Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Oncoceutics

2. **Reporting Period (start and end date of grant award period):** 6/1/2012 – 5/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Lee Schalop, MD

4. **Grant Contact Person's Telephone Number:** 917-327-6423

5. **Grant SAP Number:** 4100059195

6. **Project Number and Title of Research Project:** Development and Commercialization of Novel Cancer Therapeutic TIC10

7. **Start and End Date of Research Project:** 6/1/2012 – 5/31/2014

8. **Name of Principal Investigator for the Research Project:** Lee Schalop, M.D.

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $1,298,642.77

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Schalop, Lee	Chief Business Officer	25	$39,636.59
Wolfgang Oster	Chief Executive Officer	25	$39,636.59
Martin Stogniew	Chief of Development	25	$39,636.59
Joshua E. Allen	Director of Development	33	$39,636.59

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Clinical efficacy of antitumor agent ONC201 in GBM	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)	4/2014	$1,150,000	$ Pending
Target Identification of ONC201, a First-in-Class Drug to Treat Glioblastoma	☐NIH ☐ Other federal (specify:_____) ✓Nonfederal source (specify: VABC)	12/2013	$78,029	$ Pending
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify:		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X___ No_____

If yes, please describe your plans:
Additional funding to support clinical evaluation (e.g. phase II and Ib/II studies) and nonclinical research studies (e.g. target identification).

12. Future of Research Project. What are the future plans for this research project?

Evaluate the safety and efficacy of ONC201 in advanced cancer patients by leveraging a combination of grants and private funding mechanisms.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X___ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			1	1
Female				
Unknown				
Total			**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			1	1
Unknown				
Total			**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				1
Black				
Asian			1	
Other				
Unknown				
Total			**1**	**1**

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X___ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

These funds enabled access to GLP- and GMP-compliant facilities that are needed for IND studies.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes__X____ No_____

If yes, please describe the collaborations:
Yes, research enabled by the grant lead to collaborations between Oncoceutics and Penn State, MD Anderson, and Rutgers Cancer Institute of New Jersey.

16(B) Did the research project result in commercial development of any research products?

Yes____X_____ No_____

If yes, please describe commercial development activities that resulted from the research project:
Yes, this research project advanced TIC10 from the discovery stage to a clinical stage product.

16(C) Did the research lead to new involvement with the community?

Yes_____ No___X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Project goals, objectives and specific aims, as contained in the research proposal

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.

Accomplishments

1. Complete remaining preclinical components of IND application.
   A. Development of correlative assays for the clinical protocol.

Surface TRAIL as a correlative marker of response

A previous publication has demonstrated the ability of TIC10 to increase TRAIL expression and that modulating this induction affects efficacy. To more directly evaluate the predictive potential of surface TRAIL as a marker of TIC10 response we evaluated the dose-response relationship between in vitro efficacy and surface TRAIL expression in lymphoma cell lines, which revealed a positive linear correlation (Figure 1). We also generated human colon cancer cells with acquired resistance to TIC10 that revealed striking relationships with TRAIL induction as well as pAkt and pERK levels between the parental and resistant cells. These findings support the utility of surface TRAIL as a marker of TIC10 response.

Kinase markers of TIC10 sensitivity

We conducted a siRNA screen in HCT116 cells using a kinase library to identify kinases that effect TIC10 response to potentially identify predictive markers of sensitivity and potentially gain further mechanistic insight regarding TIC10. This screen identified a number of negative and positive modulators of TIC10 sensitivity (Figure 2). Further validation studies have revealed a short-list of markers that may be used to predict an enhanced response to TIC10. Some of these kinases regulate genes that are also affected by FDA-approved small molecules that synergize with TIC10 in vitro identified in a screen (Figure 3).

Pharmacodynamics assays in normal cells

We assayed the effects of TIC10 on normal fibroblast proliferation in cell culture to assess their potential use in surrogate pharmacodynamic assays. We found that TIC10 imparts only a marginal decrease in the proliferation of normal cells that is reversible and does not cause cell death. This observation was similar in comparator studies of the combination of MEK and Akt inhibitors in normal cells. Furthermore, a mild upregulation of TRAIL and no change in DR5 were noted along with an impartial activation of the Akt/ERK/Foxo3a pathway. These observations may explain the wide therapeutic window of TIC10 in addition to the natural selectivity of TRAIL and suggest that some normal tissues may be used to assay TRAIL, though the sensitivity may be limited.

Cancer stem cell markers

We evaluated the efficacy of TIC10 in several in vitro models of colon cancer stem cells (CSCs) to evaluate the possibility of monitoring CSC markers as correlative assays. These studies revealed that TIC10 generally causes a significance decrease in CSCs that was saturable in a

similar dose range where efficacy is also saturated. Anti-CSC efficacy in colon cancer was also observed in vivo against 5-FU-resistant CSCs as well as CSC marker-positive tumor xenografts. The anti-CSC effects of TIC10 appeared to track with and depend on surface TRAIL induction, at least in vitro.

To identify additional markers of response, we also searched for transcriptional changes in response to TIC10 that may be associated with stem cell pathways and therefore may contribute to the anti-CSC activity of TIC10. Ingenuity Pathway Analysis performed on previously conducted TIC10 microarray data found that TIC10 caused significant change in stem cell-related genes. These results identified a number of stem-associated genes that may contribute to the anti-CSC activity of TIC10 in addition to TRAIL.

B. Define the PK profile of TIC10 in mice.

We developed and further optimized an LC-UV protocol to detect TIC10 in serum. Application of this assay allowed for a pharmacokinetic study in C57/B6 that revealed a half-life of ~6 hours with intravenous administration. In contrast to these pharmacokinetics we observed sustained activity for days in tumor xenograft models when measuring TRAIL, cell death, and the overall efficacy. These observations prompted us to examine the efficacy of various dose schedules (once a week, twice a week, once every two weeks). Tumor volume measurements in subcutaneous xenograft models revealed that all dose schedules had obvious antitumor effects, though regression was not observed in the long term. These findings suggest that an infrequent dose schedule may be safe and effective in clinical trials.

C. CMC and GMP-compliant synthesis of TIC10.

Synthetic route optimization and scale up to >1g yield has been performed with TIC10 using a 1-step synthesis to yield a novel salt. The biological activity (efficacy, signaling, and therapeutic window) of the novel salt is equivalent to the free base by in vitro assays (Figure 4). We found that the novel salt possessed the same dose-dependent cytotoxicity against tumor cells as the free base and, importantly, retains its therapeutic window.

The novel salt is remarkably more soluble in water than the free base, which has previously been formulated in dimethyl sulfoxide for adequate solubility in preclinical studies. Based on this observation we examined the effect of pH on TIC10 solubility using a UV absorbance assay. TIC10 was strikingly more soluble at pH<6 in aqueous solution. Titration of a novel salt solution with sodium hydroxide revealed that an apparent pKa ~ 5.3, suggesting that the solubility of TIC10 may be related to its pKa.

LC-MS analysis of the pH 5 novel salt solution stored at 60°C for 2 weeks revealed optimal stability at pH~3 and that this sample contained a synthetic intermediate as one of the prominent synthetic impurities (Figure 5). Starting materials and synthetic intermediates involved in the synthesis of TIC10 possessed no appreciable effects on the cell viability of tumor or normal cells at doses up to 20 μM. These findings identify a relationship between pH and the solubility and stability of TIC10 that suggests that TIC10 reconstituted in an aqueous solution at pH 3 may be a stable formulation for future studies.

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 changes observed under the accelerated conditions (40°C/75%RH) where a slight increase in moisture content was observed, 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 tolerated 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 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).

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

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

The request for a preIND meeting and the briefing package was submitted to the FDA on April 4, 2013 and favorable written feedback was received on April 30, 2013.

The IND application for TIC10 to treat advanced human cancer was drafted by Oncoceutics, which 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 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 were 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, malignant melanoma, triple negative breast cancer, and others.

Figures

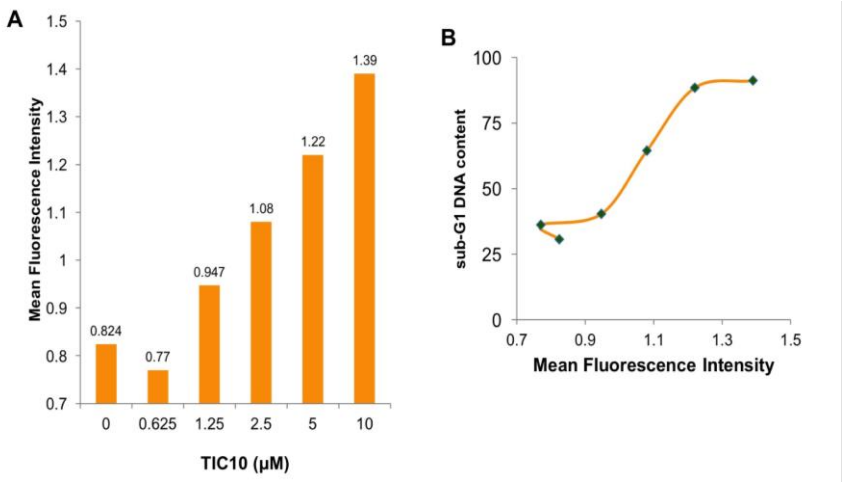

Figure 1. Surface TRAIL correlates with TIC10 efficacy in lymphoma. (A) Surface TRAIL analysis shown as a dose response following treatment with TIC10 in Ramos cells (60 hr). (B) Correlation between cell death and surface TRAIL in Ramos cells (mean fluorescence intensity).

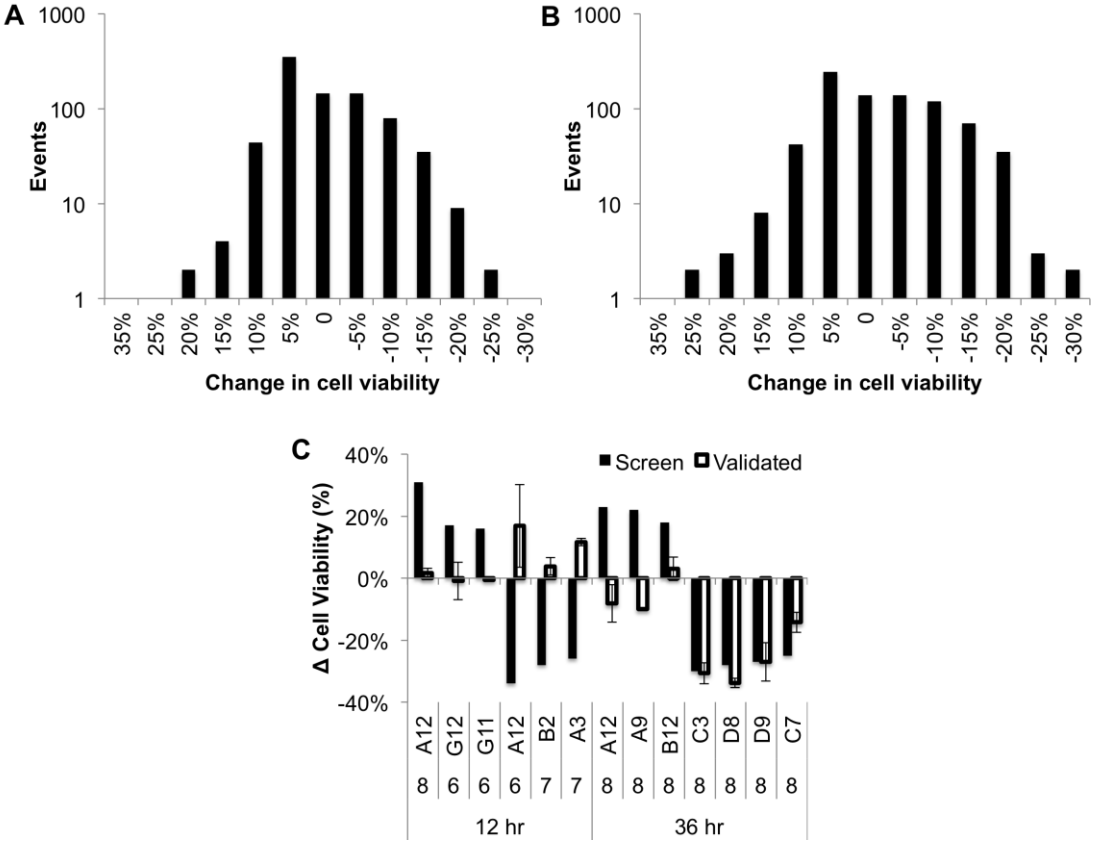

Figure 2. siRNA kinase library screen for modulators of TIC10 sensitivity. Change in cell viability in HCT116 cells associated with the combination of TIC10 treatment (1 uM) and knockdown by siRNA using human kinase library. Results are shown for (A) 12 hours and (B) 36 hours post-treatment. Data is shown relative to TIC10 treatment alone. (C) Genes showing

comparison of validation and screen results for changes in cell viability associated with the combination of TIC10 treatment (1uM) and siRNA knockdown at indicated time points.

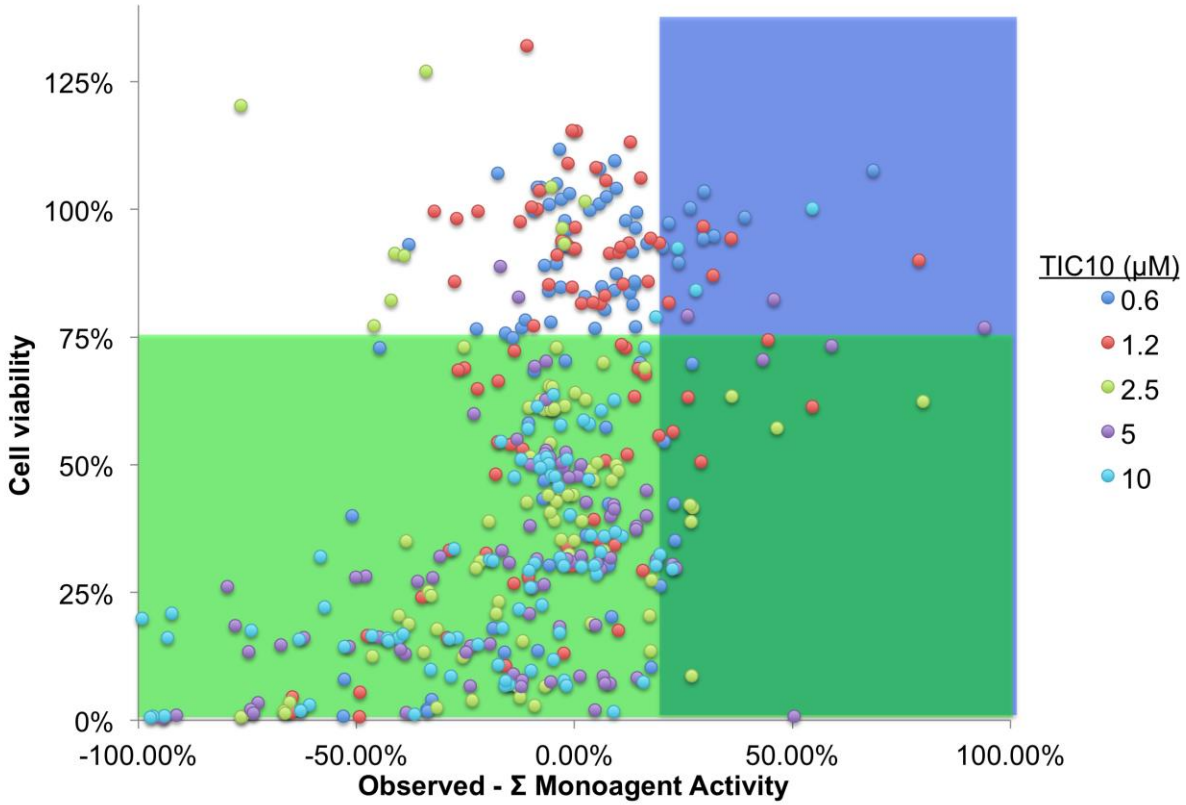

Figure 3. Prioritization of TIC10 combinations with approved anticancer drugs. Combinatorial data as a function of efficacy and synergistic activity (n=2). The prioritization criteria was defined as the lower right quadrant.

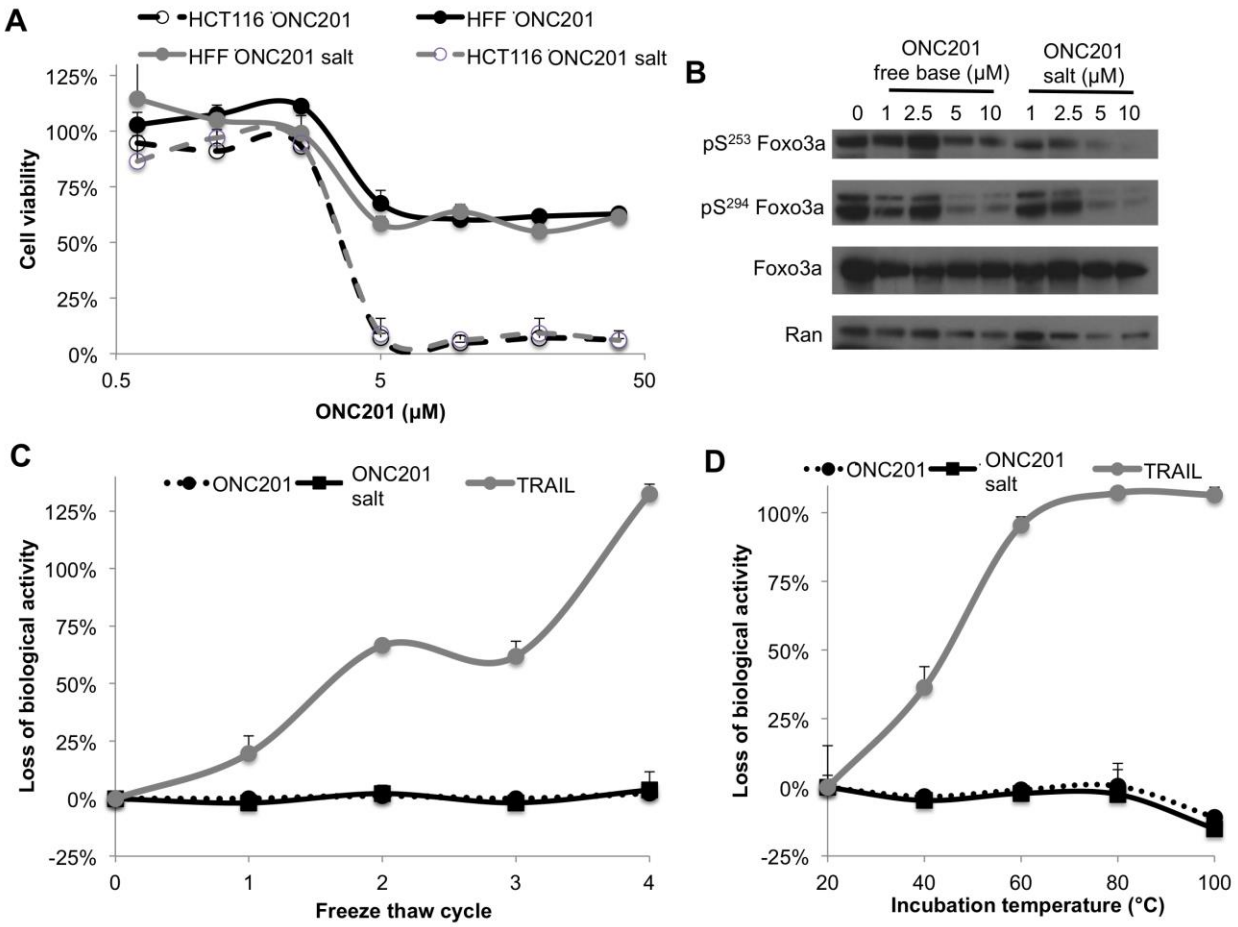

Figure 4. TIC10 novel salt (ONC201) retains the biological activity of its free base. (A) Cell viability assay in HCT116 human colon cancer cells or HFF normal human fibroblasts following a 72 hour treatment with TIC10 free base or salt at indicated concentrations (n=3). (B) Western blot analysis of HCT116 cells treated with TIC10 free base or salt at indicated concentrations (48 hours). Biological activity of TIC10 free base or salt following (C) freeze-thaw cycles or (D) thermal incubation for 1 hour (n=3). Recombinant TRAIL was used as a positive control for these assays.

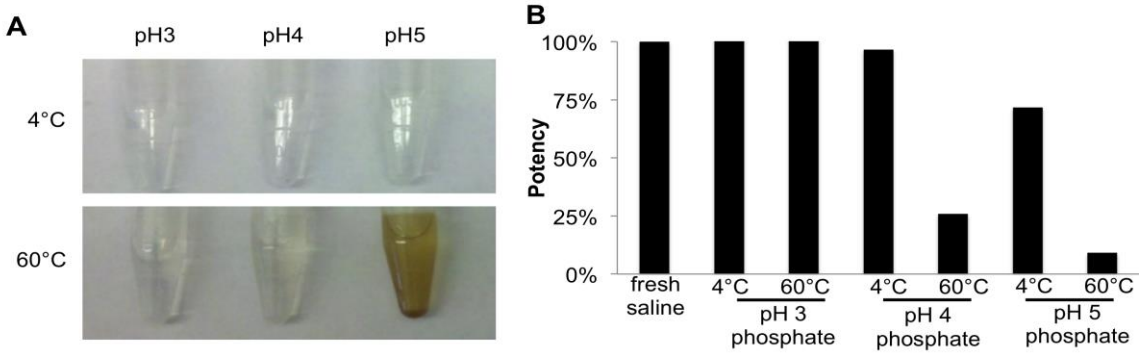

Figure 5. The stability of aqueous TIC10 is pH-dependent. (A) Gross appearance and (B) potency of TIC10 (5 mg/mL) in phosphate buffer following a 2 week incubation a 4°C and 60°C.

Tables

Table 1. Stability Data for TIC10 novel salt.

Test		Temperature	Months 0	1	2	3	6	Specification
Appearance		(25°C/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		(40°C/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

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
_X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X_ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one

publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1.				☐Submitted ☐Accepted ☐Published
2.				☐Submitted ☐Accepted ☐Published
3.				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X___ No_____

If yes, please describe your plans:

Some of the preclinical efficacy and mechanistic with TIC10, a portion of which were supported by this grant, plan to be submitted to a peer reviewed journal in the future.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

This research project allow Oncoceutics to develop TIC10 into a clinical stage product and the FDA accepted the IND for TIC10 that includes a phase I/II protocol. This means that with sufficient funding, TIC10 will be available to patients with advanced cancers that are eligible for the clinical trial and successfully enroll.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

TIC10 is a first-in-class molecule with a unique mechanism of action to address advanced cancers that no longer have standard treatment options. If this preclinical profile of TIC10 translates into the clinic, an effective drug will be made available to advanced cancer patients without other treatment options while avoiding the debilitating side effects routinely observed with cancer therapies.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes__X_____ No_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention: 7-Benzyl-10-(2-methylbenzyl)-2,6,7,8,9,10-hexahydroimidazo[1,2-a]pyrido[4,3-d]pyrimidin-5(3H)-one, Salts thereof And Methods of Using The Same in Combination Therapy

b. Name of Inventor(s): Martin Stogniew and Joshua E. Allen

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

   Inventions related to novel salts of TIC10, optimal dosing of TIC10, and combination therapies

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
   Yes X No____

   If yes, indicate date patent was filed: 3-13-2014

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ NoX
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ NoX

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? YesX No____

If yes, describe the commercial development activities:
Inventions described in this patent will be implemented in the clinical evaluation of TIC10.

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes__X___ No_____

If yes, please describe your plans:
Inventions described in this patent will be implemented in the clinical evaluation of TIC10.

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Biosketches of investigators were included in the submitted grant application, except for Martin Stogniew whose biosketch is below.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Martin Stogniew	Chief Development Officer
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Maryland, Baltimore, MD	B.S.	06/78	Pharmacy
University of Maryland, Baltimore, MD	Ph.D.	06/81	Medicinal Chemistry
Johns Hopkins School of Medicine	Postdoc	06/82	

A. Personal Statement

I am a senior executive with over twenty nine years experience in the pharmaceutical industry. I have been responsible for all areas of domestic and international drug development (includes proprietary, generic, over the counter drugs, and nutritional supplements). My significant contributions resulted in FDA approval of nine New Drug Applications, issuance of twenty-six US patents, and closure of four major M&A deals. I will be supporting the preclinical development activities for the DR2 inhibitor project at Provid and working toward the company's business development goals.

B. Positions and Honors

Positions and Employment

NOVARTIS (formerly Ciba Geigy) Suffern, NY
- 1985-1987 Senior Research Scientist, Physical and Analytical Chemistry
- 1982-1985 Senior Scientist, Physical and Analytical Chemistry

PHARMACIA-UPJOHN (formerly Adria Labs, Inc.), Dublin OH
- 1987-1992 Section Head, Analytical Research and Development

MEDIMMUNE, INC., (formerly US Bioscience) West Conshohocken, PA
- 1998-2000 Corporate Officer
- 1997-2000 Vice President, Pharmaceutical Sciences
- 1994-1996 Senior Director, Pharmaceutical Chemistry
- 1992-1994 Director, Pharmaceutical Chemistry

NEXT PHARMACEUTICALS, INC. Irvine, CA
- 2000 Chief Scientific Officer

OVATION PHARMACEUTICALS, Lincolnshire, IL
- 2001-2003 Scientific Advisory Board

VICURON PHARMACEUTICALS, King of Prussia, PA (Acquired by Pfizer 09/05)
- 2004-2005 Executive Vice President, Scientific Affairs
- 2004-2005 Executive Corporate Officer
- 2003-2004 Senior Vice President, Nonclincial Development

2001-2003 Vice President, Preclinical Development
ZELOS THERAPEUTICS, West Conshohocken, PA
2006-2008 Executive Vice President of Development and Corporate Officer
PRESTWICK PHARMACEUTICALS INC, Washington, DC
2007-2008 Executive Vice President, Chief Technology Officer
YAUPON THERAPEUTICS INC., RADNOR, PA (2009-present)
2010- Chief Technology Officer (2010-present)
2009-2010 Consultant (2009-2010)
MARTIN STOGNIEW, LLC, Blue Bell, PA
2008- Managing Member
PROVID PHARMACEUTICALS, INC., Monmouth Junction, NJ
2011- Director and consultant
ONCOCEUTICS, INC., Hummelstown, PA
2012- Chief Development Officer

Other Experience and Professional Memberships

2001-2003 Scientific Advisory Board, Ovation Pharmaceuticals

Honors
1978 B.S. degree in Pharmacy with Honors, University of Maryland, Baltimore

C. Publications
Selected Peer-reviewed Publications (Selected from 22 peer-reviewed publications)

1. P.S. Callery, M. Stogniew, M.F. Kaiser and R.M. Denmin Jr. Carbon-13 NMR Characterization of an 0-Alkylated Derivative of the Theophylline Metabolite 1,3-Dimethylaric Acid. Analytical Letters, 18, 2537 (1985).
2. R.B. v Breemen, M. Stogniew and C. Fenselau. Characterization of Acyl-Linked Glucuronides by Electron Impact and Fast Atom Bombardment Mass Spectrometry. Biomedical and Environmental Mass Spectrometry, 17, 97, (1988).
3. Pharmacokinetic-pharmacodynamic modeling of dalbavancin, a novel glycopeptide antibiotic. J.A. Dowell, B.P. Goldstein, M. Buckwalter, M. Stogniew, and B. Damle. J Cli n Pharmacol. In Press.
4. Anidulafungin does not require dosage adjustments in subjects with varying degrees of hepatic or renal impairment. J.A. Dowell, M. Stogniew, D. Krause, and B. Damle. J Clin Pharmacol. 47:461-470, 2007.
5. Lack of pharmacokinetic interaction between anidulafungin and tacrolimus. J.A. Dowell, M. Stogniew, D. Krause, T. Henkel, and B. Damle. J Clin Pharmacol. 47:305-314, 2007.
6. Pharmacokinetics and excretion of dalbavancin in the rat. M. Cavaleri, S. Riva, A. Valagussa, M. Guanci, L. Colombo, J.A. Dowell, and M. Stogniew. J Antimicrobial Chemotherapy. 55(Suppl. S2):31-35, 2005.
7. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. J.A. Dowell, M. Stogniew, D. Krause, T. Henkel, and I.E. Weston. J Clin Pharmacol. 45:227-233, 2005.
8. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. J.A. Dowell,
9. W. Knebel, T. Ludden, M. Stogniew, D. Krause, and T. Henkel. J Clin Pharmacol. 44:590-598, 2004.

US Patents, Issued

1. Methods for Treatment of Neuro-and Nephro-Disorders and Therapeutic Toxicities Using Aminothiol Compounds; Stogniew, Martin; Alberts, David S. and Kaplan, Edward H. November 30, 1999, #5,994,409
2. Thermally Stable Trimetrexates and Processes for Producing the Same; Stogniew, Martin; Grafe, Ingomar and Morsdorf, Johann P.; January 25, 2000, #6,017,922
3. Methods for the Administration of Amifostine and Related Compounds; Stogniew, Martin and Schein, Philip S. April 18, 2000 #6,051,563.
4. Methods for the Administration of Amifostine and Related Compounds; Stogniew, Martin and Schein, Philip S.; October 3, 2000 #6,127,351
5. Methods for the Administration of Amifostine and Related Compounds; Stogniew, Martin and Schein, Philip S.; April 17, 2001; #6,218,377.
6. Topical Administration of Amifostine and Related Compounds; Stogniew, Martin and Bourhis, Jean; May 29, 2001; #6,239,119
7. Compositions Comprising Trimextrexate and Methods of their Synthesis and Use; Stogniew, Martin; and Zadei, Javad M.; July 10, 2001; 6,258,821.
8. Thermally-Stable Trimextrexate and Processes for Producing Same; Stogniew, Martin; Grafe, Ingomar and Morsdorf, Johann P.; July 10, 2001; #6,258,952.
9. Stable Amorphous Amifostine Compositions and Dosage Form; Stogniew, Martin and Zadei, Javad M.; May 7, 2002; #6,384, 259
10. Stable Amorphous Amifostine Compositions and Methods for the Preparation and Use of the Same; Stogniew, Martin and Zadei, Javad M.; June 18, 2002, 6,407,278
11. Pharmaceutical formulations comprising aminoalkyl phosphorothioates; Stogniew, Martin and Zadei, Javad M.; December 3, 2002; 6,489,312.
12. Methods for the administration of amifostine and related compounds; Stogniew, Martin; June 3, 2003; 6,573,253.
13. Compositions compromising trimetrexate; Stogniew, Martin and Zadei, Javad M.; June 10, 2003; 6,576,635.
14. Compositions and methods of use for extracts of magnoliaceae plants; Stogniew, Martin and Garrison, Jr., Robert; June 24, 2003; #6,582,735.
15. Methods for the treatment of nephro-disorders using aminothiol compounds; Stogniew, Martin; Alberts, David S; Kaplan, Edward H.; July 1, 2003; #6,586,476
16. Topical administration of amifostine and related compounds; Stogniew; Martin; Bourhis; Jean. ; June 22, 2004; # 6,753,323
17. Compositions and methods of use for extracts of magnoliaceae plants; Stogniew, Martin; Chambliss, Walter; Garrison Jr., Robert; November 9, 2004; #6,814,987
18. Stable amorphous amifostine compositions and methods for the preparation of same; Stogniew, Martin; Zadei, Javad M; January 11, 2005; #6,841,545
19. Methods of administering dalbavancin for treatment of bacterial infections; Cavaleri; Marco; Jabes; Daniela; Henkel; Timothy; Malabarba; Adriano; Mosconi; Giorgio; Stogniew; Martin; White; Richard J.; May 31, 2005; #6,900,175
20. Antifungal parenteral products; Stogniew; Martin; January 31, 2006; #6,991,800
21. Methods for the treatment of neuro- disorders using aminothiol compounds; Stogniew, Martin; Alberts, David S; Kaplan; Edward H; September 12, 2006; #7,105,575
22. Stable pharmaceutical compositions of dalbavancin and methods of administration; Cavaleri, Marco; Jabes, Daniela; Henkel, Timothy; Malabarba, Adriano; Mosconi, Giorgio; Stogniew, Martin; White, Richard J; October 3, 2006; #7,115,564
23. Dalbavancin compositions for treatment of bacterial infections; Stogniew; Martin; October 10, 2006; #7,119,061
24. Topical administration of amifostine and related compounds; Stogniew, Martin; Bourhis,

Jean; December 19, 2006; #7,151,094
25. Antifungal parenteral products; Stogniew, Martin; April 3, 2007; #7,198,796
26. Stable amorphous amifostine compositions and methods for the preparation and use of same; Stogniew, Martin; Zadei, Javad M.; December 8, 2009; #7,629,333

D. Research Support

Ongoing Research Support

Completed Research Support

1997-1999 Served as principal investigator for National Cancer Institute contract for stability testing of drug product