Oncoceutics, Inc.

Annual Progress Report: 2011 Nonformula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Nonformula Grant Overview

Oncoceutics, Inc. received $1,295,646 in nonformula funds for the grant award period June 1, 2012 through May 31, 2014. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Development and Commercialization of Novel Cancer Therapeutic TIC10 – The overall purpose of the proposed research studies is to enable and complete phase I/II clinical trials with the novel antitumor agent TIC10 to improve treatment options and outcomes for cancer patients in Pennsylvania. While we have obtained a vast and comprehensive body of evidence regarding the preclinical efficacy, mechanism, and toxicity of TIC10, there are critical components of the Investigational New Drug (IND) application that must be completed prior to human studies. Completion of such studies will allow for IND and IRB clinical protocol approval, thereby potentiating a phase I/II clinical trial at Penn State Hershey Medical Center. This clinical study will determine the toxicity and pharmacokinetic profile of TIC10 in humans to directly assess the viability of TIC10 as novel treatment for human cancer.

Duration of Project

6/1/2012 – 5/31/2014

Project Overview

The goal of this research proposal is to enable and conduct a phase I/II clinical trial with the promising new small molecule TIC10 as a new and potent treatment for therapy-resistant cancer. The objectives of this research proposal are to (i) complete remaining preclinical and administrative components of the Investigational New Drug (IND) application, (ii) obtain IND and IRB clinical protocol approval, and (iii) conduct a phase I/II trial with TIC10 to determine its safety, optimal dose, pharmacokinetics (PK), and efficacy in humans. To enable and complete a first-in-man phase I/II clinical trial with TIC10 as a novel antitumor agent, we aim to:

1. Complete remaining preclinical components of IND application.
    - A. Development of correlative assays for the clinical protocol.
    - B. Define the PK profile of TIC10 in mice.
    - C. CMC and GMP-compliant synthesis of TIC10.

D. Complete IND-enabling animal toxicity studies.

2. Conduct phase I/II clinical trial with TIC10.
   A. Development and submission of IRB clinical protocol and IND application.
   B. Enroll and conduct phase I/II clinical trial.
   C. Conduct pharmacokinetic and pharmacodynamic assays on TIC10 in humans.
   D. Interpretation of results to support further development and commercialization of TIC10.

Methods: Aim 1A-B will develop assays for markers of response to TIC10 based on its mechanism and for serum detection of TIC10 for pharmacokinetic profiling. Aim 1C will secure a GMP-compliant source of TIC10 for GLP toxicity studies and the phase I/II clinical trial. For Aim 1D, GLP-compliant toxicology studies will be conducted in rats and beagle dogs along with brain tumor efficacy/toxicity studies in dogs. Aim 2A will submit applications for IND and IRB clinical protocol for the phase I/II study in Aim 2B. Aims 2C-D will execute and interpret assays to define molecular marker of response/resistance, the PK/toxicity profile, any preliminary signs of tumor response, and cumulatively guide the future development of TIC10 in terms of future clinical trial design and strengths/limitations. A multi-faceted fund-raising approach and partnering will be implemented for commercialization of TIC10 in the world market.

Principal Investigator

Lee Schalop, MD
Chief Financial Officer, Secretary and Treasurer
Oncoceutics, Inc.
1214 Research Blvd.
Hummelstown, PA 17037

Other Participating Researchers

Bimalendu Dasmahapatra, PhD; Wolfgang Oster, MD, PhD – employed by Oncoceutics, Inc.
Wafik S. El-Deiry, MD, PhD; Joshua E. Allen; Michael Glantz, MD; Zhaohai Yang, MD, PhD; Jiangang Liao, PhD; Thomas O'Leary, PhD – employed by The Pennsylvania State University
Dorothy C. Brown, DVM, MSCE; Erika Krick, VMD, DACVIM; Michael DiGregorio, CVT – employed by the University of Pennsylvania
Gary Olson, PhD – employed by Provid Pharmaceuticals, Inc.

Expected Research Outcomes and Benefits

The expected benefit from this research project is to gain a new cancer therapy, TIC10, for the treatment of therapy-resistant malignancies including triple-negative breast cancer, non-small cell lung cancer, and brain tumors. Brain tumors are an urgent priority in clinical oncology as survival time is generally 6 months and the standard of care treatments offer little improvement in outcome. Importantly, TIC10 doubles the survival of mice with brain tumors and triples the survival when combined with bevacizumab, which is used for the treatment of brain tumors as

well as metastatic colorectal cancer. In lung cancer, TIC10 also synergizes with paclitaxel and docetaxel to yield cures. Lung cancer is the leading cause of cancer-related death in the US with tobacco use by far being the major culprit. The malignancies targeted in this study are considered unmet clinical needs and patients harboring such disease are left with few, if any, treatment options. Chemotherapy remains the predominant class of cancer medicines but causes dose-limiting toxicity due to its effects on normal cells. Several targeted anticancer agents have been approved over the past two decades such as bevacizumab, cetuximab, sorafenib, etc. These agents have possessed generally favorable toxicity profiles but clearly more treatment options are necessary as they do not offer cures and many are biological agents that are very expensive to produce. TIC10 is an inexpensive small molecule that possesses therapeutically desirable properties such as oral activity, thermal stability, temporally sustained activity, ability to cross the blood-brain barrier, and safety. TIC10 is expected to provide cancer patients an inexpensive and practical targeted antitumor agent in clinical settings where other available therapies are ineffective. As a result, TIC10 is expected to improve the quality of life, decrease disease progression, and help alleviate practical issues that burden cancer patients.

In addition to the direct patient benefits, the proposed studies will provide critical academic benefits such as preliminary validations of efficacy, toxicity, and pharmacokinetic profiles in humans. While these profiles appear favorable in mice, they may be altered in human patients and the proposed phase I/II trial will identify any potential limitations or strengths of TIC10 as an anticancer agent for humans. Correlative assays will be conducted in trials to validate the mechanism of TIC10 and will directly assess the viability of this therapeutic mechanism as a new class of therapeutics in cancer management. If the novel mechanism of TIC10 is conserved in humans, it will pave the way for generating other therapeutics within its class. The toxicity and pharmacokinetic profiles will be particularly important for TIC10 as any limitations in these properties may be overcome by derivatives of the molecule in future development.

Outside of health-related benefits, the majority of these funds will go to Pennsylvania institutions and will serve to support and create jobs within the state. The construction of this proposal has been an efficient collaborative effort between Oncoceutics and the indicated subcontractors. The execution of this proposal will continue to foster collaboration between these Pennsylvania (PA)-based institutions that include Oncoceutics, Penn State Hershey Medical Center, and the University of Pennsylvania. The timeline, allocation of responsibilities, and communication routes have already been planned and are summarized in section VI. In summary, this research project is expected to translate the novel anticancer treatment TIC10 as a new practical and unparalleled treatment option for cancer, inform on its strengths and limitations in humans, enable the commercialization of TIC10, improve the health status and outcomes of cancer patients in PA, create and support jobs in PA, and foster collaborations among small business and academic institutions in PA.

Summary of Research Completed

1. Complete remaining preclinical components of IND application.
   A. Development of correlative assays for the clinical protocol.
   Completed in first reporting period.

B. Define the PK profile of TIC10 in mice.
Completed in first reporting period.

C. CMC and GMP-compliant synthesis of TIC10.
Optimization of the synthesis of a novel salt of TIC10 (ONC201) was performed in the first reporting period. The clinical batch of GMP material for use in human trial has been produced. A suitable oral formulation of TIC10 has been identified for use in human trials. Table 1 shows the stability results for up to 6 months storage under accelerated conditions. The available results show little to no change in assay, impurities or appearance. The only change that occurred under the accelerated conditions (40°C/75%RH) was a slight increase in moisture content, from 1.2% at time 0, to 6.5% at 2 months, and to 6.2% at 3 months. The moisture content plateaued at approximately the monohydrate. The increase in moisture content did not result in increased impurity levels or decreased potency. These results suggest robust stability of the drug substance when stored at room temperature and accelerated conditions.

D. Complete IND-enabling animal toxicity studies.

Non-GLP Safety Studies
Initially intravenous administration with 30-minute infusion was the intended route of administration for the first-in-man trial. However, superior tolerance was observed with extended infusion time in rats and dogs. Thus, oral dosing was utilized in the GLP safety studies and will be used in human studies. Preclinical pharmacology study results support equivalent efficacy with oral or parenteral administration of TIC10.

GLP Safety Studies

In GLP safety studies in rats and dogs with TIC10, there were no deaths or dose limiting toxicities. In general, adverse events associated with exaggerated doses of TIC10 were mild and reversible. The only findings that were observed in both rats and dogs were decreased activity, decreased food consumption (weight loss only seen in rats), and salivation. The no observed adverse effect level (NOAEL) following oral administration of TIC10 at single doses of 12.5, 125 or 225 mg/kg to Sprague-Dawley rats is considered to be 125 mg/kg. No TIC10 related changes were noted during the functional observational battery (CNS activity) performed on Day 1 between 1 and 2 hr post-dose with the exception of one 225 mg/kg female noted as having decreased activity. The NOAEL following oral administration of TIC10 at single doses of 4.2, 42 or 120 mg/kg to Beagle dogs is considered to be at least 42 mg/kg.

The starting dose in the phase I trial was selected as 125 mg based on allometric scaling and rounding the lowest NOAEL from the GLP toxicology studies (Table 2). Allometric scaling was used in these calculations, which held true when scaling between rats and dogs in GLP toxicology studies. This dose was calculated as 1/10th of the rat NOAEL (rat 125 mg/kg and dog 42 mg/kg translates into a starting dose of 123 mg or 138 mg for a patient with a body weight of 60 kg, respectively).

2. Conduct phase I/II clinical trial with TIC10.

A. Development and submission of IRB clinical protocol and IND application.

The IND application for TIC10 to treat advanced human cancer was drafted by Oncoceutics. The IND includes a phase I/II protocol designed to evaluate the safety and preliminary efficacy profile of TIC10 in patients with advanced glioblastoma multiforme, triple-negative breast cancer, non-small cell lung cancer, and colorectal cancer. The IND was filed with the FDA on January 30, 2014 and was accepted by the FDA on February 28, 2014.

The clinical protocol for the first-in-man phase I/II clinical trial with TIC10 was slightly modified in response to FDA review. The clinical protocol accepted by the FDA has been submitted for regulatory review at Massachusetts General Hospital (MGH). The informed consent forms and laboratory manual have been created for this trial. The protocol received conditional approval from the Scientific Review Board at MGH and is under review by the IRB.

B. Enroll and conduct phase I/II clinical trial.

The phase I/II trial protocol is pending IRB approval at MGH.

C. Conduct pharmacokinetic and pharmacodynamic assays on TIC10 in humans.

Pharmacokinetics

An LC-MS-MS assay for the detection of TIC10 in plasma has been optimized and validated in animal studies. According to the first-in-man trial study design accepted by the FDA, 2 tubes of 5 mL of blood will be obtained at baseline, at 30 minutes (± 15 minutes), 2 hours (± 30 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), 24 hours (± 1 hour), 2 days (± 3 hours), and 7 days (± 1 day) following the first dose of TIC10 in the first-in-man trial. If after the first cohort of 3 patients these time-points require adjustment the protocol will be amended to sample at more optimal time points. Pre-dose samples will also be drawn for PK. For the second dose of TIC10, pre-dose blood samples will be drawn as a trough of the first dose.

Addition pharmacokinetic data was obtained in Sprague-Dawley rats and beagle doses. In rats, exposure to TIC10 was dose-dependent and approximately dose-proportional. Exposure to TIC10 was slightly greater in female rats after a single oral gavage dose. Plasma T1/2,e ranged from 2.3 to 8.4 hours and clearance ranged from 7.5 to 23.5 L/hr/kg. Volume of distribution ranged from ~49 to ~103 L. Exposure to TIC10 in dogs was dose-dependent and increased with greater TIC10 dose levels. Exposure to TIC10 was similar in male and female dogs with the observation that all mean male Cmax and AUC values were slightly greater than those corresponding female values. Elimination of TIC10 from plasma was similar between the mid and high dose levels; mean T1/2,e ranged from 4.6 to 7.8 hours. Mean T1/2,e following the low dose of 4.2 mg/kg was ~1 hour, which is likely underestimated due to several samples being BQL. Overall elimination of TIC10 was greater following the low dose.

Pharmacodynamics
In addition to pharmacokinetics, the first-in-man study will preserve samples to conduct correlative assays to measure biomarkers of therapeutic response to TIC10 including molecular markers involved in the mechanism of action of TIC10. Soluble TRAIL levels in the serum of treated patients will be performed in addition to immunohistochemistry on solid tumor specimens obtained following treatment when available. IHC analysis will assay for molecules involved in the mechanism of TIC10.

D. Interpretation of results to support further development and commercialization of TIC10.
The safety, efficacy, and mechanistic data available for TIC10 enable a number of development options. Several tumors that are highly responsive to TIC10 in preclinical models are viewed as unmet medical need indications and would qualify for expedited development programs, including glioblastoma multiforme, triple negative breast cancer, and others.

Table 1. Stability Data for TIC10 novel salt.

Test		Temperature	Months					Specification
			0	1	2	3	6	
Appearance		(25ºC/60%RH)	Conforms	----	----	Conforms	Conforms	White to off-white solid
Assay by HPLC (wt%)			100.5%	----	----	100.1%	99.8%	97.0 -103.0%
Impurities HPLC (Area%)	Total		0.3%	----	----	0.3%	0.3%	Total ≤ 2%
	RRT 0.87		0.03%	----	----	0.03%	0.03%	Single ≤ 0.5%
	RRT 1.18		0.08%	----	----	0.09%	0.07%	
	RRT 1.32		0.04%	----	----	0.07%	0.04%	
	RRT 1.35		0.13%	----	----	0.12%	0.12%	
pH(1% in water)			3.4	----	----	3.3	3.3	Report
Water content by KF			1.2%	----	----	4.3%	5.2%	Report
Appearance		(40ºC/75%RH)	Conforms	Conforms	Conforms	Conforms	Conforms	White to off-white solid
Assay by HPLC (wt%)			100.5%	101.1%	101.5%	100.7%	101.1%	97.0 -103.0%
Impurities HPLC (Area%)	Total		0.3%	0.3%	0.3%	0.3%	0.3%	Total ≤ 2%
	RRT 0.87		0.03%	0.03%	0.03%	0.03%	0.05%	Single ≤ 0.5%
	RRT 1.18		0.08%	0.09%	0.08%	0.09%	0.08%	
	RRT 1.32		0.04%	0.06%	0.07%	0.06%	0.04%	
	RRT 1.35		0.13%	0.13%	0.12%	0.11%	0.09%	
pH(1% in water)			3.4	3.3	3.3	3.3	4.3	Report
Water content by KF			1.2%	4.9%	6.5%	6.2%	7.8%	Report

Table 2 NOAEL and Dosing of Cohorts in GLP Safety Studies with TIC10. NOAEL doses are boxed in red.

		Species dose (mg/kg)	Human equivalent dose (mg)*	Ratio to Expected Therapeutic Dose
Rats	Cohort 1	0	0	N/A
	Cohort 2	12.5	125	1
	Cohort 3	125	1250	10
	Cohort 4	225	2250	18
Dogs	Cohort 1	0	0	N/A
	Cohort 2	4.2	125	1
	Cohort 3	42	1250	10
	Cohort 4	120	3571	28.6

*Allometrically scaled to a human fixed dose