CENTER *for* APPLIED MOLECULAR MEDICINE

University of Southern California Physical Sciences in Oncology Center

Monthly Seminar Series

DEAN FELSHER M.D., PH.D.

Professor of Medicine-Oncology, Pathology and Molecular Imaging, Department of Medicine, Stanford University

"Modeling and Predicting Oncogene Addiction"

FRIDAY, APRIL 26, 2013

NOON - 1:00 P.M.

Q & A to follow

(Pizza and beverages will be served for attendees at 11:45 a.m.)

HARKNESS AUDITORIUM

HSC - Clinical Sciences Building, **2nd Floor**
2250 Alcazar Street, Los Angeles, CA

ABSTRACT:

Cancers are largely caused by the activation of oncogenes. We have developed an experimental system to model and predict the therapeutic efficacy of targeted therapy of oncogenes. Using the Tet system, we can conditionally regulate oncogene expression in vivo in a temporally controlled and tissue specific manner. We have shown that many oncogenes (MYC, RAS, BCR-ABL) induce tumorigenesis that is completely reversible upon their inactivation. We have described this phenomena as oncogene addiction. Oncogene addiction is associated with proliferative arrest, apoptosis, differentiation, cellular senescence and the shutdown of angiogenesis. The specific consequences of oncogene inactivation depend both on the genetic and cellular context. In some cases, even brief inactivation of an oncogene can result in sustained tumor regression. In other cases, oncogene inactivation is associated with tumor dormancy. Tumor cell intrinsic and host-dependent cell autonomous mechanisms are involved. Tumor cell intrinsic mechanisms appear to involve mechanisms that are dependent upon DNA repair processes, the regulation of protein synthesis and of cellular metabolism. Host-dependent mechanisms include the regulation of angiogenesis and immune cell elimination. In addition, tumor cells secrete autocrine factors critical to oncogene addiction. We have uncovered that oncogene addiction is not cell autonomous and requires an intact host immune system. Specifically, CD4+ T-cells are required for MYC or BCR-ABL inactivation to induce sustained tumor regression. We have found that in the absence of an immune system, oncogene inactivation failed to both induce cellular senescence in tumor cells as well as to shut down angiogenesis in the host. Finally, our experimental model system can be used to model Oncogene Addiction. We have shown that we can use simple mathematical model to predict the therapeutic consequences of oncogene inactivation.

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