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:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814-935-1081

5. **Grant SAP Number:** # 4100047645

6. **Project Number and Title of Research Project:** 21 - In Vivo Anti Tumoral Properties of Ceramide Nano Liposomes in a Murine Hepatocellular Cancer

7. **Start and End Date of Research Project: 5/1/2009 – 6/30/2011**

8. **Name of Principal Investigator for the Research Project:** Hephzibah Rani S. Tagaram, PhD

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:

   $ 84,208

   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
None			

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
Hephzibah Rani S. Tagaram	Research Assistant, PI	10%
Kevin Staveley-O'Carroll	Professor	1%
Mark Kester	Professor	1%
Harriet Isom	Professor	1%

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
Imaris software + computer	provides crucial 3D and 4D Image analysis capacities	$45,475

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	☐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_____ No_____X____

If yes, please describe your plans:

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

We want to further demonstrate the efficacy of LipC6 in novel orthotopic murine HCC model in our laboratory. The model was developed by seeding the tumorigenic hepatocytes from SV40 T antigen transgenic MTD2 mice into the livers of syngeneic C57BL/6 mice. This resulted in SV40 T antigen specific tumors in the immune competent C57BL/6 liver that will allow us to evaluate the efficacy of combinatorial effects of LipC6 and antigen directed immunotherapy on HCC progression. The work is in progress.

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				
Total				

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

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

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.

    This project further strengthened the science base for translational research related to hepatocellular cancer which is a high priority for the Penn State Hershey Cancer Institute.

    The Imaris Confocal Analysis software package provides crucial 3D and 4D Image analysis capacities not previously available for multiple projects in Clinical and Basic Science projects at the PSU CoM

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 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.

Specific Aim 1: Determine the efficacy of ceramide liposome (lip-C6) on inhibiting solid tumor growth our murine model.
Our laboratory has developed a spontaneous murine model of HCC by injecting tumorigenic hepatocytes intrasplenically into the normal syngeneic C57BL/6 mice. These mice reliably develop solid tumors by 8 weeks of age, and display immunological tolerance. Previous studies suggest that the liposome encapsulated ceramide inhibits the growth of solid tumor in a breast cancer model. We hypothesize that liposome encapsulated ceramide will inhibit the growth of spontaneously developed solid HCC, which would give a close approximation of human hepatocellular cancer. We will test this hypothesis in this specific aim. Inhibition of tumor growth will be monitored by magnetic resonance imaging (MRI).

Specific Aim 2: Determine the efficiency of ceramide liposome to inhibit proliferation and promote apoptosis in tumor vasculature.
In vitro studies have demonstrated the role of ceramide liposome in promoting apoptosis. Ceramide liposome treatment in a breast adenocarcinoma model showed a significant inhibition of CD31 (PECAM-1 for platelet endothelial cell adhesion molecule), a marker for tissue regeneration. We will analyze CD31 and CD105 as a marker of angiogenesis. While CD31 plays a key role in removing the aged neutrophils from the body, CD105 (endoglin) is a receptor for TGF-β, modulates TGF-β signaling and is a promising tumor vascular marker of angiogenesis. We hypothesize that treatment of our murine model with ceramide liposome will impact tumor vasculature by inhibiting proliferation and/or induction of endothelial cell (EC) apoptosis. Moreover our working hypothesis is that ceramide liposome can slow tumor angiogenesis by inhibiting CD31 and CD105.

Specific Aim 3: Mechanisms of action of Ceramide Liposome on promitogenic, prosurvival signaling cascades.
ERK cascade function in cellular proliferation, differentiation, and survival, and their inappropriate activation is a common occurrence in human cancers. We have preliminary *in vitro* data suggesting that ceramide liposome diminishes ERK and AKT signaling cascades. We hypothesize that ceramide liposome will diminish ERK/AKT signaling cascade which will lead to tumor and/or endothelial cell apoptosis. The underlying mechanism of promitogenic prosurvival signaling cascade in our HCC murine model will be explored with ceramide

treatment.

All the research goals and specific aims have been successfully achieved.

1. We have successfully determined the efficiency of ceramide liposome in inhibiting proliferation and promoting apoptosis in human Hepatocellular carcinoma cell lines.
We initially evaluated the *in vitro* efficacy of nanoliposomal C6-ceramide for the treatment of human SK-HEP-1 cells, a model of metastatic HCC. SK-HEP-1 human HCC cells were maintained at 37°C, and 5% CO_2, in MEM supplemented with 10% FBS, 1% sodium pyruvate, 1% non-essential amino acids, 1% sodium bicarbonate, 1% L-glutamine, and 1% penicillin/streptomycin. For subculture, cells were subject to trypsin/EDTA detachment, centrifuged, resuspended in growth media, and replated at appropriate cell density. Proliferation assay was performed by MTT assay (Fig 1A). Nanoliposomal C6-ceramide, pegylated to improve retention and limit toxicity, has been shown to effectively treat cellular and animal models of breast cancer and melanoma. 10 µM nanoliposomal C6-ceramide induced a significant 30% decrease in SK-HEP-1 cellular viability *in vitro*, compared to the PBS control and ghost nanoliposome, as indicated by MTS viability assay (Fig. 1A).

We further determined the apoptotic effect of Lip-C6 on SK-HEP-1 cell by caspase assay, annexin-V staining and Tunel staining. SK-HEP-1 cells were plated at $5x10^3$ cells per well in 96-well tissue culture plates, and grown in 10% serum fortified media for 48 hours prior to treatment. Cells were exposed to PBS, ghost nanoliposomes, or nanoliposomal C6-ceramide for 24 hours in media containing 1% FBS. Caspase 3/7 enzymatic activity was measured following treatment using an Apo-ONE Homogeneous Caspase 3/7 Assay according to the manufacturer's instructions (Promega, Madison, WI). Caspase 3/7 activity was determined by measuring fluorescence of the cleaved substrate using a microplate reader (excitation: 498 nm; emission 521 nm). We determined that caspase with 10 µM nanoliposomal C6-ceramide, but not ghost nanoliposomes or PBS controls, stimulated a robust 5-fold increase in caspase 3/7 activity, indicative of an apoptotic death pathway (Fig. 1B).

To further substantiate the apoptotic potential of ceramide in SK-HEP-1 cells, we assessed annexin-V expression and TUNEL staining. SK-HEP-1 cells were treated, harvested and stained ($1x10^6$ cells/ml of annexin-binding buffer) with annexin-V FITC labeled antibody (Molecular Probes) for 15 min at RT. Stained cells were analyzed by flow cytometry. Annexin V staining of SK-HEP-1 cells showed a 2 fold increase with 10 µM nanoliposomal C6-ceramide (Fig 1C). Terminal Deoxynucleotide Transferase dUTP Nick End Labeling (TUNEL) Assay determines the fragmented DNA as an indication of apoptosis. SK-HEP-1 cells were plated at 1000 – 10,000 cells per well in 8-well chamber slides, and grown in 10% serum fortified media for 48 hours prior to treatment. Cells were exposed to PBS, ghost nanoliposomes, or C6-ceramide-containing nanoliposomes for 24 hours in media containing 1% FBS. Fragmented DNA of apoptotic cells was stained using an ApopTag Red *In Situ* Apoptosis Detection Kit according to the manufacturer's instructions (Chemicon, Temecula, CA), and visualized by fluorescence microscopy using appropriate filters. TUNEL staining of SK-HEP-1 cells further showed that 10 µM nanoliposomal C6-ceramide, but not ghost nanoliposomes, induced apoptosis of SK-HEP-1 cells *in vitro* (Fig. 1D).

2. Blockade of G_2-M phase of cell cycle of SK-HEP-1 cells with Lip-C6 treatment
SK-HEP-1 cells were grown at $5x10^3$ in 10% serum fortified media for 48 hours prior to treatment. Cells were exposed to PBS, ghost nanoliposomes, or C6-ceramide-containing nanoliposomes for 24 hours in media containing 1% FBS. Cells were dissociated from culture plates, resuspended in PBS, and DNA stained with propidium iodide. Flow cytometry was used to determine cell cycle distribution based on total DNA content per cell. Cell cycle arrest is often a preliminary event that leads to apoptosis. As ceramide has previously been documented to interfere with cell cycle progression in HCC, we evaluated the effect of nanoliposomal C6-ceramide on the cell cycle. We utilized flow cytometry following DNA staining with propidium iodide, and quantified the proportion of SK-HEP-1 cells in the G_1, S, and G_2 phases of the cell cycle (Fig. 2). We demonstrate a significant percentage of SK-HEP-1 cells treated with 10 µM nanoliposomal C6-ceramide in the G_2 phase (37.98% ± 0.36), compared to cells treated with ghost nanoliposomes (18.34% ± 1.65) or control PBS (20.22% ± 0.43), indicative of blockade at the G_2-M checkpoint (Fig 2). Similar G_2-M blockade as well as decreases in cellular viability and increases in caspase3/7 activity and TUNEL staining were observed with C3A human HCC cells lines when treated with liposomal C6 ceramide (data not shown).

3. Nanoliposomal C6 decreases the phosphorylation of AKT
AKT phosphorylation is often associated with resistance to apoptosis in cancer cells. The effect of C6 nanoliposomal ceramide on prosurvival AKT signaling was studied by western blot analysis. Cell lysates were prepared by treating tissues with lysis buffer (0.1% NP40, 50mM HEPES, 137mM NaCl, 10mM $Na_4P_2O_7$, 50mM NaF, 5mM b-glycerophosphate, 1mM EGTA, 2mM EDTA, 1% glycerol, 2mM) containing protease inhibitor (Calibiochem) for 20 min on ice followed by centrifugation at 4 ^{o} C for 15 minutes to sediment particulate materials. The protein concentrations were measured using Bio-Rad protein assay kit. (Bio-Rad Laboratories, Hercules, CA). Protein (30ug) from whole cell extracts were separated on SDS- polyacrylamide gels and transferred onto nitrocellulose membrane. Membranes were blocked with 1% BSA in TBS containing 0.05% Tween and incubated with pAKT and β-actin primary antibodies (Cell Signaling, Beverly, MA) before visualization with enhanced chemiluminescence detection (Thermo Scientific, Rockport, IL). Following 24h of treatment with C6 nanoliposomal ceramide, phosphorylation of AKT was reduced in a dose dependent manner (Fig 3). Equal loading of lanes was confirmed by β-actin staining. The results are consistent with previous studies showing that nanoliposomal C6 ceramide can target cancer cells by diminishing activated AKT signaling.

4. Growth of SK-HEP-1 tumors in vivo is prevented by systemic administration of nanoliposomal C6-ceramide
Bilateral human HCC tumor xenografts were established in female athymic nude mice (Jackson Laboratories, Bar Harbor, ME) by subcutaneous injection of SK-HEP-1 cells over the rib cage. For each tumor, $5x10^6$ cells were resuspended in 200 µl of cell culture media. Tumors were allowed to establish for one week prior to commencement of treatment regime. Treatments occurred on alternate days via tail vein injection of sterile saline, ghost nanoliposomes, or C6-ceramide-containing nanoliposomes at 36mg/kg body wt of the mice. Each treatment group consisted of 5 animals, each with bilateral tumors. Tumor volumes were quantified by measuring with calipers, and multiplying tumor length, width, and height. At the conclusion of the trial, animals were sacrificed, and tumors were excised and processed for histological analysis by formalin fixation, paraffin embedding, and microtome sectioning. All animal procedures were

approved by, and carried out according to the standards and guidelines of the Pennsylvania State University College of Medicine Institutional Animal Care and Use Committee. Tumor volume was monitored by measuring the length, width, and height of tumors with calipers. We observed that systemic administration of nanoliposomal C6-ceramide completely prevented the growth of human HCC xenografts in athymic nude mice, whereas saline or ghost nanoliposomes did not (Figure 4). Specifically, by the end of the trial (>7 weeks post tumor initiation), mice receiving saline or ghost nanoliposomes had tumor volumes over 3.5 times greater than those in mice that were treated with nanoliposomal C6-ceramide (Fig 4).

The incidence of HCC continues to grow, possibly as a result of chronic liver disease, which often precedes HCC. The long-term survival for patients with HCC is poor and the cancer often becomes metastatic before or during the course of treatment. Liver transplantation is currently a primary treatment option that can offer a cure if the cancer has not become metastatic, but leaves patients with a lifetime of taking immunosuppressive drugs to avoid transplant rejection. However, this surgical option remains limited owing to the scarcity of replacement organs as well as late diagnosis. No promising therapies exist for patients with advanced HCC. Although the multikinase inhibitor sorafenib has been found marginally to prolong survival in patients with advanced HCC, novel treatments are needed. Nanoliposomal C6-ceramide was designed as a therapeutic alternative to common chemotherapeutics. Liposomal formulation of short-chain ceramide analogues allows for the systemic delivery of this very hydrophobic cell-impermeable precipitating pro-apoptotic sphingolipid. Intriguingly, nanoliposomal C6-ceramide was shown to be toxic to cancer cells and not to normal cells, a paradigm arising from distinct ceramide metabolic regulation between these cells. Thus, the therapeutic utility of this cancer cell-selective antineoplastic agent depends on nanoscale delivery modalities.

In vivo administration of nanoliposomal C6-ceramide restricts HCC tumor vascularisation and initiates apoptosis:

To confirm the in vivo mechanisms by which nanoliposomal C6-ceramide prevents tumor growth, we assessed cellular proliferation and survival markers in excised tumors. SK-HEP-1 HCC tumors from mice treated systemically with either saline or ghost nanoliposomes had robust PCNA staining and nearly no TUNEL-positive staining (Figure 5A). However, tumors from mice treated systemically with nanoliposomal C6-ceramide had virtually no PCNA staining, yet dramatic TUNEL-positive staining was observed. Consistent with increased apoptosis and decreased cellular proliferation, nanoliposomal C6-ceramide-treated animals but not ghost-treated or saline-treated animals had significantly reduced phospho-AKT staining, a marker of pro-survival signaling (Figure 5B). As ceramide has previously been shown to restrict angiogenesis which could also lead to tumor apoptosis, we evaluated tumor sections for CD31 and CD105, both markers of angiogenesis (Figure 5C). Tumors from mice treated systemically with nanoliposomal C6-ceramide had dramatically less CD31 and CD105 staining than tumors from mice treated systemically with ghost nanoliposomes or saline control. Furthermore, significant VEGF staining was observed in tumor sections from mice treated with ghost nanoliposomes or with saline, but not from those treated with nanoliposomal C6-ceramide (Figure 5D). VEGF is a growth factor that promotes vascularisation. These findings suggest that the efficacy of nanoliposomal C6-ceramide *in vivo* is also due to restriction of angiogenesis and therefore to diminished vascularisation of the tumors. Taken together, these results indicate that the efficacy of nanoliposomal C6 ceramide is the result of a decrease in tumor vascularization as

well as a decrease in tumor cell proliferation and an increase in tumor cell apoptosis.

Many chemotherapeutics as well as radiation therapy have been shown to induce accumulations of ceramide. Specific to our study, we showed that nanoliposomal delivery of C6-ceramide in vivo to SK-HEP-1 HCC tumors blocked tumor vascularization, which was visualized in tumor sections as a reduction in CD31 and CD105 staining as well as a reduction in VEGF staining. Tumor vascularization or angiogenesis into and within tumors is necessary to establish nutrient support. It is not coincidental that studies have shown that nutrient deprivation can lead to cellular ceramide generation and cellular death. It is thus plausible that preventing HCC tumor vascularization with systemic nanoliposomal C6-ceramide treatment could induce widespread apoptosis within the tumors. In fact, short-chain ceramide treatment has been shown to generate more physiological long-chain ceramide species within tumors. The efficacy of our nanoliposomal C6-ceramide in the treatment of diverse cancers lends significant therapeutic promise as it translates from the bench to the bedside.

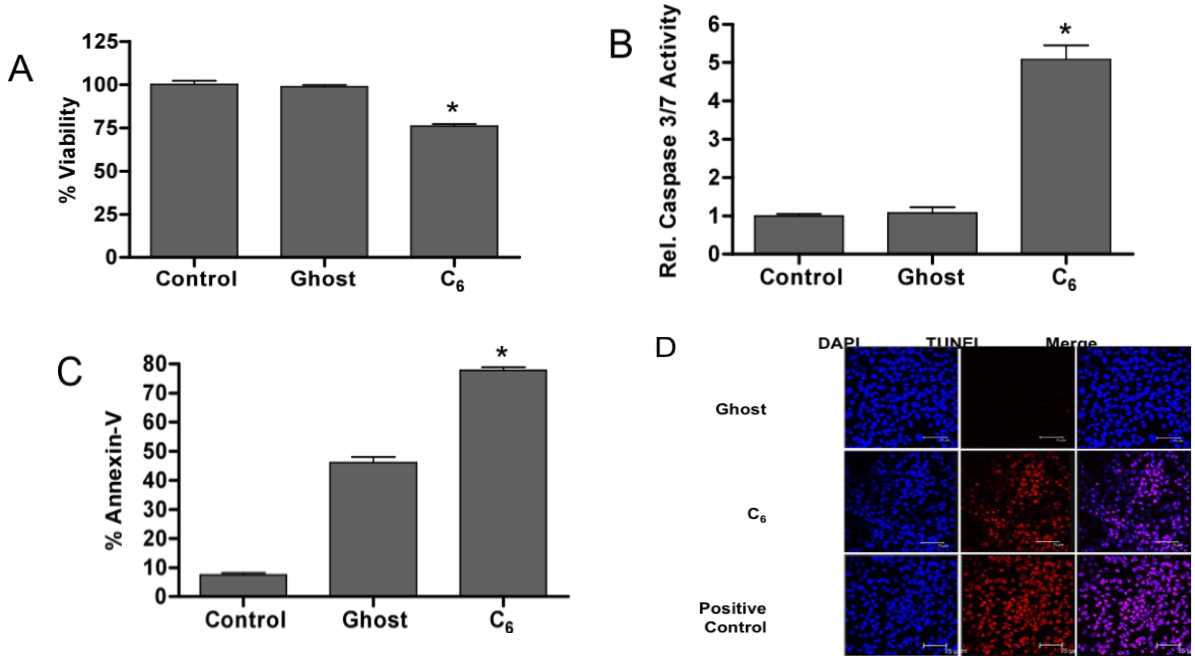

Figure 1. Nanoliposomal C6-ceramide decreases the viability of SK-HEP-1 cells in vitro by inducing apoptosis. Human SK-HEP-1 hepatocellular carcinoma cells were treated with 10 µM nanoliposomal C6-ceramide (C6), nanoliposomes without C6-ceramide (Ghost) or PBS (Control), in growth media supplemented with 1% FBS. (**A**) Cellular viability was determined by MTS viability assay after 24 h treatment. (**B**) Caspase 3/7 activity was determined by fluorometric assay after 24 h treatment. (**C**) Annexin-V staining detects the externalized phosphatidylserine from within the cells to the surface, as an indication of apoptosis. (**D**) DNA fragmentation was analyzed by TUNEL staining after 24 h treatment. The TUNEL positive control is treated with DNAase. All data represent the averages of at least three independent experiments $\bar{x} \pm$ SEM, *$p<0.05$, 1-way ANOVA. Images are representative of at least three independent experiments.

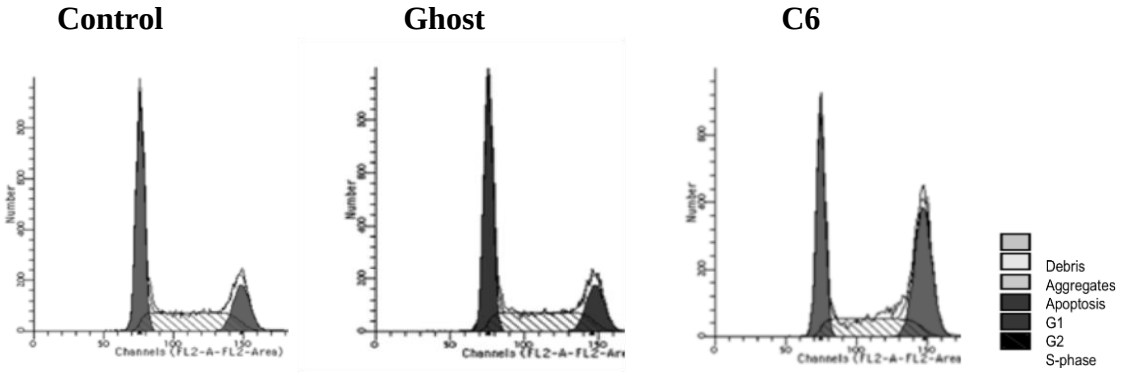

Figure 2. SK-HEP-1 cells treated with nanoliposomal C6-ceramide accumulate in the G_2 phase of the cell cycle. SK-HEP-1 cells were treated with 10 µM ghost nanoliposomes or 10 µM C6 nanoliposomal ceramide in growth media supplemented with 1% FBS for 24 h. Cells were collected, stained with propidium iodide, and analyzed by flow cytometry. DNA histograms are representative of at least three independent experiments.

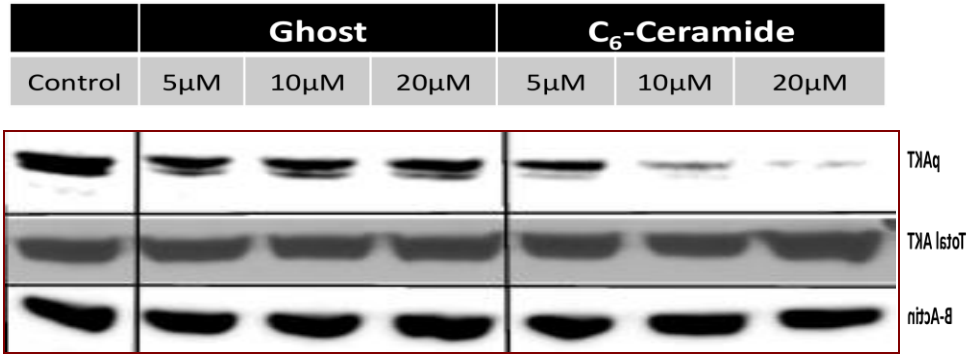

Figure 3. SK-HEP-1 cells treated with nanoliposomal C6-ceramide have diminished phosphorylation of AKT. SK-HEP-1 cells treated with 5, 10, and 20 μM nanoliposomal ceramide, but not ghost nanoliposome and control treatment, have significantly decreased pAKT levels. β-actin and total AKT served as controls for protein loading. A representative blot of n = 2 experiments.

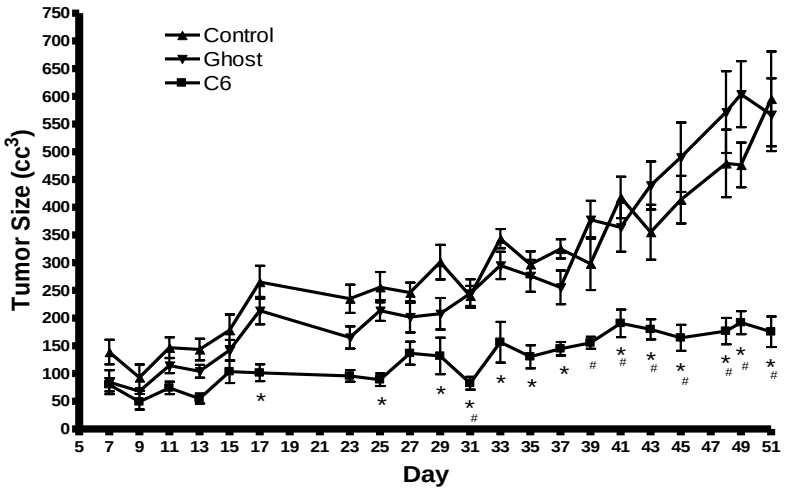

Figure 4. Nanoliposomal C6-ceramide prevents in vivo growth of SK-HEP-1 xenografted tumors in nude mice. Bilateral human SK-HEP-1 hepatocellular carcinoma xenografts were established in female athymic nude mice (5 mice per treatment group). Systemic tail vein injections of sterile isotonic NaCl, 36mg/kg of ghost nanoliposomes (Ghost), or 36 mg/kg of nanoliposomal C6-ceramide (C6) were given on alternate days, and tumor volume was determined by caliper measurement. The average tumor volume of the nanoliposomal C6-ceramide group was significantly different from the other treatment groups, as determined by 2-way ANOVA: *$p<0.05$ vs. Control, $^{\#}p<0.05$ vs. Ghost.

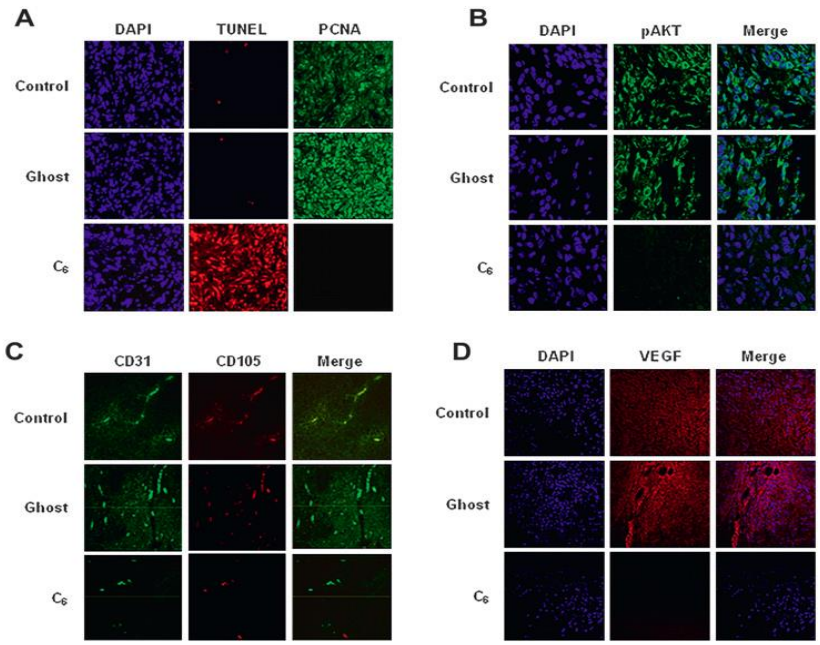

Figure 5. Systemic administration of nanoliposomal C6-ceramide induces widespread apoptosis and decreased proliferation by decreasing pAKT activity in SK-HEP-1 tumors, concomitant with a reduction in markers of angiogenesis. Formalin-fixed paraffin-embedded SKHEP-1 tumor sections were deparaffinised and stained for markers of proliferation, apoptosis and angiogenesis. Tumor sections from mice treated with phosphate buffer solution, ghost nanoliposomes or nanoliposomal C6-ceramide were treated as follows: (*A*) stained with DAPI to reveal cellular nuclei, stained by the TUNEL method to reveal apoptotic cells, stained with PCNA to reveal proliferating cells; (*B*) stained for the presence of phospho-AKT; (*C*) stained for the presence of PECAM-1/CD31 and endoglin/CD105; and (*D*) stained for the presence of vascular endothelial growth factor. All were then visualized by confocal microscopy. Photomicrographic images are representative of three separate tumor sections per treatment.

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
__X___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, 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.Nanoliposomal Ceramide prevents in vivo growth of hepatocellular carcinoma	Hephzibah Tagaram, Nicole DiVittore, Brian Barth et al	GUT	Jan 2011	☐Submitted ☐Accepted X☐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:

The growth inhibition and pro-apoptotic properties of nanoliposomal C6-ceramide (LipC6) were demonstrated in human HCC. We further demonstrate the efficacy of LipC6 in novel orthotopic murine HCC model. The model was developed by seeding the tumorigenic hepatocytes from SV40 T antigen transgenic MTD2 mice into the livers of syngeneic C57BL/6 mice. This resulted in SV40 T antigen specific tumors in the immune competent C57BL/6 liver and is a source to evaluate the efficacy of combinatorial effects of LipC6 and antigen directed immunotherapy on HCC progression. We first evaluated the effects of LipC6 on *in vitro* murine HCC for their ability to inhibit tumor growth and demonstration of proapoptotic capabilities. LipC6 demonstrated decrease in cell viability and increase in pro-apoptotic caspase 3/7 in a dose dependent manner in MTD2 cells. We demonstrate that cell permeable LipC6 along with adoptive immunotherapy facilitates the reversal of immune tolerance in a hepatocellular cancer (HCC) murine model resulting in $CD8^+$ T cell immunity. Significant amounts of transferred T cells were able to proliferate and produce IFN-γ. LipC6 treatment alone regressed the tumor burden, however LipC6 combined with adoptive immunotherapy further regressed tumors to 5 fold. The life span of the mice prolonged for 60 days with adoptive immunotherapy compared to LipC6 alone. Another manuscript is under preparation.

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:

23. 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.*

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Hephzibah Rani S. Tagaram	Research Assistant (Non-Tenure Track)
eRA COMMONS USER NAME HTAGARAM	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Osmania University, AP, India	B.Sc.	05/87	Botany, Zoology, Chemistry
Hyderabad Central University, AP, India	M.Sc.	05/89	Life Sciences Biochemistry
Osmania University, AP, India	Ph.D.	07/96	Genetics ImmunoGenetics

Variances from Ordinary Career Progression

My name that was most commonly used in India for publications was T.S. Hephzibah Rani or Rani T.H. After moving to the United States in 2003, I started using my last name, then first, second and third initials (Tagaram, H. R. S. or Tagaram, H. R.).

A. Personal Statement

I am a junior basic scientist, committed to the validation of novel targeted chemo and immuno-therapies for the treatment of Hepatocellular Cancer under the mentor ship of Dr. Staveley-O'Carroll, Assoc. Professor of Surgery, Microbiology & Immunology; Dir., Program for Liver, Pancreas & Foregut Tumors, PSCI My first internal grant as a principal investigator on ceramide nano liposome on Hepatocellular Cancer demonstrates my experience and capabilities of transition into independent faculty. My research expertise will impact the potential for the clinical basis for the better management of patients with hepatocellular cancer.

B. Positions and Honors

Positions and Employment

1990 – 1995	Role of the T-cell Fc gamma receptor and certain Biochemical and Genetic Markers in the Etiopathogenesis of Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM).
1995 – 2000	Lecturer in Genetics and Biochemistry Undergraduates, Shadan Degree College, AP, India.
2000 – 2002	Research Associate, Department of Genetics, Osmania University, Hyderabad. AP, India Isolated and Characterized the T-cell Fc gamma receptors from the diabetic patients.
2003 – 2005	Post doctoral scholar, Department of Cellular and Molecular Physiology, The Pennsylvania State University, College of Medicine, Hershey,PA Produced and Characterized gene-specific and allele-specific antibodies for Surfactant protein A.
2006 – May 2008	Post doctoral scholar, Department of Surgery, and Microbiology and Immunology, The Pennsylvania State University, College of Medicine, Hershey, PA Developing strategies for immunomodulation of cancer progression

	Elucidate mechanisms involved in the development of effective vaccines for the cure of tumor by using the Simian Virus 40 T antigen (SV40 Tag) as a model system.
2008 – present	Research Assistant (Non-Tenure Track) Department of Surgery, The Pennsylvania State University, College of Medicine, Hershey, PA Immunomodulation of Hepatocellular Cancer

Honors and Awards

1989	National Eligibility Test (NET) conducted by UGC-CSIR, India
1989 – 1991	Junior Research Fellowship (JRF), University Grants Commission, India
1991 – 1994	Senior Research Fellowship (SRF), University Grants Commission, India
4/2001 – 12/2002	Research Associate Fellowship (RA), Council of Industrial and Scientific Research (CSIR), India

Professional Memberships

1. American Association for Cancer Research (AACR)
2. American Association of Immunology (AAI)
3. American Association of Virology (AAV)

C. Selected peer-reviewed publications (in chronological order)

1. **Rani TSH**, Ishaq M, Sudhakar Rao N, Sastri P. Estimation of T-Cell Fc gamma receptor in Insulin dependent Diabetes**.** *Med Sci Res*.1992;20,777-778.
2. Shaheen S, **Rani TSH**, Ishaq M. Effect of Tinidazole in in vitro Lymphokine production. *Med Sci Res*. 1993;21:19.
3. Kalavacherla US, Ishaq M, Rao UR, Sachindranath A, **Hepsiba T**. Malonaldialdehyde as a sensitive marker of inflammation in patients with Rheumatoid Arthritis. *J Assoc Phyicians India*. 1994;42(10):775-776.
4. **Rani TSH**, Siraj M, Ishaq M, Khan GA. Analysis of ABO blood groups and age at onset in IDDM and NIDDM**.** *Int J Dia Deve Coun*. 1999;19(3):105-107.
5. Siraj M, Ishaq, Khan MGA, **Rani TH**. Significantly low Levels of Urinary Pepsinogen in Type I Diabetes. *Int J Diab Dev Coun*. 1999;19(4):165-166.
6. **Rani TS**, Siraj M, Ishaq M, Khan GA. Low Trypsin levels in type-I Diabetes: an index of low exocrine output. *J Assoc Phy Ind*. 2000;48(4):454.
7. Ishaq M, **Rani TH**, Khan N, Siraj M, Khan GA. Demonstration of pepsin activity in circulating immune complexes isolated from diabetic patients. *Int J Diab Dev Countries*. 2000;20:122-124.
8. Ishaq M, **Rani TH**, Khan GA, Khan N, Siraj M. Detection of circulating immune complexes in diabetes mellitus. *Int J Dia Dev Coun*. 2001.
9. Khan GA, Khan N, Ishaq M, SastryEP. **Rani TH**. Increased Frequency of Haptoglobin Phenotype Hp 1-1 in Diabetic Patients with Complication. *Int J Dia Dev Coun*. 2002;22:100-102.
10. **Tagaram HR**, Wang G, Umstead TM, Thomas NJ, Jane TM, Mikerov AN, Phelps DS, Floros J. Characterization of a human surfactant protein A1 (SP-A1) gene-specific antibody; SP-A1 content variation among individuals of varying age and pulmonary health. *Am J Physiol Lung Cell Mol Physiol*. May 2007;292(5):L1052-63.
11. Oberley RE, George CLS, Snyder JM. A new tool to investigate differences between human SP-A1 and SP-A2. *Am J Physiol Lung Cell Mol Physiol*. 2007;292:L1050-L1051. (Editorial comments on Reference # 10 above).
12. **Tagaram HR**, Watson AM, Lemonnier FA, Staveley-O'Carroll K, Tevethia SS, Schell TD. An SV40 VP1-derived epitope recognized by CD8+ T Cells is naturally processed and

presented by HLA-A*0201 and cross-reactive with human polyomavirus determinants. *Virology*. Jun 2008;376(1):183-190. PMCID: PMC2464359.

13. Avella DM, Kimchi ET, Donahue RN, **Tagaram HR**, McLaughlin PJ, Zagon IS, Staveley-O'Carroll KF.The opioid growth factor-opioid growth factor receptor axis regulates cell proliferation of human hepatocellular cancer. *Am J Physiol Regul Integr Comp Physiol*. 2010 Feb;298(2):R459-66. Epub 2009 Nov 18. PMCID: PMC2828179 [Available on 2011/2/1

14 **Tagaram HR**, DiVittore NA, Barth BM, Kaiser JM, Kimchi ET, Jiang Y, Isom HC, Kester M, Staveley-O'Carroll KF. Nanoliposomal ceramide prevents in vivo growth of hepatocellular carcinoma. *Gut*. 2011;60(5):695-701. Epub 2010 Dec 30.

15 Jiang Y, DiVittore NA, Kaiser JM, Shanmugavelandy SS, Fritz JL, Heakal Y, **Tagaram HR,** Cheng H, Cabot MC, Staveley-O'Carroll KF, Tran MA, Fox TE, Barth BM, Kester M. Combinatorial therapies improve the therapeutic efficacy of nanoliposomal ceramide for pancreatic cancer. *Cancer Biol Ther*. 2011 Oct 1;12(7):574-85. Epub 2011 Oct 1.PMID: 21795855

16. Avella DM, Li G, Schell TD, Liu D, Zhang SS, Lou X, Berg A, Kimchi ET, **Tagaram** HR, Yang Q, Shereef S, Garcia LS, Kester M, Isom HC, Rountree CB, Staveley-O'Carroll KF. Regression of established hepatocellular carcinoma is induced by chemoimmunotherapy in an orthotopic murine model. *Hepatology*. 2012 Jan;55(1):141-52. doi: 10.1002/hep.24652. PMID: 21898502

17. Krishnegowda G, Prakasha Gowda AS, **Tagaram** HR, Carroll KF, Irby RB, Sharma AK, Amin S. Synthesis and biological evaluation of a novel class of isatin analogs as dual inhibitors of tubulin polymerization and Akt pathway. *Bioorg Med Chem*. 2011 Oct 15;19(20):6006-14. Epub 2011 Aug 26.

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
Kester, Mark	G.Thomas Passananti Professor of Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login) Mxk38@psu.edu	

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
State University of New York at Stonybrook, NY	B.S.	05/76	Biology, Economics
State University of New York at Buffalo, NY	Ph.D.	05/82	Cell Biology

A. Positions and Honors

Positions

1982-1984 Research Associate, The University of Illinois at Chicago, Chicago, IL; Michael Barany, M.D., Ph.D., Professor of Biological Chemistry
1984-1986 Research Instructor, The University of Texas Health Science Center at San Antonio, San Antonio, TX; Donald Hanahan, Ph.D., Professor of Biochemistry
1986-1995 Assistant Professor, Medicine/Physiology, Case Western Reserve University, Cleveland, OH
1995-1997 Associate Professor, Medicine/Physiology, Case Western Reserve University, Cleveland, OH
1997-2001 Associate Professor, Dept. Pharmacology, Penn State Univ. College of Medicine, Hershey, PA
2001-2006 Professor, Department of Pharmacology, Penn State Univ. College of Medicine, Hershey, PA
2002-2003 Interim Chair, Dept. Pharmacology, Penn State University College of Medicine, Hershey, PA
2005-pres. Professor, Department of Cellular and Molecular Physiology, Penn State University College of Medicine, Hershey, PA
2006-2007 Distinguished Professor of Pharmacology, Penn State University College of Medicine, Hershey, PA
2007-pres. G.Thomas Passananti Professor of Pharmacology, Penn State University College of Medicine

Honors

1972-1976 Regents Scholarship – SUNY Stonybrook
1976 Economics Honor Society, SUNY Stonybrook
1978 Graduate Research Access Development Grant – SUNY Buffalo
1981 University Student Teaching Award – SUNY Buffalo
1982-1984 Muscular Dystrophy Association Post-doctoral Fellowship
1984 Midwest Medical Research Forum, Award Winner, University of Illinois at Chicago
1985-1986 American Heart Association, Texas Affiliate, A.N. Rocco Fellowship
1988-1989 Kidney Foundation of Ohio, John Lowey Award
1990-1995 National Institutes of Health, FIRST Award
1993 American Society of Nephrology, Travel Award
1994 Kidney Foundation of Ohio, Medical Advisory Board

1996	Award of Tenure, The Pennsylvania State University
2000	National Institutes of Health Study Section, Site Visit, PO2 DJ 958349-07, Dec. 2000
2000-2003	National Institutes of Health Study Section, Physiological Chemistry, Ad Hoc Member
2001	National Institutes of Health Grant Review, Ad hoc member, COBRE Awards
2001	Award of Teaching Excellence – Presented by Class of 2004, Penn State College of Medicine
2002-pres.	Editorial Board, Archives of Biochemistry and Biophysics
2002	NIH National Cancer Institute, Subcommittee D, Reporter
2004-2006	Graduate Student Association Award of Teaching Excellence
2004-2008	Graduate Student Teaching Award, Penn State University
2003	Guest Editor, Archives of Biochem. & Biophy. (The Next Generation of Sphingolipid Strategies)
2003	NIH Study Section Site Visit, P01 CA106494-01
2005-pres.	NIH Study Section, Biochemistry and Biophysics of Membranes, Ad Hoc Member
2006	Cancer Nanobiology Think Tank, CCR Nanobiology Program, NCI Frederick, NIH
2007	Mini Symposium Organizer, Charleston Ceramide Conference, Monterey, CA
2007	NIH Study Section, NCI subcommittee F (T32 and K99/R00)
2007	NIH National Cancer Institute, NCI-F Training Review Committee, Ad hoc member
2008	Keynote Speaker, International Conference on Nanotechnology, Abu Dhabi, United Arab Emirates
2009	Invited Speaker, Gastro 2009, World Congress of Gastroenterology, London, UK
2009	National Institutes of Health Study Section, RC1 applications (ZRG1 OTC K(58)R), Ad hoc Member
2010	International Advisory Council, International Ceramide Conference
2010	NCI Cancer Nanotechnology Training (R25) and Career Development Award (K99/R00) Applications Special Emphasis Panel ZCA1 RTRB-2 (M1)
2010	Invited Speaker, Third Annual Unither Nanomedical and Telemedical Technology Conference, Quebec, Canada
2010	National Institutes of Health Study Section Special Emphasis Panel/Scientific Review Group 2010/08 ZRG1 CB-B (55) R

B. Selected peer-reviewed publications (in chronological order).

1. Tran MA, Smith CD, Kester M, Robertson GP. Combining nanoliposomal ceramide with sorafenib synergistically inhibits melanoma and breast cancer cell survival to decrease tumor development. *Clin Cancer Res*. 2008;14(11):3571-3581.
2. Heakal Y, Kester M. Nanoliposomal short-chain ceramide inhibits agonist-dependent translocation of neurotensin receptor 1 to structured membrane microdomains in breast cancer cells. *Mol Cancer Res*. 2009;7(5):724-734. Epub 2009 May 12. PMCID: PMC2732571
3. Kline CL, Shanmugavelandy SS, Kester M, Irby RB. Delivery of PAR-4 plasmid in vivo via nanoliposomes sensitizes colon tumor cells subcutaneously implanted into nude mice to 5-FU. *Cancer Biol Ther*. 2009;8(19):1831-1837.
4. Matters GL, Harms JF, McGovern CO, Jayakumar C, Crepin K, Smith ZP, Nelson MC, Stock H, Fenn CW, Kaiser J, Kester M, Smith JP. Growth of human pancreatic cancer is inhibited by down-regulation of gastrin gene expression. *Pancreas*. 2009;38(5):e151-61. PMCID: PMC2704379

5. Salli U, Fox TE, Carkaci-Salli N, Sharma A, Robertson GP, Kester M, Vrana KE. Propagation of undifferentiated human embryonic stem cells with nano-liposomal ceramide. *Stem Cells Dev*. 2009;18(1):55-65.
6. Adair JH, Parette MP, Altinoglu EI, Kester M. Nanoparticulate alternatives for drug delivery. *ACS Nano*. 2010;4(9):4967-4970.
7. Barth BM, Gustafson SJ, Young MM, Shanmugavelandy SS, Kaiser JM, Cabot MC, Kester M, Kuhn TB. Inhibition of NADPH oxidase by glucosylceramide confers chemoresistance. *Cancer Biol Ther*. 2010;10(11):1126-1136. Epub 2010 Dec 1. PMCID: PMC3047104 [Available on 2011/12/1]
8. Barth BM, Sharma R, Altinoglu EI, Morgan TT, Shanmugavelandy SS, Kaiser JM, McGovern C, Matters GL, Smith JP, Kester M, Adair JH. Bioconjugation of calcium phosphosilicate composite nanoparticles for selective targeting of human breast and pancreatic cancers in vivo. *ACS Nano.* 2010;4(3):1279-1287. PMCID: PMC2894697
9. Chapman JV, Gouaze-Andersson V, Messner MC, Flowers M, Karimi R, Kester M, Barth BM, Liu X, Liu YY, Giuliano AE, Cabot MC. Metabolism of short-chain ceramide by human cancer cells--implications for therapeutic approaches. *Biochem Pharmacol*. 2010;80(3):308-315. Epub 2010 Apr 10. PMCID: PMC2883648
10. Liu X, Ryland L, Yang J, Liao A, Aliaga C, Watts R, Tan SF, Kaiser J, Shanmugavelandy SS, Rogers A, Loughran K, Petersen B, Yuen J, Meng F, Baab KT, Jarbadan NR, Broeg K, Zhang R, Liao J, Sayers TJ, Kester M, Loughran TP, Jr. Targeting of survivin by nanoliposomal ceramide induces complete remission in a rat model of NK-LGL leukemia. *Blood*. 2010;116(20):4192-4201. Epub 2010 Jul 29. PMCID: PMC2993625 [Available on 2011/11/18]
11. Fox TE, Bewley MC, Unrath KA, Pedersen MM, Anderson RE, Jung DY, Jefferson LS, Kim JK, Bronson SK, Flanagan JM, Kester M. Circulating sphingolipid biomarkers in models of type 1 diabetes. *J Lipid Res*. Mar 2011;52(3):509-517. Epub 2010 Nov 10. PMCID: PMC3035687 [Available on 2012/3/1]
12. Takahashi Y, Meyerkord CL, Hori T, Runkle K, Fox TE, Kester M, Loughran TP, Wang HG. Bif-1 regulates Atg9 trafficking by mediating the fission of Golgi membranes during autophagy. *Autophagy*. 2011;7(1):61-73. Epub 2011 Jan 1. PMCID: PMC3039731
13. Ryland LK, Fox TE, Liu X, Loughran TP, Kester M. Dysregulation of sphingolipid metabolism in cancer. *Cancer Biol Ther*. Jan 15 2011;11(2):138-149. Epub 2011 Jan 15.
14. Fox TE, Young MM, Pedersen MM, Giambuzzi-Tussey S, Kester M, Gardner TW. Insulin signaling in retinal neurons is regulated within cholesterol-enriched membrane microdomains. *Am J Physiol Endocrinol Metab*. Mar 2011;300(3):E600-609. Epub 2011 Jan 4.
15. Tagaram HR, Divittore NA, Barth BM, Kaiser JM, Avella D, Kimchi ET, Jiang Y, Isom HC, Kester M, Staveley-O'Carroll KF. Nanoliposomal ceramide prevents in vivo growth of hepatocellular carcinoma. *Gut*. May 2011;60(5):695-701. Epub 2010 Dec 30.

C. Research Support

<u>Ongoing Research Support</u>

5 R01 CA133525-04 Loughran (PI) 3/1/2008 - 2/28/2013
NIH/NCI
Title: Targeted Therapeutics of LGL Leukemia Utilizing Ceramide Nanoliposomes
Project goal: The major goal of the project is to utilize nanotechnology to deliver hydrophobic therapeutics for treatment of leukemia.
Role: Co-Investigator

5 R01 EY018336-03 Kester (PI) 8/1/2009 - 7/31/2013
NIH/NEI

Title: The Role of Glycosphingolipids in Diabetic Retinopathy
Project goal: The overall objective of the proposed project is to understand the molecular basis for vision impairment in diabetic retinopathy. The specific objective is to investigate the role of ceramide metabolism and glycosphingolipid-enriched lipid microdomains (rafts) in insulin signaling and cell survival in retinal neurons.
Role: PI

2 R01 CA098472-08 Loughran (PI) 6/1/2011 - 5/31/2016
NIH/NCI
Title: Survival Mechanisms of Leukemic NK Cells
Project goal: The long-term goal of this project is to develop better therapeutics for NK-LGL leukemia which is an incurable illness.
Role: Co-Investigator

Completed Research Support

No number Kester and Claxton (Co-PIs) 04/20/2009 - 06/30/2010
HMC Dean's Feasibility Grant (PA-DOH)
Title: Development of Nanoliposomal Therapeutics for Leukemia
Project goal: This proposal seeks to test the anti-cancer potential of nanoliposomes containing ceramide, siRNA molecules, or both in mouse cancer cells as well as in a mouse model of myeloid leukemia.
Role: PI

1R43CA141849-01 Parette (PI) 09/28/2009 - 09/27/2010
NIH/NCI
Title: Targeting NanoJacketed Doxorubicin to Tumor Sites for Improved Treatment of Breast Cancer
Project goal: Using the current Doxorubicin NanoJacket prototype, the goals of this project are to 1) identify antibodies that target human breast cancer cells, 2) attach Fab fragments of those antibodies to Doxorubicin NanoJackets and 3) characterize the resulting targeted NanoJacket prototype in terms of colloidal stability and ability to target human breast cancer cells.
Role: PI, subaward

#4100045897 Kester (PI) 01/01/2009 - 12/31/2010
PA Department of Health
Title: The Role of Glycosphingolipids in Diabetic Retinopathy
Project goal: The role and consequences of decreased caveolin content in models of diabetic retinopathy is investigated.
Role: PI

No number Kester/Loughran (PI) 1/1/2011 - 6/30/2012
PA DOH/Planning Grants for Large Research Programs
Title: Sphingolipid-based Therapeutics for AML
Project goal: The long term goal is to develop new therapies for the treatment of AML. These funds will support three specific aims that provide additional/ new/ critical data that are essential for submission of an integrated interdisciplinary NIH P01 application in 2011 that will investigate the role of dysfunctional sphingolipid metabolism in acute myeloid leukemia. The funds will support three team projects that will benefit each of the eventual P01 projects.
Role: Co-P.I.

7-09-BS-98, Yr. 3 Kester (PI) 7/1/2009 - 6/30/2012
American Diabetes Association
Title: Therapeutic modulation of glycosphingolipid metabolism in a model of Type 1 Diabetes
Project goal: The therapeutic role of pharmacologically manipulating glucosylceramide content is investigated in models of diabetic retinopathy.
Role: PI

5 R01 HL076789-05 Kester (PI) 8/1/2006 - 5/31/2012
NIH/NHLBI
Title: PKC zeta as a Target for Ceramide
Project goal: The goals of this project are to identify ceramide-enriched lipid rafts as the site at which PKC zeta is phosphorylated and optimally activated by upstream kinases, as well as to characterize and validate ceramide-binding domains or clefts on PKC zeta. These studies will elucidate the biophysical and biochemical mechanisms by which inflammatory cytokine receptor-induced ceramide formation limits cellular proliferation in models of inflammatory vascular diseases.
Role: PI

No number Kester/Loughran (PI) 1/1/2011 - 6/30/2012
PA DOH/Planning Grants for Large Research Programs
Title: Sphingolipid-based Therapeutics for AML
Project goal: The long term goal is to develop new therapies for the treatment of AML. These funds will support three specific aims that provide additional/ new/ critical data that are essential for submission of an integrated interdisciplinary NIH P01 application in 2011 that will investigate the role of dysfunctional sphingolipid metabolism in acute myeloid leukemia. The funds will support three team projects that will benefit each of the eventual P01 projects.
Role: Co-P.I.

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
Kevin F. Staveley-O'Carroll, MD, PhD	Professor of Surgery, Medicine, Microbiology and Immunology
eRA COMMONS USER NAME (credential, e.g., agency login) KFSOC1	

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 Notre Dame, Notre Dame, IN	B.S.	06/86	Chemistry
University of Oklahoma College of Medicine	M.D.	06/90	Medicine
The Johns Hopkins University School of Medicine Baltimore, Maryland	Ph.D.	06/00	Pharmacology and Molecular Biology
The Johns Hopkins Hospital, Baltimore, Maryland	Resident	6/90-6/98	Surgery
The Johns Hopkins Hospital, Baltimore, Maryland	Research Fellow	06/92-06/96	Oncology, Immunology, Pharmacology
Royal College of Surgeons, Dublin, Ireland	Registrar	01/98-06/98	Thoracic Surgery
The Johns Hopkins Hospital, Baltimore, Maryland	Fellow	06/98-06/99	Surgical Oncology

A. Positions and Honors

1999 - 2000	Assistant Chief of Staff, Instructor, Fellow in Surgical Oncology,The Johns Hopkins Hospital, Baltimore, Maryland
2000 - 2006	Assistant Professor of Surgery, Department of Surgery, Pennsylvania State University School of Medicine, Hershey, PA
2006-2011	Associate Professor with tenure, Departments of Surgery, Microbiology & Immunology; Director, Program for Liver, Pancreas & Foregut Tumors, Penn State Cancer Institute, Pennsylvania State University School of Medicine, Hershey, PA
2011 - present	Professor of Surgery, Medicine, Microbiology & Immunology; Director, Program for Liver, Pancreas & Foregut Tumors, Penn State Cancer Institute, Pennsylvania State University School of Medicine, Hershey, PA
2009 - present	Chief, Section of Surgical Oncology, Penn State University College of Medicine, Hershey, PA

Honors

1988	Alpha Omega Alpha, The University of Oklahoma, Oklahoma
1993-1995	George D. Zuidema Research Award, The Johns Hopkins University, Baltimore, Maryland
2001	Franklin Martin, MD, FACS, Memorial Faculty Research Award, American College of Surgeons
2004	Mentored Clinical Scientist Award
2007	Pfizer Visiting Professorship in Oncology, Albany Medical College
2009	Gardner Smith Memorial Lecture, Johns Hopkins Medical Institutions

2009-2010 President, Association for Academic Surgery
2010 Visiting Professorship, The University of Auckland, Auckland, New Zealand

B. Selected Peer-reviewed Publications (Selected from 55)

Most relevant to the current application

1. **Staveley-O'Carroll K**, Sotomayor E, Montgomery J, Borello I, Hwang L, Fein S, Pardoll D, Levitsky H. Induction of antigen-specific T cell anergy: an early event in the course of tumor progression. *Proc Natl Acad Sci U S A*. Feb 3 1998;95(3):1178-1183. PMCID: PMC18712
2. Sotomayor E, Borrello I, Rattis F, Cuenca A, Abrams J, **Staveley-O'Carroll K**, Levitsky H. Cross-presentation of tumor antigen by bone marrow-derived antigen-presenting cells is the dominant mechanism in the induction of T-cell tolerance during B-cell lymphoma progression. *Blood.* Aug 15 2001;98(4):1070-1077.
3. **Staveley-O'Carroll K**, Schell TD, Jimenez M, Mylin LM, Tevethia MJ, Schoenberger SP, Tevethia SS. In vivo ligation of CD40 enhances priming against the endogenous tumor antigen and promotes CD8+ T cell effector function in SV40 T antigen transgenic mice. *J Immunol*. Jul 15 2003;171(2):697-707.
4. Fulchiero Jr G, Salvaggio H, Drabick J, **Staveley-O'Carroll K**, Billingsley E, Marks J, Helm K. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *J Am Acad Dermatol*. May 2007;56(5 Suppl):S65-67.
5. Tagaram HR, Watson A, Lemonnier F, **Staveley-O'Carroll K**, Tevethia S, Schell T. An SV40 VP1-derived epitope recognized by CD8+ T cells is naturally processed and presented by HLA-A*0201 and cross-reactive with human polyomavirus determinants. *Virology*. Jun 20 2008;376(1):183-190. Epub 2008 Apr 10. PMCID: PMC2464359
6. Ryan C, **Staveley-O'Carroll K**, Schell T. Combined anti-CD40 conditioning and well-timed immunization prolongs CD8+ T cell accumulation and control of established brain tumors. *J Immunother.* Nov-Dec 2008;31 (9):906-920.
7. Gusani NJ, Jiang Y, Kimchi ET, **Staveley-O'Carroll KF**, Cheng H, Ajani JA. New pharmacological developments in the treatment of hepatocellular cancer. Drugs. 2009;69(18):2533-2540. doi: 10.2165/11530870-000000000-00000
8. Avella DM, Kimchi ET, Donahue RN, Tagaram HR, McLaughlin PJ, Zagon IS, **Staveley-O'Carroll KF**. The opioid growth factor - opioid growth factor receptor axis regulates cell proliferation of human hepatocellular cancer. *Am J Physiol Regul Integr Comp Physiol*. Feb 2010;298(2):R459-466. Epub 2009 Nov 18. PMCID: PMC2828179
9. Tagaram H, DiVottore N, Barth B, Kaiser J, Kimchi E, Jiang Y, Isom H, Kester H, **Staveley-O'Carroll K**. Nanoliposomal ceramide prevents *in vivo* growth of hepatocellular carcinoma. *Gut*. May 2010;60(5):695-701. Epub 2010 Dec 30.
10. Avella DM, Li G, Schell TD, Liu D, Shao-Min Zhang S, Lou X, Berg A, Kimchi ET, Tagaram HR, Yang Q, Shereef S, Garcia LS, Kester M, Isom HC, Bart Rountree C, **Staveley-O'Carroll KF**. Regression of established hepatocellular carcinoma is induced by chemo- immunotherapy in an orthotopic murine model. *Hepatology*. 2011 Sep 2. doi: 10.1002/hep.24652. [Epub ahead of print].
11. Krishnegowda G, Prakasha Gowda AS, Tagaram HR, **Carroll KF**, Irby RB, Sharma AK, Amin S. Synthesis and biological evaluation of a novel class of isatin analogs as dual inhibitors of tubulin polymerization and Akt pathway. Bioorg Med Chem. Oct 15 2011;19(20):6006-6014. Epub 2011 Aug 26.

Additional recent publications of importance to the field

12. Nikfarjam M, Shereef S, Kimchi ET, Gusani NJ, Jiang Y, Avella DM, Mahraj RP, **Staveley-O'Carroll KF**. Survival outcomes of patients with colorectal liver metastases

following hepatic resection or ablation in the era of effective chemotherapy. *Ann Surg Oncol*. Jul 2009;16(7):1860-1867. Epub 2008 Nov 27.

13. Kimchi ET, Nikfarjam M, Gusani NJ, Avella DM, **Staveley-O'Carroll KF**. Combined pancreaticoduodenectomy and extended right hemicolectomy: outcomes and indications. *HPB (Oxford).* Nov 2009;11(7):559-564. PMCID: PMC2785950
14. Nikfarjam M, Kimchi ET, Gusani N, **Staveley-O'Carroll KF**. Complete surgical resection of giant mucinous hepatic cystadenomas. *Am Surgeon.* May 2010;76(5):E17-19.
15. Kaifi JT, Gusani NJ, Jiang Y, Mackley HB, Dye CE, Mathew A, Kimchi ET, Reed MF, **Staveley- O'Carroll KF.** Multidisciplinary management of early and locally advanced esophageal cancer. *J Clin Gastroenterol.* 2011 May-Jun;45(5):391-399.

C. RESEARCH SUPPORT

Ongoing Research Support

CST 1571BUS282 Staveley-O'Carroll (PI) 07/14/2009 – 06/30/2022
NovartisPharmaceuticals Corporation
Title: A Phase II, Non-randomized, open-label multicenter study of long-term (5 year) adjuvant imatinib mesylate (Gleevac) in patients following complete resection of high risk primary gastrointestinal stromal tumor (GIST)
Project goal: The clinical trial shall investigate the safety, efficacy and/or related properties of one or more active ingredients (each a "Study Drug"), alone or in comparison to a placebo and/or one or more other active ingredients (each a "Comparator Drug").
Role: PI

Completed Research Support

Clinical & Translational Science Award (CTSA) Staveley-O'Carroll (PI) 07/01/08 – 6/30/2011
Penn State College of Medicine, Hershey, PA
Title: Dissecting the Interaction between Radiofrequency Ablation and Tumor Antigen-specific Immune Response In Hepatocellular Cancer: A Murine Model and a Human Protocol
Project goal: Specific HCC epitope responses will be analyzed in the peripheral blood after radiofrequency ablation from hepatocellular cancer patients.
Role: PI

5 K08 CA100094-01A1 Staveley-O'Carroll (PI) 07/01/2004 - 06/30/2010
NIH Mentored Clinical Scientist Award
Title: Tumor Antigen Presentation in Mice Developing Cancer
Project goal: Overcoming tumor antigen specific immune tolerance in murine model developing spontaneous cancer.
Role: PI

Clinical & Translational Rsch Feasibility Grant Staveley-O'Carroll (PI) 1/1/2008-12/31/2010
Penn State College of Medicine, Hershey, PA
Title: Tumor Antigen-Specific CD8+ T Cell Immune Responses Following Radiofrequency Thermal Ablation In Hepatocellular Cancer Patients
Project goal: To determine the antigen specific $CD8^+$ T cell immune responses in the patients who are undergoing radiofrequency ablation.
Role: PI

No number Kester & Staveley-O'Carroll (PI's) 11/01/2011 – 10/31/2012
V Foundation
Title: Novel Therapeutic Approaches to Gastrointestinal Malignancies
Project goal: to engineer non-cationic immune-targeted nanoliposomes that can deliver anti-fibrotic, anti-viral or anti-mitogenic agents systemically.
Role: Multiple PI

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
Isom, Harriet C.	Distinguished Professor
eRA COMMONS USER NAME (credential, e.g., agency login) harrietisom	

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
Bryn Mawr College, Bryn Mawr, PA	B.A.	06/69	Biology
University of Illinois, Urbana, IL	M.S.	06/71	Microbiology
University of Illinois, Urbana, IL	Ph.D.	12/73	Microbiology

A. Positions and Honors

1973 - 1974 National Institutes of Health Postdoctoral Trainee, Dept. of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA
1974 - 1976 Pennsylvania Plan Scholar, Dept. of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA
1976 - 1981 Assistant Professor, Dept. of Microbiology, Penn State College of Medicine, Hershey, PA
1981 - 1987 Associate Professor, Dept. of Microbiology, Penn State College of Medicine, Hershey, PA
1987 - 2000 Professor, Dept. of Microbiology & Immunology, Penn State College of Medicine, Hershey, PA
1989 - 1992 Member, Pathology B Study Section
1996 - 2000 Member, Pathology B Study Section
1999 - 2000 Chair, Pathology B Study Section
2004 - 2008 Member, Hepatobiliary Pathophysiology (HBPP) Study Section
1993- Ad hoc Member, Pathology B and other NIH Study Sections
1989 - 1990 Vice Chair, Dept. of Microbiology and Immunology, Penn State's College of Medicine, Hershey, PA
1991 - 1992 Wellcome Visiting Professor in the Basic Medical Sciences
1992- Professor, Dept. of Pathology, Penn State's College of Medicine, Hershey, PA
1993 - 1996 Member, American Cancer Society Advisory Committee on Carcinogenesis and Nutrition
1999 - 2001 Assistant Director of M.D./Ph.D. Program, Penn State's College of Medicine, Hershey, PA
2000- Distinguished Professor, Dept. of Microbiology, Penn State's College of Medicine,
Hershey, PA
2001 - 2004 Assistant Dean and Director, M.D/Ph.D. Program, Penn State College of Medicine, Hershey, PA
2001 - 2003 Research Director for the Penn State Cancer Institute
2003- Associate Director for Program Development, Penn State Cancer Institute

2003- Program Leader, Viral Oncogenesis and Host Defense Program, Penn State Cancer Institute

B. Selected Peer-reviewed Publications (Selected from 76 peer-reviewed publications)

Most relevant to the current application

1. Delaney WE, IV, Isom HC. Hepatitis B virus replication in human HepG2 cells mediated by hepatitis B virus recombinant baculovirus. *Hepatology*. 1998;28(4):1134-1146.
2. Delaney WE, Miller TG, Isom HC. Use of the hepatitis B virus recombinant baculovirus-HepG2 system to study the effects of (1)-β-2',3'-dideoxy-3'-thiacytidine on replication of hepatitis B virus and accumulation of covalently closed circular DNA. *Antimicrob Agents Chemother*. 1999;43(8):2017-2026. PMCID: PMC89407
3. Abdelhamed AM, Kelley CM, Miller TG, Furman PA, Isom HC. Rebound of hepatitis B virus replication in HepG2 cells after cessation of antiviral treatment. *J Virol*. 2002;76(16):8148-8160. PMCID: PMC155168
4. Abdelhamed AM, Kelley CM, Miller TG, Furman PA, Cable EE, Isom HC. Comparison of anti-hepatitis B virus activities of lamivudine and clevudine by a quantitative assay. *Antimicrob Agents Chemo*. 2003;47(1):324-336. PMCID: PMC148955
5. Chen RY, Edwards R, Shaw T, Colledge D, Delaney WE 4th, Isom H, Bowden S, Desmond P, Locarnini SA. Effect of the G1896A precore mutation on drug sensitivity and replication yield of lamivudine-resistant HBV in vitro. *Hepatology*. 2003;37(1):27-35.
6. Bilello JP, Cable EE, Myers RL, Isom HC. Role of paracellular junction complexes in baculovirus-mediated gene transfer to nondividing rat hepatocytes. *Gene Ther*. 2003;10(9):733-749.
7. Bilello JP, Cable EE, Isom HC. Expression of E-cadherin and other paracellular junction genes is decreased in iron-loaded hepatocytes. *Am J Pathol*. 2003;162(4):1323-1338. PMID: PMC1851226
8. Stoehr SA, Isom HC. Gap junction mediated intercellular communication in a long-term primary mouse hepatocyte culture system. *Hepatology*. 2003;38(5):1125-1135.
9. Heipertz Jr RA, Miller TG, Kelley CM, Delaney IV WE, Locarnini SA, Isom HC. *In Vitro* study of the effects of precore and lamivudine resistant mutations on HBV replication. *J Virol*. 2007;81(7):3068-3076. Epub 2007 Jan 10. PMCID: PMC1866076
10. Starkey JL, Chiari EF, Isom HC. Hepatitis B virus (HBV)-specific short hairpin RNA is capable of reducing the formation of HBV covalently closed circular (CCC) DNA but has no effect on established CCC DNA in vitro. *J Gen Virol*. 2009;90(Pt 1):115-126. PMCID: PMC2659548
11. Heipertz RA, Starkey JL, Miller TG, Hu J, Isom HC. Trans-complementation of HBV rtM204I mutant replication by HBV wild-type polymerase. *Virology*. 2009;388:57-67. Epub 2009 Apr 19.
12. Moon MS, Richie JP, Isom HC. Iron potentiates acetaminophen-induced oxidative stress and mitochondrial dysfunction in cultured mouse hepatocytes. *Toxicol Sci.* 2010;118(1):119-127. Epub 2010 Jul 28. PMCID: PMC20667997 [Available on 2011/11/1]
13. Tagaram HR, DiVittore NA, Barth BM, Kaiser JM, Avella D, Kimchi ET, Jiang Y, Isom HC, Kester M, Staveley-O'Carroll KF. Nanoliposomal ceramide prevents in vivo growth of hepatocellular carcinoma. *Gut*. 2011;60(5):695-701. Epub 2010 Dec 30.

14. Avella DM, Li G, Schell TD, Liu D, Shao-Min Zhang S, Lou X, Berg A, Kimchi ET, Tagaram HR, Yang Q, Shereef S, Garcia LS, Kester M, Isom HC, Bart Rountree C, Staveley-O'Carroll KF. Regression of established hepatocellular carcinoma is induced by chemo-immunotherapy in an orthotopic murine model. *Hepatology.* 2011 Sep 2. doi: 10.1002/hep.24652. [Epub ahead of print]
15. Moon MS, Kang BH, Krzeminski J, Amin S, Aliaga C, Zhu J, McDevitt EI, Kocher S, Richie JP, Isom HC.
3,5,5-Trimethyl-hexanoyl-ferrocene diet protects mice from moderate transient acetaminophen-induced hepatotoxicity. *Toxicol Sci.* 2011 Sep 9. [Epub ahead of print]

C. Research Support

Ongoing Research Support

3 R01 DK073897-03 Isom (PI) 07/25/2008 - 06/30/2013
Title: Iron-Induced Changes in Liver that Predispose to Malignancy NCE
Project goal: Our laboratory has generated a novel in vivo mouse model of chronic hepatic iron overload of liver using 3,5,5-trimethyl-hexanoyl ferrocene (TMHF) as an iron donor. The goals of this grant are (1) to determine the effect of hepatic iron overload on the antioxidant defense system in liver, (2) to evaluate the effects of iron overload on the cadherin-catenin complex, (3) to determine whether hepatic iron overload can promote hepatocarcinogenesis, and (4) to evaluate the effects of chelation and antioxidant therapy alone and in combination on iron induced molecular and cellular changes in liver.
Role: PI

5 R01 CA140369-02 Peters (PI) 07/01/2010 - 06/30/2015
NIH
Title: Modulation of Liver Cancer by PPARbeta/delta
Project goal: The goal of this grant is to determine the mechanisms by which PPARb/d modulates liver cancer and whether epigenetic modulation of NF-kB by PPARb/d in Kupffer cells is central to these mechanisms.
Role: Co-Investigator

Completed Research Support

3 R01 DK073897-02S1 Isom (PI) 09/21/2009 - 06/30/2011
NIH-ARRA Administrative Supplement
Title: Iron-Induced Changes in Liver That Predispose to Malignancy
Project goal: This grant is to fund a summer research experience for students and science educators under the Recovery Act Funds for Administration Supplements
Role: PI

3 R01 DK073897-01A2S1 Isom (PI) 06/15/2009 - 08/20/2011
NIH ARRA Administrative Supplement
Title: Iron-Induced Changes in Liver the Predispose to Malignancy
Project goal: This grant is to fund a summer research experience for students and science educators under the Recovery Act Funds for Administration Supplements
Role: PI

5 R01 CA023931-30 Isom (PI) 02/15/2004 - 01/31/2010
Title: Analyzing Hepatitis B Virus Pathogenesis
NCE

Project goal: Our laboratory has developed a novel transient mechanism for studying HBV gene expression and replication using recombinant wild type and mutant HBV baculoviruses to deliver the HBV genome to human hepatic HepG2 cells. This grant focuses on understanding the life cycle of drug resistant and mutant HBVs using the HBV recombinant baculovirus system. In order to achieve these goals the mechanism of transcription from CCC DNA will be studied both from wild type HBV and mutant HBVs
Role: PI

No Number Assigned Isom (PI) 05/01/2009 - 04/30/2010
Research Bridge Grant
Title: Analyzing Hepatitis B Virus Pathogenesis
Project goal: Develop an *in vitro* system for chronic HPV replication.
Role: PI