Cancer Science Institute of Singapore

SEMINAR ANNOUNCEMENT

Samuel Sidi

Assistant Professor of Medicine and Oncological Sciences
Icahn School of Medicine at Mount Sinai



Zebrafish Chemical-Genetic Screen Identifies IRAK1 Kinase as a Therapeutic Target in Radio-Resistant Cancer

Date: Monday, 3 Oct 2016
Time: 4pm – 5pm
Venue: #01-01A, Level 1, CeTM (14 Medical Drive, Singapore 117599)
Host: Dr Takaomi Sanda

Abstract:

One in two cancer patients receive radiation therapy (RT), of which tens of thousands resist treatment annually. Tumor resistance to RT (R-RT) commonly arises from mutation of TP53, which impairs the induction of proapoptotic genes after DNA damage. Platinums and other genotoxins currently used as radiosensitizing agents fail to eradicate the cancer in many instances, and also cause toxicity to normal tissues outside the irradiated area. We screened for small molecules that suppress R-RT in p53 mutant zebrafish embryos while having no effect on non-irradiated wild-type siblings. This screen identified the benzimidazole anthelmintic, oxfendazole (OXF). Surprisingly, in vivo SAR of OXF analogs dismissed tubulin as the target underlying OXF's radiosensitizing properties. To the contrary, the data implicate tubulin as an anti-target whose inhibition by nocodazole and other OXF analogs, but relative lack thereof by OXF, explains OXF's unique lack of toxicity among benzimidazoles. Through combinations of computational target prediction, enzymatic assays, and chemical genetic validation in vivo, we identify the interleukin receptor-associated kinase, IRAK1, as an off-target of OXF whose inhibition is responsible for overcoming R-RT in p53 mutant fish. We tie the radiosensitizing effect to inhibition of an IRAK1-dependent survival pathway that involves IRAK4 and TRAF6 but is otherwise distinct from TLR/IL-1R immune signaling. Finally, IRAK1 inhibitors selectively suppress R-RT in TP53 mutant head-and-neck, breast, rectal, medulloblastoma and glioblastoma cell lines. The data identify a novel, IRAK1-dependent DNA damage response pathway as a key mediator of tumor R-RT, thus defining a viable targeted strategy for radio-resistant cancer.

Biography:

Samuel Sidi is an Assistant Professor of Medicine and Oncological Sciences at the Icahn School of Medicine at Mount Sinai, NYC. Originally from Paris, France, Dr Sidi completed his graduate studies at the Max-Planck Institute in Tubingen and the Ecole Normale Superieure (Paris VI University), graduating in 2004. His Ph.D. thesis focused on a large-scale screen for mutations affecting balance in zebrafish, which identified ion channels essential for hair cell function (Science 2003; J. Neurosci 2004). Dr. Sidi conducted his postdoctoral studies with A. Thomas Look at the Dana-Farber Cancer Institute, Harvard Medical School, where he developed zebrafish screening platforms for drug and target discovery in radio-resistant cancer. In a series of genetic and small-molecule screens performed on a p53 mutant background, Dr. Sidi's lab identified several targets whose inhibition restores sensitivity to RT in mutant embryos without adverse effects on zebrafish development (Cell 2008; Liu et al., in revision). Inhibitors of the majority of these enzymes validate in mammalian models of radio-resistant cancer including TP53 mutant HNSCC, GBM and medulloblastoma. Dr Sidi's current research focuses on the mechanisms by which these novel radiosensitizers bypass p53 deficiency. Several pathways define new signaling branches in the DNA damage response, including the apoptotic PIDDosome pathway triggered by Chk1 inhibitors (Mol Cell 2012; Mol Cell 2015). Dr. Sidi's prior honors and awards include PhD scholarships from the Max-Planck Gesellshaft, ARC and FRM, and cancer research grants from NIH/NCI, the Claudia Adams Barr Foundation, JJR Foundation, and the prestigious Pershing Square Sohn Alliance and Searle Scholars Program.