

# 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:** Temple University – of the Commonwealth System of Higher Education
2. **Reporting Period (start and end date of grant award period):** 01/01/2009 – 12/31/2012
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Germaine A Calicat
4. **Grant Contact Person’s Telephone Number:** 215/204-7655
5. **Grant SAP Number:** 4100047651
6. **Project Number and Title of Research Project:** 8 - *Interactions Between Cytotoxic and Antiangiogenic Drugs*
7. **Start and End Date of Research Project:** 01/01/09 – 8/30/2009
8. **Name of Principal Investigator for the Research Project:** James Gallo, PhD
9. **Research Project Expenses.**

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

\$ 26,664

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	Position Title	% of Effort on Project	Cost
Zhou, Stephanie	Associate Scientist	100	25,346

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	Position Title	% of Effort on Project
James Gallo, PhD	PI	

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
None		

**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 \_\_\_\_\_ No X \_\_\_\_\_

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:
None	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> 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:

A NIH grant [competitive renewal] was submitted in March 2010.

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

Pending grant review.

**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 \_\_\_\_\_ No X \_\_\_\_\_

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
<b>Total</b>				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
<b>Total</b>				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
<b>Total</b>				

**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 \_\_\_\_\_ No  X

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

**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 \_\_\_\_\_ No  X

If yes, please describe the collaborations:

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

Yes \_\_\_\_\_ No  X

If yes, please describe commercial development activities that resulted from the research project:

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 application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. 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.

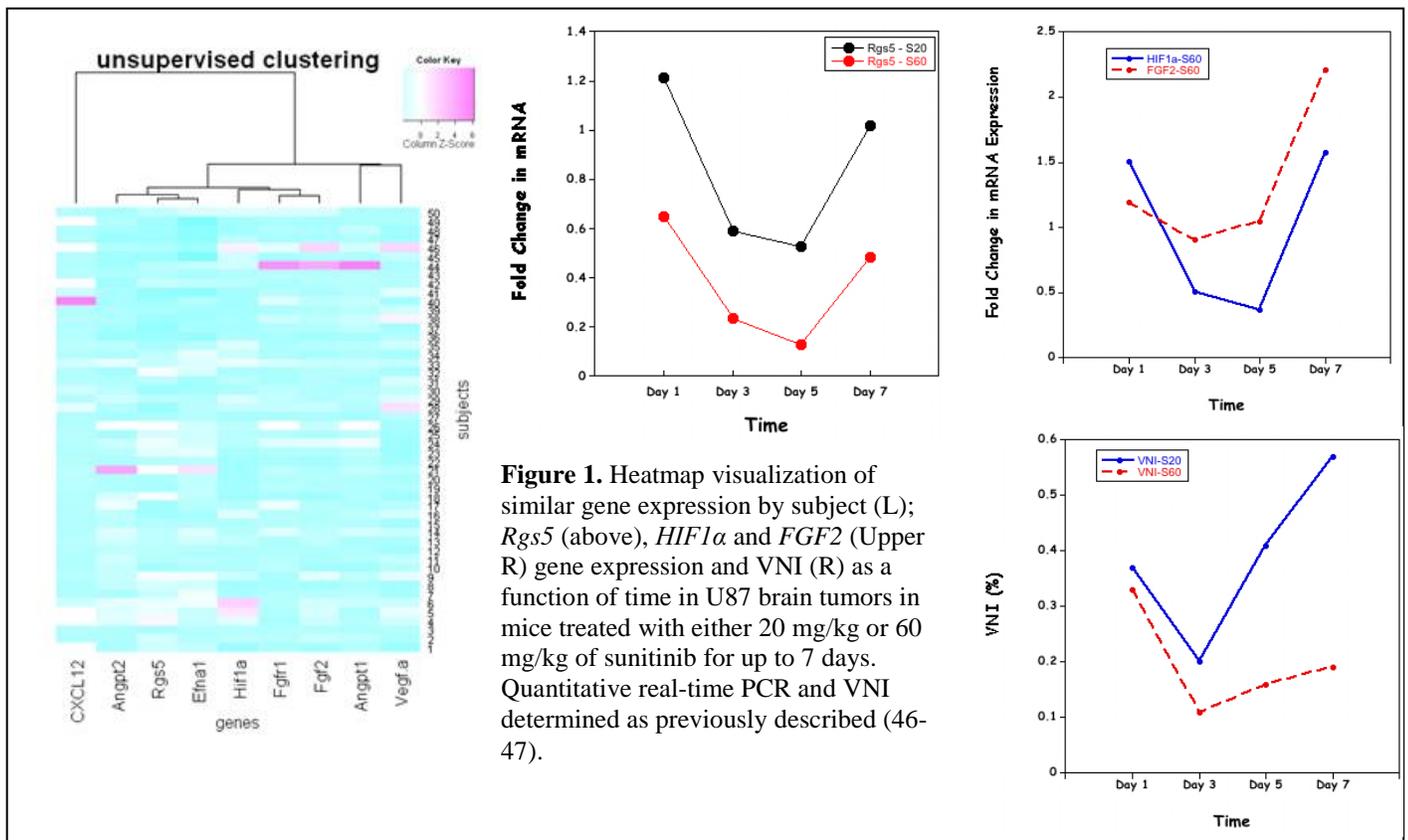
This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still 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 ( $\alpha$ ) and beta ( $\beta$ ) should not print as boxes ( $\square$ ) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.**

The goal of this project is to examine the pharmacokinetic [PK] and pharmacodynamic [PD] properties of a combination of two targeted drugs, sunitinib and a PI3K/mTOR inhibitor that may influence angiogenesis. We have completed the PK/PD studies of sunitinib as a single agent, which included both single- and multiple-dose studies in mice bearing intracerebral tumors. Sunitinib plasma, normal brain and brain tumor concentrations were measured as well as gene expression and PD endpoints that indicate the antiangiogenic effects. The PK results from the 20 mg/kg and 60 mg/kg single-dose sunitinib studies indicated high brain tumor uptake relative to normal brain, about 15 to 18-fold greater, consistent with blood-brain barrier breakdown.

The PD and gene expression data of single agent sunitinib is illustrated in figure 1 below. The gene expression analyses indicate both dose- and time-dependent changes in gene expression with upregulation of proangiogenic genes [*i.e.* *Fgf2*, and *HIF-1 $\alpha$* ], particularly at the higher-dose after 7 days of therapy, which could support the use of a lower 20 mg/kg dose. It was also observed that the vascular normalization index (VNI), see Figure 1, increased more at the lower sunitinib dose, and further supports the use of a lower dose in combination studies. The VNI is used as a measure of drug delivery to the tumor for drugs coadministered with sunitinib, such as temozolomide.



We have completed an initial screen of a PI3K inhibitor [and two dual PI3K/mTOR inhibitors in brain tumor bearing mice. In this regard, we used a cassette dosing strategy to simultaneously administer each compound to mice bearing intracerebral U87 tumors, and found that compound C was the most selective based on the highest brain tumor/normal brain ratio of 3.7 [see Table 1].

<b>Table 1.</b> Steady-state drug concentration ratios in mice bearing intracerebral U87 tumors. Mice were sacrificed at 4 hours after the initiation of drug administration and all drugs were quantitated by LC/MS/MS.			
<b>Steady-state concentration ratios</b>	<b>Compounds</b>		
	<b>BEZ236</b>	<b>BGT226</b>	<b>BKM120</b>
<b>Tumor/Plasma</b>	1.174 ± 0.496	1.378 ± 0.441	1.979 ± 0.732
<b>Brain/Plasma</b>	0.912 ± 0.298	0.649 ± 0.362	3.693 ± 1.902
<b>Tumor/Brain</b>	1.277 ± 0.329	3.701 ± 3.918	0.560 ± 0.091

We have conducted PK/PD studies of sunitinib and compound C in mice bearing orthotopic brain tumors. PD assays have determined that both pAKT and pS6 could serve as PD endpoints in tumor, and that there was no negative interaction with sunitinib.

**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

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, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the “Cognition and MRI in Older Adults” research project (Project 1), and two publications for PI Zhang for the “Lung Cancer” research project (Project 3), the filenames should be:

- Project 1 – Smith – Publication 1 – Cognition and MRI
- Project 1 – Smith – Publication 2 – Cognition and MRI
- Project 3 – Zhang – Publication 1 – Lung Cancer
- Project 3 – Zhang – Publication 2 – Lung Cancer

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. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

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

Yes \_\_\_\_\_ No  X

If yes, please describe your plans:

**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.

None

**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.

None

**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 \_\_\_\_\_ No  X

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:
- b. Name of Inventor(s):
- c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):
- 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 \_\_\_\_\_ No \_\_\_\_\_

If yes, indicate date patent was filed:

- 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 \_\_\_\_\_ No \_\_\_\_\_  
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 \_\_\_\_\_ No \_\_\_\_\_

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? Yes \_\_\_\_\_ No \_\_\_\_\_

If yes, describe the commercial development activities:

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 \_\_\_\_\_ No \_\_\_\_\_ X \_\_\_\_\_

If yes, please describe your plans:

**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.*

Dr. Gallo has left Temple University

## James M. Gallo, PhD

- PROFESSOR Pharmacology and Systems Therapeutics, Mt Sinai Hospital, New York, New York
- Email: james.gallo@mssm.edu

### Education

- B.S., Pharmacy, Massachusetts College of Pharmacy
- Pharm.D., University of Florida
- Ph.D., Pharmacy, University of Arizona

### Biography

I'm a pharmacokineticist focused on the experimental therapeutics of anticancer drugs. In particular we are interested in using pharmacokinetic [PK] and pharmacodynamic [PD] approaches to advance drug development and improve drug therapy. Currently, these efforts are directed towards experimental models of brain tumors. We hope to identify new chemotherapeutic strategies that are derived from tumor-directed PK/PD investigations and enhance the translational foundation of preclinical to clinical research.

At Mount Sinai, I plan to continue my work on the experimental therapeutics of brain tumors, and hope to establish new collaborations in anticancer drug therapeutics and PKs and PDs.

### Research

Drug Disposition and Dynamics in Tumors

My lab is focused on the experimental therapeutics of brain tumors that is cast into a foundation of pharmacokinetic [PK], and pharmacodynamic [PD] methods and strategies. We use in silico, in vitro and in vivo investigations to characterize the PK and PD properties of anticancer drugs. These studies have a common goal of understanding the variables that influence drug disposition and dynamics in the tumor, the target site. Through the use of detailed measurements of drug concentrations in tissues and the associated PD endpoints we build physiologically-based PK/PD models that not only provide mechanistic information, but further allow for model predictions to be made in patients where tumor data is sparse. The progression of preclinical studies may lead to new drug treatment strategies and means to optimize drug treatment regimens in patients.

### Publications

Wang S, Zhou Q, Gallo JM. Demonstration of the equivalent pharmacokinetic/pharmacodynamic dosing strategy in a multiple-dose study of gefitinib.. *Mol Cancer Ther* 2009 Jun; 8(6): 1438-1447.

Russo L, Brock CS, Gallo JM, Saleem A, Price PM, Turkeimer FE, Aboagye EO. A new model for prediction of drug distribution in tumor and normal tissues: pharmacokinetics of temozolomide in glioma patients.. *Cancer Res* 2009 Jan; 69(1): 120-127.

Zhou Q, Gallo JM. Differential effect of sunitinib on the distribution of temozolomide in an orthotopic glioma model.. *Neuro Oncol* 2009 Jun; 11(3): 301-310.

Zhou Q, Guo P, Gallo JM. Impact of angiogenesis inhibition by sunitinib on tumor distribution of temozolomide.. *Clin Cancer Res* 2008 Mar; 14(5): 1540-1549.

Wang S, Guo P, Wang X, Zhou Q, Gallo JM. Preclinical pharmacokinetic/pharmacodynamic models of gefitinib and the design of equivalent dosing regimens in EGFR wild-type and mutant tumor models.. *Mol Cancer Ther* 2008 Feb; 7(2): 407-417.

Zhou Q, Guo P, Kruh GD, Vicini P, Wang X, Gallo JM. Predicting human tumor drug concentrations from a preclinical pharmacokinetic model of temozolomide brain disposition.. *Clin Cancer Res* 2007 Jul; 13(14): 4271-4279.

Zhou Q, Guo P, Wang X, Nuthalapati S, Gallo JM. Preclinical pharmacokinetic and pharmacodynamic evaluation of metronomic and conventional temozolomide dosing regimens.. *J Pharmacol* 2007 Apr; 321(1): 265-275.

Gallo JM, Vicini P, Orlansky A, Li S, Zhou F, Ma J, Pulfer S, Bookman MA, Guo P. Pharmacokinetic model-predicted anticancer drug concentrations in human tumors.. *Clin Cancer Res* 2004 Dec; 10(23): 8048-8058.

Gallo JM, Li S, Guo P, Reed K, Ma J. The effect of P-glycoprotein on paclitaxel brain and brain tumor distribution in mice.. *Cancer Res* 2003 Aug; 63(16): 5114-5117.

Ma J, Li S, Reed K, Guo P, Gallo JM. Pharmacodynamic-mediated effects of the angiogenesis inhibitor SU5416 on the tumor disposition of temozolomide in subcutaneous and intracerebral glioma xenograft models.. *J Pharmacol Exp Ther* 2003 Jun; 305(3): 833-839.