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Small molecule fluorescence probe to evaluate potential risk for Parkinson's disease

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A team of researchers from National University of Singapore (NUS) have created the first two-photon, small molecule fluorogenic probe that can serve as a useful tool for the rapid assessment of an individual's potential risk for Parkinson's disease. The highly sensitive fluorescence probe can detect with high precision the activity of Monoamine Oxidase B (MAO-B), an enzyme that is found in elevated levels in patients with Parkinson's disease. This innovation paves the way for the development of less costly non-invasive technologies and devices to help monitor the risk and progression of Parkinson's disease.

The study is co-led by Professor Yao Shao Qin from the Department of Chemistry, Faculty of Science at NUS and Associate Professor Lim Kah Leong, from the National Neuroscience Institute, Singapore and also the Department of Physiology at NUS Yong Loo Lin School of Medicine. The findings are published in *Nature Communications* journal this month.

Enabling highly sensitive, specific and real-time imaging of MAO-B activities

Monoamine oxidases (MAOs) are enzymes that are found mainly in the human brain. Its two isoforms – MAO-A and MAO-B – work together to help maintain the balance of neurotransmitters in the brain. But when the enzymes are over-activated, the brain produces an excessive level of

neurotoxic byproducts, causing neuronal dysfunctions that lead to psychiatric disorders and neurodegenerative diseases. In the case of Parkinson's disease, it is found that the expression of MAO-B, but not MAO-A, is significantly enhanced in the brain of patients and increases with age.

The high MAO-B activity consistently observed in patients with Parkinson's disease has been proposed as a biomarker, but there has been a lack of suitable small molecule probes for MAO-B specific detection in live cells and tissues. Some of the existing fluorescence-based MAO-B probes require the addition of activating reagents, which can affect the properties of the enzymes and reduce the accuracy of detection, while some others are unable to distinguish precisely between MAO-B and the closely related MAO-A.

The small molecule probe designed and synthesised by the NUS team addresses these inadequacies of existing probes. Their probe is highly sensitive and can detect MAO-B specifically with greater precision. The fluorescence label on the probe also allows it to be detected via high-resolution imaging techniques in tissues and organs at depths of up to one millimeter, which enables researchers to effectively monitor the in vivo enzymatic activities of MAO-B in living systems. These were all not possible previously with the existing MAO probes.

MAO-B as a biomarker for Parkinson's disease

The study also found that in patients with Parkinson's disease, MAO-B activities are present only in human B-lymphocytes (a type of white blood cell), but not in fibroblasts (cells typically found in connective tissues).

"This suggests that MAO-B activity in peripheral blood cells of a patient might serve as an accessible and economical biomarker to evaluate the

potential risk of an individual for this disease", said Assoc Prof Lim. Presently there is no reliable biomarker for Parkinson's disease, either at the diseased or preclinical state, except for dopamine-based PET imaging, which is costly and requires highly specialised skills to perform.

"The probe may potentially be useful to monitor patient's response to medication", said Associate Professor Louis Tan, Senior Consultant, Department of Neurology at the National Neuroscience Institute, whose team has recently shown in a separate study that long term use of a MAO-B inhibitor reduces the progression of early Parkinson's disease.

The probe also has no apparent toxicity in most mammalian cells, so it can be used to monitor in vivo MAO-B activities during various stages of the disease. As such, the probe can also become a useful tool to understand how Parkinson's disease progresses as well as for drug development.

"Our findings for this study provide important starting points for using small molecule imaging techniques to explore MAO-B further at the organism level, and in fact, opens up future prospects for non-invasive imaging-based diagnostic applications", said Dr Li Lin, the first author of the paper and a post-doctoral fellow in Prof Yao's lab.

The NUS research team intends to further their research on the probe. One of their immediate priorities is to validate the effectiveness of their probe in detecting MAO-B in a larger pool of patient samples, with an aim of eventually developing the probe into a commercial test kit to monitor the progression of Parkinson's disease.

The team also recently obtained a grant from the National Medical Research Council in Singapore to pursue a study using the probe to examine the relationship between key Parkinson's disease-linked genes

and MAO-B expression and activity to further understand the causes of the disease and illuminate the role of MAO-B in this.

More information: "A sensitive two-photon probe to selectively detect monoamide oxidase B activity in Parkinson's disease models." Lin Li, Cheng-Wu Zhang, Grace Y. J. Chen, Biwei Zhu, Chou Chai, Qing-Hua Xu, Eng-King Tan, Qing Zhu, Kah-Leong Lim & Shao Q. Yao. *Nature Communications* 5, Article number: 3276, Published 13 February 2014

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