令和 4 年 10 月 24 日 Oct. 24, 2021

大学院学生各位 To All Graduate Students

基盤医学特論 開講通知
Information on Special Lecture Tokuron AY2022

Title: **An Innovative Non-Hormonal, Pharmacological Strategy Targeting Metals to Down-Regulate Estrogen, Progesterone, Androgen, and Prolactin Receptors in Breast Cancer.**

Teaching Staff: **Des Richardson; Professor of Cancer Cell Biology, Bosch Institute Department of Pathology, University of Sydney, Sydney, Australia**

日時: 令和 4 年 11 月 7 日(月) **17:00-18:30**
Time and Date : **17:00-18:30, Nov 7th (Mon.), 2022**

場所: 医系研究棟3号館3階 共通会議室 310
Room: **Conference Room 310, Medical Science Research Building 3 (3F)**

Language: **English**

Abstract: Estrogen receptor-α (ER-α) is a key driver of breast cancer (BC) targeted by tamoxifen. However, tamoxifen resistance is a major problem. An important mechanism of resistance is the activation of EGFR/HER2/HER3 signaling and other hormone receptors (androgen receptor (AR), progesterone receptor (PR), prolactin receptor (PRL-R)) that intrinsically activate ER-α. Hence, therapeutics targeting multiple receptors, rather than ER-α alone, would be extremely useful and may overcome tamoxifen resistance.
This study examined the activity of redox-active di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT) and di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC), on the expression and activation of crucial hormone receptors, their co-factors, and key resistance pathways in ER-α-positive BC. Strikingly, DpC differentially regulated 106 estrogen-response genes with Sankey diagram analysis demonstrating this was linked to decreased mRNA levels of 4 central hormone receptors (*ER*, *PR*, *AR*, and *PRL-R*) involved in BC pathogenesis. Mechanistic dissection demonstrated that due to DpC and Dp44mT binding metal ions, these agents caused a striking decrease in ER-α, AR, PR, and PRL-R protein expression. Ablation of the metal-binding site in the thiosemicarbazone totally prevented its suppressive activity, demonstrating a unique non-hormonal mechanism. DpC and Dp44mT also inhibited EGFR, HER2, and HER3 activation, their downstream signaling, and the expression of co-factors that promote ER-α transcriptional activity, including SRC3, NF-κB p65, and SP1. *In vivo,* DpC was highly tolerable and effectively inhibited ER-α-positive BC growth.
In conclusion, through a bespoke non-hormonal mechanism targeting redox active metals, Dp44mT and DpC disrupt multiple key inter-receptor interactions between PR, AR, PRL-R, and tyrosine kinases that act with ER-α to promote BC, constituting an innovative therapeutic approach.

Information about the speaker:
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[注意] 事前連絡は不要です。Notice: No registration required.

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