Date: Thursday, January 15, 2015
Time: 10:00 – 11:00
Venue: Seminar Room C209, Center Bldg, Level C
Speaker: **Professor Takashi Yonetani**
Affiliation: **University of Pennsylvania,**
Department of Biochemistry and Biophysics

Title: How Does Hemoglobin Regulate its O_2-Affinity and Cooperativity?

Abstract:

Human hemoglobin (Hb) is an efficient O_2-transporter in the blood. This red tetramer hemoproteins binds four O_2/tetramer at an arterial O_2-pressure of 100 Torr (in the lung) and releases them at a venous O_2-pressure of <40 Torr (in the capillary) at 37°C, in order to deliver O_2 to the tissues, by reversibly changing its O_2-affinity depending on the O_2-pressure of the environment (the cooperativity). The current widely-accepted hypothesis of the mechanism of the cooperativity of Hb was proposed by Perutz [1], that was based upon the stereochemical molecular structures of deoxy- and oxy-Hb, which he had determined by X-ray crystallography. Deoxy-Hb has a more rigid tetramer structures (the T-quaternary structure), which constrains the coordination structure of the heme group, leading to a low O_2-affinity state. As four O_2 bind successively to Hb, its structure changes to a less rigid R-quaternary state, in which all the structural constraints are removed, resulted in the unconstrained coordination structure of the heme groups with a high O_2-affinity.

However, we found that the O_2-affinity of either deoxy- or oxy-Hb can be reduced as much as $>10^3$-folds by heterotropic effectors such as 2,3-BPG, IHP, and BZF without detectable changes in the T-/R-quaternary/tertiary structure as well as the coordination structures of the heme group [2-4]. Thus, we were not able to find the casual correlation between T-/R-quaternary structures and the low/high O_2-affinities, as proposed by Perutz [1].

In Hb, the apparent O_2-affinity is controlled by regulating the physical barrier of globin against the migration of O_2 through protein matrix from the "caged" state to solvent [5-7]. The physical barrier is lowered by the heterotropic effector-linked, high-frequency thermal fluctuations [8], which make the protein barrier more and more transparent to small ligands like O_2. Thus, the apparent O_2-affinity of Hb is controlled by protein-structural dynamics rather than the static T-/R-quaternary/tertiary structural changes of Hb [4].

References: [1] Perutz, M.F., *Nature 228* (1970) 726; [2] Yonetani, T. *et al., JBC 277* (2002) 34508; [3] Yonetani, T. & Laberge, M., *BBA 1784* (2008) 1146; [4] Yonetani, T. & Kanaori, K., *BBA 1834* (2013) 1837; [5] Iizuka, T. *et al., BBA 351* (1974) 182; [6] Iizuka, T. *et al*., *BBA* 371 (1974) 126; [7] Yonetani, T. *et al*., *JBC 249* (1974) 2168; [8] Laberge, M. & Yonetani, T., *Biophys. J. 94* (2008) 2737