Geminin, a molecular switch turning on and off quiescence or blood cell production in hematopoietic stem cells

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- **Date: May 13th (WED) from 17:30**

//Attention//
Please notice that
we've changed the room.

- **Place: Lecture room 4,**

  Medical Education & Library Building 4F.

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- 日時：平成２７年５月１３日（水）１７：３０.
- 場所：医学教育図書棟４階 第４講義室

- **Inviter: Prof. Seiji Okada (AIDS Research Ⅲ)**
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Abstract

Hematopoietic stem cell (HSC) transplantation therapy has provided an epochal clinical outcome. Currently three kinds of different cellular sources, bone marrow cells, peripheral blood stem cells and umbilical cord blood, are available for the transplantation. A technology for expanding HSCs *ex vivo* could not only advance HSC transplantation therapy but may pave the way to further application of HSCs for advanced immunotherapy and gene therapy. There developed has, however, been no practically available technology for the expansion. Since hematopoietic cytokines and niche molecules have been shown not to be enough for the expansion, we have focused on the cell intrinsic factors. By utilizing a biochemical as well as genetic approaches, we previously demonstrated that Polycomb-group complex 1 and Hoxb4/Hoxa9 regulate HSCs through the ubiquitin proteasome system-mediated direct regulation of Geminin protein, and shRNA-mediated knockdown of Geminin and visualization of Geminin in Geminin-EYFP knock-in mice further supported our hypothesis that Geminin acts as a key regulator for determining cell fate of HSCs, *i.e.*, cellular quiescence, self-renewal and differentiation. Geminin negatively regulates DNA replication and chromatin remodeling through the direct interaction with Cdt1 and Brahma/Brg1, respectively. We then generated a recombinant Geminin protein fused with a membrane translocating motif (MTM) of FGF4, which was designated as cell-penetrating (CP-) Geminin. We have demonstrated that amount as well as timing of Geminin expression in NIH 3T3 cells was altered by direct transduction of a CP-Geminin protein. Biologically, CP-Geminin transduction controlled the cell cycle in NIH 3T3 cells, *i.e.*, CP-Geminin efficiently suppressed G_0/G_1 to S-phase transition to keep cellular quiescence. We currently aim at regulating activity as well as expression of Geminin to perform detailed verification of our hypothesis described above and further to generate a new strategy for manipulating the HSC activity.