Dr. Warren J Leonard
Open Seminar Announcement

Date : Oct 27th 2017 Fri 2:30-4:00PM

Place : Shiran Kaikan Annex 2F Seminar Room

芝蘭会館別館［国際交流会館］

Organizers :

JBPA［日本バイオストレス研究振興アライアンス］

Biostress & Redox Research Network ［バイオストレス研究会］

Title：

“Fine tuning IL-2: superenhancers, STAT5 tetramerization, and partial agonists”

Invited Speaker：

Warren J Leonard M.D./Ph.D.

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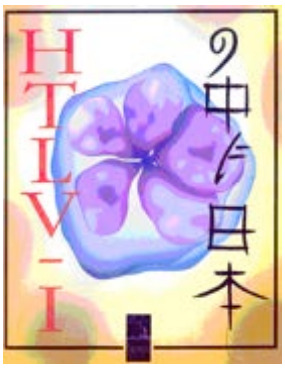

Abstract：

Fine tuning IL-2: superenhancers, STAT5 tetramerization, and partial agonists.

IL-2 is a pleiotropic cytokine that along with IL-4, IL-7, IL-9, IL-15, and IL-21 shares the common cytokine receptor γ chain, γ_c, which is mutated in humans with X-linked severe combined immunodeficiency. Discovered as a T cell growth factor, IL-2 also serves critical other roles, for example in augmenting NK cytolytic activity, promoting activation-induced cell death, in Treg biology, and for T helper differentiation. IL-2 substantially signals via the JAK-STAT pathway, activating primarily STAT5. We have discovered that STAT5 tetramerization versus dimerization is a mechanism by which IL-2 signaling is fine-tuned, and that STAT5 tetramerization is critical for normal proliferation of $CD8^+$ T cells and the maturation and survival of NK cells, with critical regulation of genes involved in cell cycle progression and survival. Moreover, we have discovered that the gene encoding a component of the IL-2 receptor, IL-2Rα, contains the most highly ranked STAT5-dependent superenhancer. We have functionally dissected this superenhancer and elucidated properties of STAT5 in the regulation of highly inducible genes. Furthermore, with Chris Garcia's lab at Stanford, we have created and studied novel IL-2 partial agonists that attenuate IL-2Rβ-γ_c dimerization and thus inhibit STAT5 activation and IL-2-dependent gene expression. Such inhibition prolongs survival in a mouse model of graft-versus-host disease and can block proliferation of IL-2-dependent human adult T cell leukemia cells. Thus, we have identified physiological and pharmacological modes of fine-tuning IL-2 and STAT5 signaling, with therapeutic implications.

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