25th IRCMS Seminar

Date: **June 9, 2017 (Friday)**

Time: 16:00 - 17:00

Venue: 2F Seminar Room,
Center for AIDS Research (CAIDS)

Speaker: **Eishu Hirata, M.D. Ph.D.**

Senior Assistant Professor
Department of Oncologic Pathology,
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Title: **Imaging 'Failure'**
How BRAF inhibition generates drug tolerant microenvironments

Abstract:

Intravital imaging of BRAF-mutant melanoma cells containing an ERK/MAPK biosensor reveals how the tumor microenvironment affects response to BRAF inhibition by PLX4720. Initially, melanoma cells respond to PLX4720, but rapid reactivation of ERK/MAPK is observed in areas of high stromal density. This is linked to ''paradoxical'' activation of melanoma-associated fibroblasts by PLX4720 and the promotion of matrix production and remodeling leading to elevated integrin β1/FAK/Src signaling in melanoma cells. Fibronectin-rich matrices with 3–12 kPa elastic modulus are sufficient to provide PLX4720 tolerance. Co-inhibition of BRAF and FAK abolished ERK reactivation and led to more effective control of BRAF-mutant melanoma. We propose that paradoxically activated MAFs provide a ''safe haven'' for melanoma cells to tolerate BRAF inhibition.

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