SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by the Institute of Molecular and Cell Biology:

Date: **Tuesday, 29 March 2022**
Time: **2.00PM – 3.00PM**

Join Zoom Meeting
https://zoom.us/j/95439810643?pwd=S3JFN0N5SHhteHhxQkZIdlFzNHZ1UT09

Meeting ID: 954 3981 0643
Passcode: 421695

A novel kinase inhibitor for β-catenin mutant hepatocellular carcinoma

Abstract

Currently there are few personalized therapeutic approaches for advanced hepatocellular carcinoma (HCC), which is a leading cause of cancer-related deaths worldwide. β-catenin (*CTNNB1)*-mutated HCC represents 30% of the disease and is a subset of Wnt-driven tumors particularly unresponsive to current therapies. Using focused chemical libraries derived from clinical multi-kinase inhibitor scaffolds, we screened HCC organoids to identify a *CTNNB1*-mutant selective small molecule that we dub WNTinib. WNTinib retained exquisite selectivity in human and murine models expressing oncogenic β-catenin (encoded by *CTNNB1*), including patient samples. Expansive multiomic and target engagement analyses, combined with rescue experiments and *in vitro* and *in vivo* efficacy studies, revealed that WNTinib inhibits KIT/MAPK signaling at multiple nodes. Moreover, we demonstrate that lack of direct engagement on BRAF and p38a/b kinases differentiates WNTinib from existing clinical kinase inhibitors, is necessary to avoid compensatory feedback signaling, and thereby provides a durable and selective transcriptional block of mutant β-catenin and Wnt targets through re-activation of cytoplasmic enhancer of zest homolog 2 (*EZH2)*. Finally, we demonstrate that the unique mechanism of WNTinib provides superior activity compared to clinical therapies *in vivo*, including in drug-resistant models of mutant β-catenin HCC. Our studies identify a novel inhibitor of the Wnt pathway and uncover a previously unknown mechanism to harness the KIT/MAPK/EZH2 pathway to potently and selectively antagonize β-catenin mutant HCC with an unprecedented wide therapeutic index.

Biography

Prof Ernesto Guccione
Professor of Oncological Sciences

Associate Director Mount Sinai
Center for Therapeutics Discovery

Director Bioinformatics for Next
Generation Sequencing (BiNGS)
Shared Research Resource

Icahn School of Medicine at
Mount Sinai
Hess Center for Science and
Medicine

Prof Ernesto Guccione is a full Professor at Mount Sinai and has a long-standing interest in understanding basic mechanisms of transcriptional and post-transcriptional regulation in order to identify therapeutic opportunities in oncology. In the past 15 years he has established himself as a leader in the field of Arginine Methylation and Cancer Epigenomics and Transcriptomics.

In particular he has focused his research on dissecting the role of oncogenic Protein Methyltransferases (PMTs), such as Protein Arginine Methyltransferases (i.e. PRMT6 and PRMT5), SET domain containing proteins (i.e. EZH2, G9a) and PRDMs (i.e. PRDM9, PRDM10 and PRDM15). As an example, he has characterized the function of PRMT5, a key enzyme playing a role in transcriptional and post-transcriptional modulation. PRMT5 is essential in regulating early embryogenesis and neural stem cell homeostasis and in cooperating with MYC to ensure that the levels of the core pre-mRNA splicing machinery are sufficiently elevated to fuel lymphomagenesis.

As an independent investigator, in the past 13 years his lab has collaborated with multiple Pharma companies to advance the knowledge of PRMT5 biology and helping their compounds progress to clinical trials, and I have been the lead PI and coordinator on multiple grants, including large collaborative efforts. Prof Guccione has expertise in biochemistry, molecular and computational biology, and preclinical oncological studies using mouse models of cancer (DLBCL, AML, HCC and CRC) and tumor organoids (HCC and CRC). He is additionally leading the Bioinformatics for Next Generation Sequencing (BiNGS) Shared Resource Facility to provide NGS computational analysis for TCI-affiliated faculty members.

ALL ARE WELCOME *(No registration required)*

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Thank you.