

**A Phase I dose escalation and expansion clinical trial of the novel first-in-class Polo-like Kinase 4 (PLK4) inhibitor, CFI-400945 in patients with advanced solid tumors**

**Grant Award Details**

A Phase I dose escalation and expansion clinical trial of the novel first-in-class Polo-like Kinase 4 (PLK4) inhibitor, CFI-400945 in patients with advanced solid tumors

**Grant Type:** Disease Team Therapy Development III

**Grant Number:** DR3-07067

**Project Objective:** Phase 1 clinical trial to determine safety and appropriate dose level of CFI 945 PLK4 inhibitor in patients with advanced solid tumors.

**Investigator:**

<b>Name:</b>	Dennis Slamon
<b>Institution:</b>	University of California, Los Angeles
<b>Type:</b>	PI

<b>Name:</b>	Zev Wainberg
<b>Institution:</b>	University of California, Los Angeles
<b>Type:</b>	Co-PI

**Disease Focus:** Cancer, Solid Tumors

**Human Stem Cell Use:** Cancer Stem Cell

**Award Value:** \$5,683,693

**Status:** Active

**Progress Reports**

<b>Reporting Period:</b>	Year 1
<b>View Report</b>	

<b>Reporting Period:</b>	Year 2
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## View Report

**Reporting Period:** Operational Milestone #1

## View Report

**Reporting Period:** Operational Milestone #2

## View Report

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## Grant Application Details

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**Application Title:** A Phase I dose escalation and expansion clinical trial in patients with advanced solid tumors

**Public Abstract:** Cancer is a major cause of morbidity and mortality worldwide. Many believe that progress in drug development has not been as rapid as one would have predicted based on the significant technological advancements that have led to improved molecular understanding of this disease. There are numerous explanations for the lag in clinical success with new therapeutics. However, work in the past decade has provided support for what has become known as the cancer stem cell hypothesis. This model suggests that there is a class of cells that are the main drivers of tumor growth that are resistant to standard treatments. In one model the cancer stem cells inhabit an anatomical "niche" that prevents drug efficacy. Another view is one in which tumors can achieve resistance by cell fate decisions in which some tumor cells are killed by therapeutics, while other cells avoid this fate by choosing to become cancer stem cells. These stem cells are thought to be capable of both cancer stem cell renewal and repopulation of the tumor.

Our proposal aims to conduct a Phase I clinical trial of a first-in-class mitotic inhibitor. The target is a serine/threonine kinase that was originally selected because blocking this target affects both tumor cell lines and tumor initiating cells (TICs). Our data suggest that the target kinase functions at the intersection of mitotic regulation, DNA damage and repair, and cell fate decisions associated with stem cell renewal. Preclinical work has begun to segregate "sensitive" and "resistant" groups of tumor cell lines and TICs after treatment with the drug candidate as a single agent and in combination with standard-of-care therapeutics. Our data also support the model in which cancer stem cell resistance is likely to arise, at least in some cases, due to stem cell fate decisions that happen in response to therapeutic intervention.

This grant is a natural progression of work partially funded by CIRM that enabled the isolation of Tumor Initiating Cells (TICs) from tumors in different tissue types. This facilitated the development and assessment of drug candidates that target both bulk tumor cells and TICs and has now led to the development of a potential anti-cancer drug which we are now preparing to test in humans. The goal of the Phase I trial is to determine the maximum tolerated dose, the recommended Phase II dose, and any dose-limiting toxicities. We will also characterize safety, pharmacokinetic, and pharmacodynamic profiles along with any antitumor activity. Once the maximum tolerated dose has been identified, a biomarker expansion cohort will be opened in order to determine whether appropriately selected biomarkers are associated with a predictable patient response. This will allow a rational approach to study single agent and combination studies that perturb this network and allow us the opportunity to facilitate a targeted clinical development plan.

**Statement of Benefit to California:**

It has been estimated, by the California Department of Public Health, that in 2013 about 145,000 Californians will be diagnosed with cancer and more than 55,000 of these will ultimately succumb to their disease. Furthermore, more than 1.3 million Californians are living today with a history of cancer. Therefore, innovative research programs that are able to impact this devastating disease burden are likely to have a large potential benefit to the state of California and its residents.

This grant application proposes a Phase I clinical trial for a first-in-class inhibitor of a target that has never been tested in patients. The aim of this trial is to determine the maximum tolerated dose in humans, the recommended dose for phase II trials, and evaluate any dose-limiting toxicities. The trial will also characterize safety, pharmacokinetics, and pharmacodynamic properties. It will also provide early insight into any antitumor activity.

Our group has developed a comprehensive unbiased platform that facilitates the segregation of sensitive and resistant populations of cancer based on their molecular subtypes. This capability has the promise to improve the success rate and reduce the cost of oncology clinical trials by focusing on the subsets that are most likely to benefit while avoiding unnecessarily treating patients that would otherwise benefit from alternative treatments. Our preliminary pre-clinical work, funded by CIRM in the context of a Disease Team I award, suggests that this approach can be successfully applied to the networks associated with mitotic regulation, DNA repair, and stem-cell fate decisions. Our ongoing research has tested a number of chemical compounds that are able to block pathways that are critical to the growth and proliferation of many cancer models. These compounds have all been tested in multiple in vitro and in vivo systems and have been found to inhibit the ability of the cancer stem cell to repopulate. Now that our pre-clinical enabling studies have been completed, we have submitted an Investigational New Drug (IND) application to the FDA for a first-in-human phase I clinical trial. In the current proposal, we will be able to test our hypotheses in a clinical setting, which if successful will lead to confirmation of safety and the establishment of the appropriate dose with which to test in later stage trials. This trial will set the stage for a new class of agents that has not yet been tested in clinical settings. We believe that the proposal described herein has the promise to expand the reach of targeted therapies into mechanisms that in most cases have been resistant to innovation. Finally, it is reasonable to expect that our preclinical work and the proposed clinical trials will validate a number of potential biomarkers that will identify susceptible patient subpopulations.

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