CSCB Seminar Series

Title:

"Targeting tumor microenvironment in triple negative breast cancer."

Abstract:

Immune checkpoint inhibitors (CPIs), such as the anti-programmed death-1 (PD-1) antibody pembrolizumab, have shown great promise for cancer treatment; however, they are only effective in a fraction of patients. The tumor immune microenvironment (TIME) is a critical determinant of CPI response; therefore, combinatorial immunomodulatory strategies may offer a novel approach to increase CPI efficacy. We and others have demonstrated that nitric oxide synthase (NOS) inhibitors markedly recondition the TIME *in vivo* by depleting immunosuppressive myeloid-derived suppressor cells (MDSCs), enhancing CD8+ cytotoxic T-cell (CTL) infiltration, and shifting macrophage phenotype from M2 (immunosuppressive) to M1. NOS inhibitor-mediated alterations in the TIME were associated with potent antitumor activity in *in vivo* models of melanoma and triple negative breast cancer (TNBC). Furthermore, we have robust data showing that the NOS inhibitor NG-monomethyl-L-arginine (L-NMMA) improves pembrolizumab efficacy against triple negative breast cancer (TNBC) *in vivo*. Interleukin-12 (IL-12) has been shown to promote antitumor immunity by acting upon natural killer cells, CD8+ CTLs, and CD4+ T-helper cells and by inducing a phenotypic shift from MDSCs towards myeloid dendritic antigen-presenting cells. We also speculate that IL-12 may modulate the innate immune response by inducing NOS and PD-1 expression and therefore, may act synergistically with L-NMMA to counter TIME-mediated immune suppression to improve CPI efficacy. Our goals of this talk will be to address the hypothesis that combination strategies with TIME-targeting agents will improve CPI efficacy, and to address appropriate preclinical mouse models to test combinatorial immune-based approaches.

The proposed work will advance clinical practice by establishing TIME targeting as an effective strategy to unmask CPI efficacy against relapsed/refractory triple negative breast cancers and identifying factors that influence CPI response.

Date: **19 May 2017 (Friday)**

Time: **12:00 PM to 1:00 PM**

Venue: **Duke-NUS Medical School @ Amphitheatre Lvl 2**
8 College Road, S169857 (Opposite Singapore General Hospital, Block 6/7)

Speaker:



Jenny C Chang, MD
Emily Herrmann Chair in Cancer Research & Director, Cancer Center
Professor of Cancer, Institute for Academic Medicine
Full Member, Research Institute
Houston Methodist Cancer Center
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Biography: **Dr. Chang** is Professor at Weill Cornell Medical School, and Director of Houston Methodist Cancer Center, and also holds the Emily Herrman Chair in Cancer Research. She obtained her medical degree in Cambridge University, and fellowship training at the Royal Marsden Hospital/Institute of Cancer Research in the United Kingdom. She is internationally recognized thought leader in cancer research and clinical care. Through continuous support and funding by multiple organizations including the National Institutes of Health/National Cancer Institute (NIH/NCI), Department of Defense (DOD), and investigator-initiated pharmaceutical research awards, her group is recognized as the first to describe cancer stem cells and the role in resistance to therapy. Through NIH/NCI funding, her group described some of the critical drivers of cancer stem cells, and therapeutic efficacy of targeting these stem cells in preclinical models and clinical trials. Her recent work is focused on the clinical translation of these targets, and has obtained two large DOD grants using T cell immunotherapy (>$3 million) and nanoparticles (>$16 million) to conduct clinical trials with these new exciting molecules.

Host: **Associate Professor Sin Tiong ONG, MA, MRCP**
Programme in Cancer & Stem Cell Biology, Duke-NUS Medical School

No registration is required. For enquiries, please contact Lilian Poon at tel. 6601 3779