

ARYL HYDROCARBON RECEPTOR (AhR) AND ITS PHYSIOLOGICAL FUNCTIONS

To pursue research is often an endless journey that can lead to futile and demoralised feelings especially when success is nowhere in sight. Researchers facing this dilemma often require more than mere courage to continue to believe in their dreams, even if it is only a ray of hope.

That flicker of light has been the guiding principle of Professor Yoshiaki Fujii-Kuriyama, who had spent more than 20 years of his career to uncover the mystery of dioxin receptor as a physiological function. The affable scientist was here in Singapore to deliver the 9th Humphrey Oei Distinguished Lecture at the National Cancer Centre Singapore on 4 December, 2009.



He first began work on dioxin receptor by elucidating the primary structures of AhR and cytochrome P450, functional mechanism of AhR in induction of gene expressions by dioxin and other chemicals. In the course of his research, he learned about degradation of proteins and molecular mechanism on how AhR is responsible for the toxicological adverse effects caused by dioxin. These effects include teratogenesis, immunosuppression, tumour promotion, chlorance, hepatotoxicity and endocrine disruption.

While the AhR is used as a transcriptional regulator to dispel environmental contaminants, the AhR gene was found to be a vital source in the development of limbs and nervous systems in several vertebrate and invertebrate species such as *Caenorhabditis elegans* and *Drosophila*. The physiological functions of the AhR were also apparent in AhR-null mice that were found to have reduced fertility, smaller livers and portal fibrosis.

In furthering his research in this field, Prof Fujii hopes to make breakthroughs in how the AhR can be harnessed for tumour suppression in the colon and leverage on the anti-inflammatory effects of AhR in macrophage and T-cell functions.

Explaining how it works, Prof Fujii added: "The AhR is a ligand-activated regulatory factor and AhR ligands may be useful for chemo prevention against colon cancer and for anti-inflammation. It acts as a receptor for polycyclic aromatic hydrocarbons including dioxins and is activated by binding the ligand.

"The activated AhR acts as tumor suppressor in colon by ubiquitinating and degrading beta-catenin which causes cell proliferation, and also an anti-inflammatory factor by inhibiting the secretion of an inflammatory cytokine, IL-1beta in immune cells, such as macrophages."

As a Professor of Graduate School of Life Science of the Tohoku University, Prof Fujii chanced upon AhR functions in general while studying its molecular mechanism. He became interested in the regulatory mechanism of gene expression and saw how the expression of drug-metabolising cytochrome P450 gene was remarkably upregulated by administration of polycyclic aromatic hydrocarbons including TCDD (Dioxin) to animals. The upregulation of cytochrome P450 by TCDD was mediated by AhR.

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Prof Fujii addressing an audience of scientists, researchers and healthcare professionals.

SPECIAL PULL-OUT

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Having pioneered the study of AhR, Prof Fujii hinted that the field of research in Japan had never been more promising ever since the government began to rectify the lack of scientific research in Japan after World War II.

Citing his own experience, Prof Fujii confessed that he had to learn from the West by becoming a Research Associate with the Cell Biology Department at Rockefeller University. He was glad for the opportunity as he got to rub shoulders with Drs G Palade and Gunter Blobel, who were working on the cellular transport pathway of secretory proteins and later became Nobel Laureates.

According to statistics, while the US was devoting \$108.2 billion on R&D in the 80s, research funds in Japan was hard to come by as the nation had depended much on foreign research. It was only after Prof Fujii's return from the US that things changed.

The Tokyo government had then began to rectify the deficiency by starting a "originality" campaign in schools by funding research generously and moved away from supporting large-scale industrial technology and emphasised on life sciences. It led to a boom in research with more than 700,000 researchers embarking on various R&D projects.



Prof Sven Petterson, Principal Investigator, Division of Cellular and Molecular Research presenting a memento to Prof Fujii.

The efforts came to fruition when Japan was recognised as a world leader in fundamental scientific research, produced 13 Nobel laureates and accounted for 19% of the patent applications received in the US.

At age 71 and as one who has come so far, Prof Fujii has been getting ready to hand over the reins. He has been working closely with Prof Kaname Kawajiri of the Research Institute for Clinical Oncology, Saitama Cancer Center to bring the research to the next level.

Despite going into retirement recently, he is keeping his appointments as Adjunct Professor of Medical Research Institute, Tokyo and Dental University and Visiting Scientist of the Molecular and Cellular Biosciences Faculty at the University of Tokyo to continue to inspire promising scientists. His current work often takes him around Japan and overseas. For his excellent contribution to fundamental and clinical cancer research, he was bestowed the Princess Takamatsu Research Award in 2006.

What is taking up most of Prof Fujii's time these days are his leisure activities, pursuits that he will never trade for other things: sight-seeing, taking strolls, admiring works of art and traditional European architectures across Europe.

By Veronica Lee