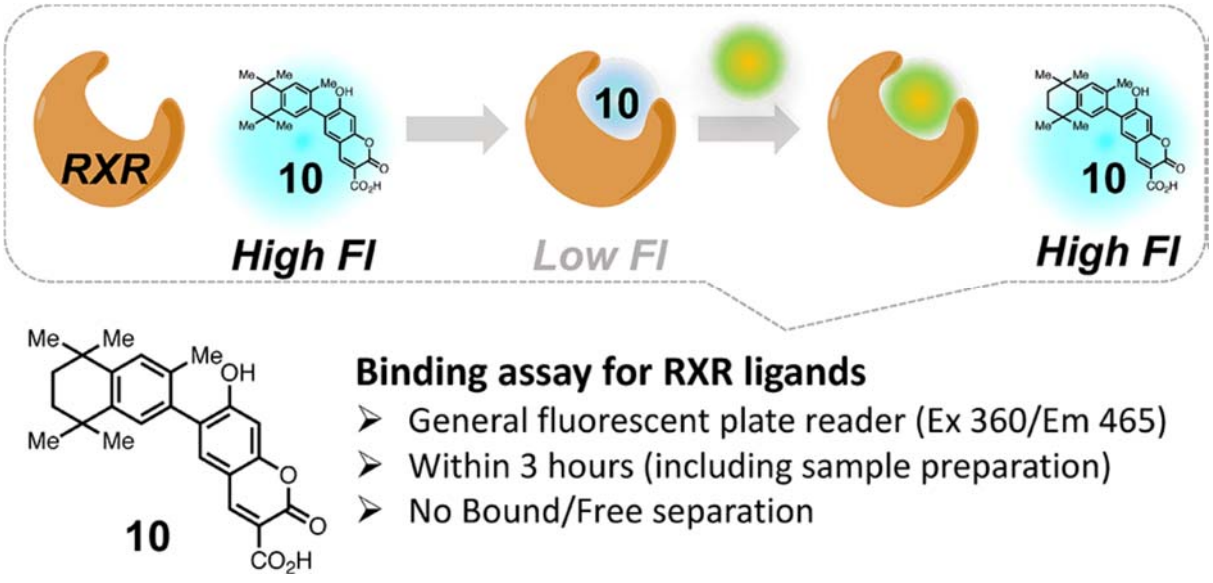
Background

Nuclear receptor activity mechanisms

Nuclear receptors are found in cells. They sense the presence of small molecules such as steroid and thyroid hormones and regulate the expression of genes to control bodily processes. The human body has 48 types of nuclear receptor. The RXR activator bexarotene is already used clinically to treat cutaneous T cell lymphoma, and recent studies have recommended its potential for treating diabetes, Alzheimer's disease, and Parkinson's disease. Polyunsaturated fatty acids including docosahexaenoic acid (DHA) are naturally occurring RXR targeting ligands and are linked to improved memory and metabolic syndrome. Conversely the impact of environmental polluters on nuclear receptors can inhibit their interaction with hormones and disrupt the endocrine system.

Current assay techniques

To test for the presence and activity of substances, researchers in medicine, pharmacology and environmental and molecular biology use assays. Previous assays for RXR targeting ligand activity have also used fluorescence, but they have had drawbacks. Those based on time-resolved fluorescence resonance energy transfer, require a special reader plate, while others have been based on quenching the autofluorescence of the molecule tryptophan, which has a weak autofluorescence signal at a wavelength that standard readers cannot detect. Alternative assays have used reporter genes and take 3-4 days to detect ligand activity, or they have used radioisotope labelled ligands, where the issues that surround use of radioactive isotopes further complicate an already complex procedure.



Caption

The fluorescence from compound **10** increases when an RXR targeting ligand displaces it, making it a useful indicator for ligand activity in assays.

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Reference

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Okayama University Image Movie (2018):
https://www.youtube.com/watch?v=WmyqOTuigBs

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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

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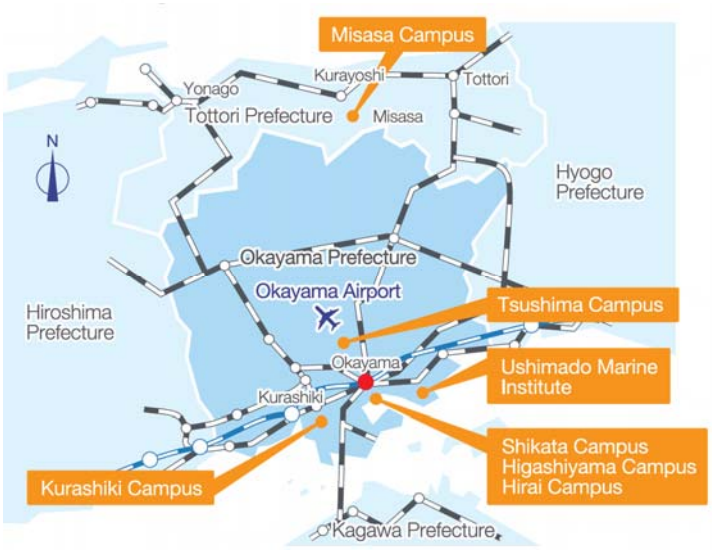

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