COVER SHEET FOR GRANT PROPOSALS

State Board of Education

SBOE PROPOSAL NUMBER: (to be assigned by SBOE)	AMOUNT REQUESTED:$50,000
TITLE OF PROPOSED PROJECT: Development of a novel drug to treat pancreatic cancer	
SPECIFIC PROJECT FOCUS: To determine the efficacy of newly synthesized drug in vitro and in vivo.	
PROJECT START DATE: March 1, 2011	PROJECT END DATE: June 30, 2012
NAME OF INSTITUTION: Idaho State University	DEPARTMENT: Biomedical and Pharmaceutical Sciences
ADDRESS: 921 S 8th Avenue, College of Pharmacy, Box 8334, Idaho State University, Pocatello, Idaho 83209-8334.	
	E-MAIL ADDRESS: abhushan@pharmacy.isu.edu / PI PHONE NUMBER: 208-282-4408

	NAME:	TITLE:	SIGNATURE:
PROJECT DIRECTOR	Alok Bhushan	Professor, Department of Biomedical and Pharmaceutical Sciences	
CO-PRINCIPAL INVESTIGATOR	Byron Bennett	Assistant Professor, Department of Chemistry	
CO-PRINCIPAL INVESTIGATOR	James C K Lai	Professor, Department of Biomedical and Pharmaceutical Sciences	
CO-PRINCIPAL INVESTIGATOR	Vikas Bhardwaj	Graduate student, , Department of Biomedical and Pharmaceutical Sciences	

	NAME:	SIGNATURE:
Authorized Organizational Representative	Dianne K. Horrocks	

1. Executive Summary: Pancreatic cancer is one of the most aggressive forms of cancers with a low mean survival of 4-5 % (1). Currently few chemotherapeutic drugs are found to be effective in reducing the cancer load and increasing the survival of pancreatic cancer patients. For now, gemcitabine and 5-fluorouracil are chemotherapeutic drugs used for treating pancreatic cancer; however, their treatment benefits are limited due to drug resistance and their toxicity on normal cells (2).

In this proposal, we aim at determining the efficacy of a novel agent (ABBB1) which has shown promising results in our studies. The agent is effective in reducing the survival of both drug-sensitive and resistant pancreatic cancer cell lines. Our *in vivo* studies using mouse model show that this analog is considerably less toxic compared to conventional drug used in pancreatic cancer chemotherapy. In this proposal, we aim at analyzing the anti-tumor activity of this agent in nude mice model and compare it with other more conventional chemotherapeutic agents used in pancreatic cancer chemotherapy. We will also determine the effect of this agent on cancer cell signaling and understand the mechanism(s) by which it overcomes drug resistance. After accomplishing the goals of the proposed studies, we intend on patenting and commercializing this agent.

2. "Gap" Project Objective and Total Amount Requested – $50,000

3. Name of Idaho public institution: Idaho State University

4. Name of faculty member directing project: Alok Bhushan

5. Description of how resource commitments reflect the priorities of the home institution(s) Expanding research and developing projects to enhance:

Idaho State University is committed to enhance research in the area of biomedical and pharmaceutical sciences. This project matches the goals of the university. Our

university is also interested in translational research. This project will help us to develop our novel project from the bench to the bedside.

6. Evidence that the project will have a potential impact to the economy of Idaho: Development of this high profile project is likely to attract pharmaceutical and venture capital companies to Idaho. The interest of such companies in investing in Idaho will ultimately open up new avenues for increasing the Idaho job market, including the hiring of Idaho graduates and other trained personal.

7. Establishes partnerships with the public or private sector or contribute to new company creation: The successful outcome of the results from this study will help us in commercializing this agent as a drug. We will partner ISU with Natural Nanopharmaceutical Innovations Inc., a company established by Dr. Alok Bhushan (PI) and Dr. Lai (Co-PI) of this proposal. The product may interest pharmaceutical companies like Pfizer, Eli Lilly, and likely others.

8. The Market Opportunity: The project aims at testing the anti-tumor activity of a novel agent which has shown promising results in our studies to treat pancreatic cancer. Only few chemotherapeutic agents are effective in increasing the survival of pancreatic cancer patients: therefore, we believe this agent has high potential to benefit the patients. The agent will have a huge market as more than 30,000 individuals die due to pancreatic cancer every year, making it the fourth leading cause of cancer-related deaths. We are planning to compare the efficacy of this agent *in v*ivo and *in vitro* with other chemotherapeutic agents used in treating pancreatic cancer. Our preliminary studies strongly suggest that this agent is more effective than the two drugs currently used. Thus, it is highly likely that this outcome will attract interests from pharmaceutical

companies. Once our pre-clinical studies are completed, clinical trials for this drug will be needed before the drug is approved. We intend on reaching out to St. Luke's Hospital, Idaho as partner for initiating clinical studies.

9. The Technology

The technology here refers to our novel agent that is effective in reducing the survival of pancreatic cancer cells. More importantly, we found this agent to be considerably less toxic compared to the currently used chemotherapeutic drugs. Currently, gemcitabine and 5-fluorouracil are used for the treatment of pancreatic cancer patients. However, these drugs are ineffective due to the drug resistant nature of the cancer cells. Before clinical studies, an agent has to show promising results in *in vitro* and *in vivo* models. Our current studies suggest that this agent has the potential for treatment of pancreatic cancer. Therefore, we intend to further analyze the efficacy and toxicity of this agent. Moreover, analyzing the effect of this agent on cellular signaling pathways allows us to elucidate the mechanism(s) of its anti-tumor activity and may allow us to come up with a strategy to improve the agents efficacy.

10. Commercialization Partners – Identify commercialization partners, if any, or methods to be used in developing commercialization partners. Provide a clear description of the business relationship between institution's personnel and their private partners. Clearly outline responsibilities for project tasks, proposed schedule of meetings and a discussion of potential future activities that would take place upon successful completion of the project.

Because of the agent's therapeutic potential, we expect that major pharmaceutical companies will show interests in this drug after the preclinical studies are carried out.

11. Specific Project Plan and Detailed Use of Funds

Pancreatic cancer is one of the most aggressive forms of cancer. With more than 30,000 deaths in the year 2009, it is the fourth leading cause of cancer related deaths (1). Any therapy that can provide beneficial effects to the pancreatic cancer patients will have a strong impact on the survival of the patients and this state's economy. In this project, we aim at determining the effect of ABBB1 in tumor model *in vivo* and studying the effect on ABBB1 on pancreatic cancer markers. ABBB1 has shown promising results in our preliminary studies. It is more cytotoxic to pancreatic cancer cells compared with the conventional chemotherapeutic drug (Fig. 1). More importantly, ABBB1 in our *in vivo* toxicity study (using mice), exhibit much less toxicity compared to that of a conventional drug. Thus, our results indicate that ABBB1 is more effective in killing cancer cells but is less toxic on normal cells.

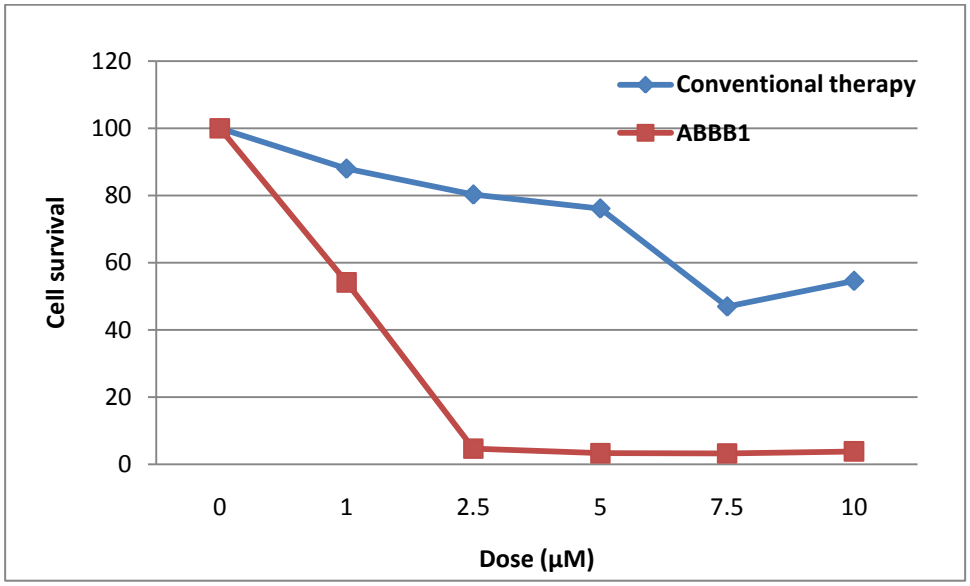

Fig. 1. Comparative effect of conventional drug used in pancreatic cancer chemotherapy and ABBB1 on pancreatic cancer survival *in vitro*.

Treatment	Dose (i.p.)	Mice died/ Total mice in study
Conventional drug	5 mg/kg	1/4 in 3 weeks
Conventional Drug	30 mg/kg	4/4 in 1 week
ABBB1	5 mg/kg	0/4 in 4 weeks
ABBB1	30 mg/kg	0/4 in 4 weeks

Table 1. Comparative *in vivo* toxicity of conventional drug used in pancreatic cancer chemotherapy and ABBB1.

These results warrant further investigation of the anti-cancer properties of this compound. To achieve this goal, we have 3 tasks in this project.

Task 1: To synthesize ABBB1 in adequate quantities for task 2 and 3.

Much more of the compound will be synthesized to allow us to conduct our *in vivo* and *in vitro* studies outlined in task 2 and 3. We have synthesized ABBB1 for our preliminary studies and have the expertise to synthesize them in our laboratories.

Task 2: To assess *in vivo* anti-cancer property of ABBB1.

The *in vivo* mice tumor model is a well characterized model to study the efficacy of an agent on tumor formation and growth. This model is currently in use in our laboratory for various other projects. For our task 1, we will divide 180 mice into 5 groups of 36 mice

each. These 5 groups will be injected with 5 different pancreatic cancer cell lines: Panc1, MiaPaCa2, AsPC1, AsPC/F and AsPC/G. Panc1, MiaPaCa2 and AsPC1 are obtained from different stages of pancreatic cancer. AsPC/F cells are cells which are resistant to 5-fluorouracil and AsPC/G cells are cancer cells resistant to gemcitabine. The cell lines were developed and characterized in our laboratory. Gemcitabine and 5-fluorouracil are FDA-approved pancreatic cancer chemotherapy agents. Therefore, by using this panel of cell lines, we will determine the effect of ABBB1 on pancreatic cancer models from different stages of cancer and elucidate its effect in drug resistant pancreatic cancer models.

The mice will be injected subcutaneously with their respective pancreatic cancer cells and then each group of 36 will be separated into three sub-groups of 12 mice each. The three subgroups will receive either of these drugs (1) ABBB1, (2) gemcitabine or (3) 5-fluorouracil. The tumors will be allowed to grow for four weeks before initiation of weekly drug administration. The tumor size will be analyzed for 10 weeks after initiation of drug administration to compare the effect of the 3 agents on growth of pancreatic cancer *in vivo* (3).

Task 2 will determine the effect of ABBB1 *in vivo* and its efficacy compared to the other commonly used anti-tumor agents for treatment of pancreatic cancer. This study is a necessary step before proceeding to clinical studies.

Task 3: To determine the effect on ABBB1 on pancreatic cancer signaling molecules/ markers.

Cancer cells have modulated signaling mechanisms which provide the cells with growth

and proliferative advantage. These signaling mechanism involve molecules/markers which are important for the cells to proliferate. Therefore, we will analyze the effect of ABBB1 on two important molecules of pancreatic cancer: K-Ras and epidermal growth factor receptor 1 and 2 (EGFR 1 and 2). These molecules are present in high levels in pancreatic cancer and have been associated with poor prognosis. For task 3, following experiments will be performed:

1) Western blot analysis: Panc1 cells (8×10^5) will be seeded in tissue culture flasks and treated with different concentrations of ABBB1. The cells will be allowed to grow for 72 hours and then harvested for preparation of cell lysates. The lysates will be subjected to gel electrophoresis (ref). The membrane will then be probed with K-Ras, EGFR 1, EGFR 2, p-EGFR 1 and p-EGFR 2 (activated EGFR) antibody. Following this step, HRP conjugated secondary antibodies antigenic to respective primary antibodies will be added to the blots. The blots will then be analyzed by the chemiluminescence method. This assay will be used to compared the expression of the analyzed proteins between untreated and ABBB1 treated Panc1 cells (4).

2) Ras activity assay: The expression of K-ras alone cannot determine the activity of ras in the cell lines. Therefore, for their further characterization we plan to compare the activity of ras in the untreated and ABBB1 treated cells. The ras activity assay will be performed by ras activation kit (Assay design, catalog # EKS-460) according to recommendations of the commercial vendor.

Task 3 will help us determine the effect of ABBB1 on cellular signaling mechanisms. These signaling mechanisms allow the cells to proliferate, therefore, by analyzing the

effect of ABBB1 on them, we will be able to better understand the mechanism by which ABBB1 show its anti-cancer effect.

Task 1 will require $ 6,300 for synthesizing the compound in adequate quantity. Task 2 and 3 will require growth media with supplemented serum from propagation of cancer cells *in vitro.* The media along with serum will cost $ 3000 for both the tasks. Mice for task 2 are available at the rate of $ 30/mice and their housing rate is set at $ 0.40 per diem. Therefore the cost for the animal study will be $ 12, 500. $ 1,500 will be used for the purchase of drugs (gemcitabine and 5-fluorouracil). $ 7,000 will be required for tissue culture supplies, antibodies and general lab supplies. $ 2,000 will be used for electrophoresis and Ras activity assay supplies mentioned in task 2. A graduate student will be hired and paid $ 16, 253 for conducting this work at the rate of $ 17 per hour part-time (16 hours/week) for the duration of this project (60 weeks).

12. Education and Outreach: Describe the education, research and development opportunities for students and faculty (e.g., support of undergraduate and/or graduate students, internship opportunities, postdoctoral researchers, industrial fellows, and faculty members from other college and universities. Clearly outline plans for attracting and involving high-quality students (undergraduate, graduate, postdoctoral) in research activities.

Part of this work will be carried out by a graduate student. Once this project is completed, grants will be written to support undergraduate, graduate and postdoctoral researchers. This work will help the students understand the process of drug

development and having industry in Idaho can help in creating jobs and improve economy. These students can serve as ambassadors of research to our community.

13. Institutional and Other Sector Support: ISU has funded us research grant to support the preliminary studies via the University Research Grant mechanism. ISU administration is committed to support us in this project. We use Coulter counter and animal facilities, laboratory space and several other facilities to carry out the studies. Summarize the home institution's commitment at a level appropriate to the project. Specific facilities are listed in the appendices below. As the

References:

1. American Cancer Society. Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009.

2. Pancreatic Cancer - H. (EDT) Riess & Andrea (EDT) Goerke & H. (EDT) Oettle; Springer Verlag; Jan 03 2008

3. Watson RL, Spalding AC, Zielske SP, Morgan M, Kim AC, Bommer GT, Eldar-Finkelman H, Giordano T, Fearon ER, Hammer GD, Lawrence TS, Ben-Josef E. GSK3beta and beta-catenin modulate radiation cytotoxicity in pancreatic cancer. Neoplasia. 2010 May;12(5):357-65.

4. Bhardwaj V, Rizvi N, Lai MB, Lai JCK and Bhushan A. Glycolytic Enzyme Inhibitors Affect Pancreatic Cancer Survival by Modulating its Signaling and Energetics. Anticancer Research 30(3): 2010.

Appendices:

1. Facilities and Equipment: Include a description of the available facilities and equipment.

Laboratory:

The laboratory occupies about 800 sq. ft. in the College of Pharmacy at Idaho State University. We have a full complement of small equipment including balances, pH meters, water baths, centrifuges etc. For cell culture, we have a large incubator, 2 sterile hoods, and several microscopes in a separate room.

Animal:

The ISU Laboratory Animal Research Facility is the AAALAC-accredited, central animal research facility for the entire campus and, as such, is open for use by all researchers on the campus, regardless of their colleges or disciplines. The facility, in the basement of the Pharmacy Building, is primarily designed for the housing of small laboratory animals such as mice, rats, rabbits, and other rodents; but is has the capability to handle larger and more exotic animals. The facility comprises approximately 9,000 square feet of environmentally controlled area. PI is currently carrying out xenograft studies in the facility.

Computer:

The laboratory is equipped with Dell desktop 380 and has a back up 500G external drive as well as server backup of files. All students own their laptops.

Office:

PI has office space in the college and a desk in the lab. Secretarial help is available from the college.

Other:

Synthetic work will be performed at Washington State University.

MAJOR EQUIPMENT:

Equipment available includes full capacity for agarose electrophoresis and blotting equipment for DNA and RNA, polyacrylamide electrophoresis equipment for proteins, electro blotting apparatus, PCR thermal cyclers, Spectrophotometers, bench-top microfuges, DNA sequencing apparatus, gel-drying systems, preparative isoelectric unit and other protein purification equipment, light boxes, laminar flow and UV hoods, culture incubators, homogenizers, rotary shaker baths, microwave ovens, dissecting scopes, light microscopes, liquid nitrogen storage dewars, Geiger counters, and biohazard and radioactive waste containment and disposal supplies, Beckman L8-80 ultracentrifuges and Sorvall RC-5B refrigerated centrifuges Following is a list of equipment in PI's laboratory. A confocal microscope will be available in the university this year.

CO2 incubators

Sterile Hoods Electrophoresis Equipment

Cold room Geiger counters

Refrigerated Centrifuges Gamma counter*

Liquid Scintillation Counter Ultracentrifuge*

Inverted microscope (over 20 years old) Hybridization Oven

UV/vis Spectrophotometer* Lieca 3D microscope (housed in Molecular

Research Core)

Dark room (In Dept.)

Coulter counter Z2	BD FACS Calibur Flow Cytometer
Vacuum oven	Peptide Mapping System
Radioactive work area	Microfuges

2. Biographical Sketching and Individual Support: Provide a one- to two-page biographical sketch that includes the five most relevant publications and a complete listing of current support for PI's and co-PI's. A full CV of the Project Director is required. Provide a description of qualifications of and services expected from all visiting professors and postdoctoral associates. This appendix may be single-spaced.

Alok Bhushan

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 Alok Bhushan	POSITION TITLE Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Delhi, India	B.S.	1975	Chemistry
University of Delhi, India	M.S.	1977	Chemistry
Punjab Agricultural University, Ludhiana, India	Ph.D.	1982	Biochemistry

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

Positions and Honors

Positions and Employment

1982-1983 Dept. of Animal Sciences, University of Maryland
1983-1984 Postdoctoral Fellow, John Hopkins University School of Medicine
1984-1987 Postdoctoral Fellow, Dept. of Pediatrics, Medical University of South Carolina,
1987-1988 Postdoctoral Fellow, Dept. of Pharmacology, University of Vermont
1988-1992 Research Associate, Dept. of Pharmacology, University of Vermont
1992-1998 Research Assistant Professor, Department of Pharmacology, University of Vermont
1998-2003 Assistant Professor, Department of Pharmaceutical Sciences, College of Pharmacy, Idaho State University
2003-present Associate Professor, Department of Pharmaceutical Sciences, College of Pharmacy, Idaho State University
2006-2009 Assistant Chair, Coordinator, Graduate Program, Department of Pharmaceutical Sciences, College of Pharmacy, Idaho State University
2007-present Professor, Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, Idaho State University

Other Experience and Professional Memberships

-Member, American Association of Cancer Research (AACR).
-Member, American Association of College of Pharmacy
-Member, American Society of Biochemistry and Molecular Biology.
-Member, John Hopkins Surgical and Medical Association, John Hopkins University, Baltimore.
-Member, Molecular Epidemiology Working Group, AACR 2003 – present.
-Member Sigma Xi.

-Member International Recruiting and Retention task force
-Member Cancer Comprehensive Alliance of Idaho (CCAI)
-Member American Association of Nanomedicine
-Life Member, Idaho Academy of Sciences (Executive committee member)
-Member Cancer Comprehensive Alliance of Idaho (CCAI)
-Founding member Idaho Cancer Researchers Association (ICRA)
-Member, Snake River Association of Neuroscience (SRAN)
-State legislative Committee of American Association of Cancer Research – (1998-2003)
-Member, Rho Chi
-Member, Cancer Prevention and Treatment Center, WSU

A. Selected Peer-reviewed Publications (Selected from over 48 peer-reviewed publications)

Most relevant to the current application

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1. Malthankar, G.V., White, B.K., **Bhushan, A**., Daniels, C.K., Rodnick, K.J. and Lai, J.C.K. Differential lowering by manganese treatment of activities of glycolytic and tricarboxylic acid (TCA) cycle enzymes investigated in neuroblastoma and astrocytoma cells is associated with manganese-induced cell death. Neurochemical Research 29, 209-717, 2004.
2. Puli, S., J.C.K. Lai and **Bhushan, A.** Inhibition of Matrix Degrading Enzymes and Invasion in Human Glioblastoma (U87MG) Cells by Isoflavones, Journal of Neuro-Oncology 90(2): 135-142, 2006.
3. Puli S, Lai JCK, Edgley KL, Daniels CK, & **Bhushan A.** Signaling Pathways mediating Manganese-Induced Neurotoxicity in Human Glioblastoma Cells (U87) Neurochemical Research, 31:1211-1218, 2006.
4. Sehdev V, Lai JC and Bhushan A Biochanin A Modulates Cell Viability, Invasion, and Growth Promoting Signaling Pathways in HER-2-Positive Breast Cancer Cells. J Oncol. 121458. 2010
5. Bhardwaj V, Rizvi N, Lai MB, Lai JC and **Bhushan A**. Glycolytic enzyme inhibitors affect pancreatic cancer survival by modulating its signaling and energetics. Anticancer Res. 2010 30(3):743-9, 2010.

B. Research Support
Ongoing Research Support

Bhushan (PI) Lai (Co-PI)4/1/06-4/30/2010 Use of Chinese Herbal Extracts for Anti-Cancer Drug Discovery: Phase II. This study determines the anti-cancer drug potentials in Chinese Herbal Extracts. Idaho State University and a Private Source Contract Grant

Principal Investigator, 2009, Mechanisms of resistance in pancreatic cancer, University Research Committee grant, Idaho State University $14,000

Biographical Sketch- Byron L. Bennett Ph.D.

Address: Department of Chemistry
Campus Box 8023
Pocatello, ID 83209 -8023

(208) 282-3314 (W)
(208) 282-4373 (fax)
E-Mail: bennbyro@isu.edu

Education:

1989-1997: University of Wyoming: Ph.D. Chemistry (April 1997)
1986-1989: Cedarville College, Ohio: B.A. Chemistry
1985-1986 Florida Institute of Technology, Melbourne

Academic Positions:

2007 : Assistant Professor of Chemistry: Idaho State University
2006-2007: Associate Professor of Chemistry: Daytona Beach Community College
2000-2006: Assistant Professor of Chemistry: University of Nevada, Las Vegas (Organic subdivision)
1998-2000: Postdoctoral Fellow: University of Nevada, Reno (Inorganic: Metallocryptate Synthesis)
1997-1998: Postdoctoral Fellow: University of Utah (Organic: Fluoroalkyl-Arene Synthesis).

Honors:

Cottrell College Science Award, Research Corporation 2004
G.E. Coates Teaching Award, University of Wyoming 1992-1993

Professional Societies:

American Chemical Society (ACS)- (Inorganic and Organometallic subdivisions) member 1991-present
Idaho Academy of Science (IAS)
American Association for the Advancement of Science (AAAS)

Major Research Interest:

Synthetic and Mechanistic Problems in Inorganic/Organometallic Chemistry
including Late Transition metal Coordination Chemistry

Provisonal Patent Applications:

"Device and Method for Non-Invasive Oxygen Sensing of Sealed Packages", Hatchett, David Wayne; Bennett, Byron Lee; Siani, Pai Singh Devinder; Submitted 4/06

Patent Applications:

"Fluorinated 2,2'-Bipyridine and 1,10-Phenanthroline Platinum(II) Complexes as Cisplatin Analogs for Cancer Treatment", Submitted 4/06

"Organic Materials with Tunable Electric and Electroluminescent Properties" Sapochak, Linda Susan; Burrows, Paul Edward; Padmaperuma, Asanga Bimalchandra; Desilva, Murukkuwadura Aruni; Bennett, Byron Lee. PCT Int. Appl. (2005), 38 pp. WO 2005073340

Publications:

1) Van Vo, Zeynep G. Kabuloglu-Karayusuf, Stephen W. Carper, Byron L. Bennett, Caryn Evilia "Novel 4,4′-diether-2,2′-bipyridine cisplatin analogues are more effective than cisplatin at inducing apoptosis in cancer cell lines."*Bioorganic & Medicinal Chemistry,* **2010**, *18,*1163-1170.
2) Kyler E. Elwell, Casey Hall, Shweta Thaker, Yvonne Giraud, Byron L. Bennett, Chulsung Bae, Stephen W. Carper "A fluorine containing bipyridine Cisplatin analog is more effective

than Cisplatin at inducing apoptosis in cancer cell lines", *Bioorganic & Medicinal Chemistry*, **2006,** *14(24), 8692.*

3) Byron L. Bennett, Kathleen A. Robins, Ryan Tennant, Kyler Elwell, Felice Ferri, Inna Bashta, and Grant Aguinaldo, "Fluorous Modification of 2,2'-Bipyridine", *Journal of Fluorine Chemistry*, **2006**, *127*(1), 140.
4) David W. Emerson, Byron L. Bennett, Spencer M. Steinberg, "A One Pot Synthesis of Bis(□-Fluoroalkyl) and Alkyl Disulfides", *Synthetic Communications*, **2005**, *35*, 631.
5) Vincent J. Catalano, Byron L. Bennett, Mark A. Malwitz, Renante L. Yson, Heidi M. Kar, Stamatis Muratidis and Stephen J. Horner, "Metallocryptands: Host Complexes for Probing Closed-Shell Metal-Metal Interactions" *Comments on Inorganic Chemistry*, **2003**, *24*(1), 39.

Presentations: (selected recent)
Byron Bennett**, Darrah Ricard**, Charles W. Mower, and Caryn Evilia, "Isomers of Dichloro (4, 4'- Di-Butyl- 2, 2'- Bipyridyl) Platinum (II): Synthesis, Chemical Characterization, and Interaction with Protein" 9th Annual NIH INBRE(IDeA Network of Biomedical Research Excellence) Paper # August 2nd – 4th 2010

Byron Bennett , R. David Grigg, Van Vo, Zeynep G. Kabuloglu-Karayusuf, Stephen W. Carper,Vikas Sehdev, James C.K. Lai, Alok Bhushan†4,4′-Disubstituted-2,2′-bipyridine Pt(II) Complexes: Cisplatin Analogues of Increased Cytotoxicity, 64th Northwest/Regional Meeting of the American Chemical Society, Tacoma WA, Paper #188, June 28th – July 1st 2009

Invited Lecture: (selected recent)
90th Annual Meeting of the California Academy of Sciences, AAAS Pacific Division, Symposium: Recent Advances in Pharmacology and Toxicology, "Pt(II) Complexes of 4,4′-disubstituted-2,2′-bipyridine: Structure and Cytotoxicity" San Francisco CA, August 18th 2009.

Manuscript Refereeing:
Tetrahedron; European Journal of Inorganic Chemistry; Journal of Fluorine Chemistry; Journal of Molecular Catalysis A: Chemical; ACS symposium "Green Chemistry; Journal of the Chemical Society, Chemical Communications; Green Chemistry; Journal of the Chemical Society, Dalton Transactions; Organometallics; New Journal of Chemistry; Journal of Chemical Education; Organic & Biomolecular Chemistry

Grant Refereeing:
Research Corporation; Petroleum Research Fund (ACS)

Text Reviews:
Topics: Organic and Organometallic Chemistry: *Publishers:* Oxford University Press; Brooks/Cole-Thomson Learning; McGraw Hill; John Wiley and Sons.

Contracts & Grants:
Current: "Synthesis of 2,2'-bipyridine Complexes of Pt(II): Generation of Potential Chemotherapeutic Agents for Cancer Treatment" Office of Research, Idaho State University ($5000)
Past: (critical - selected) "Preparation of Diimine Complexes of Pt(II) and Determination of Their In-vitro Activity", American Cancer Society #IRG-103719 ($20,000)

Current Position Description:
(45%) Teaching:
Topic Areas: General, Inorganic (U-grad & Grad), Organometallics, Organic (U-grad)
(45%) Research:
Mentorship- Current: *7 undergraduates and 1 graduate*
(10%) Service:
ACS (*Section-Chair*), Academic: Chem Dept.- NMR Lab director, TAC, GFR

Biographical Sketch-James C K Lai Ph.D.

POSITION TITLE
Professor of Pharmacology & Toxicology; Associate Director, ISU Biomedical Research Institute
Education:

University College, Cardiff, U.K.	B.Sc.(Hons)	1970	Microbiology
Birmingham University, U.K.	M.Sc.	1971	Neurocommunications
London University, UK	Ph.D.	1975	Biochemistry

A. Positions and Honors

Positions and employment

1974-1977: Research Fellow, Liver Unit, King's Col. Hosp. Med. Sch., London U., U.K.
1977-1980: Pewterers' Fellow in Neurochemistry, Inst. Neurol., London U., U.K.
1980-1981: Associate, Neurology Dept., Albert Einstein Col. Med., Bronx, NY.
1981-1985: Associate, Neurology Dept., Cornell U. Med. Col. and Burke Rehab. Ctr., White Plains, NY.
1985-1986: Instructor, Neurology Dept., Cornell U. Med. Col., New York, NY.
1986-1991: Assistant Professor of Biochemistry in Neurology, Neurology & Biochemistry Depts., Cornell U. Med. Col., New York, NY.
1991-1996: Associate Professor of Pharmacology & Toxicology, Pharmaceutical Sciences Dept., Idaho State U. Col. Pharm., Pocatello, ID.
1996-Pres: Professor of Pharmacology & Toxicology, Pharmaceutical Sciences Dept., Idaho State U. Col. Pharm., Pocatello, ID.
1997-Pres: Affiliate Member, Cancer Research Section, Mountain States Medical Research Institute, Boise, ID.
2001-2006: Assistant Chair, Pharmaceutical Sciences Dept., Idaho State U. Col. Pharm., Pocatello, ID.
2005-Pres: Associate Director, Idaho State University Biomedical Research Institute, Pocatello, ID.

Honors and awards

Medical Research Council Fellow, U.K. 1974-1977; Pewterers' Fellow in Neurochemistry, London University, U.K. 1977-1980; Idaho State University Outstanding Researcher 1994-1995 & 1995-1996; Teacher of the Year, Idaho State University College of Pharmacy 1995-1996; Idaho State University Distinguished Researcher 1996; Idaho State University Master Teacher 1997-1998 & 1998-1999; Idaho State University Distinguished Teacher 1999; Teacher of the Year, Idaho State University College of Pharmacy 2003-2004 & 2008-2009; *Neurotoxicology*, Editorial Board Member, 1985-1990; *Pharmacy Case Review*, Associate Editor, 1993-1996; *Metabolic Brain Disease*, Editorial Board Member, 1990-Pres.; *Neurochemical Research*, Editorial Board Member, 1995-2008.

Membership in Professional Societies

American Society of Pharmacology & Experimental Therapeutics; Phi Lambda Sigma; Rho Chi; Snake River Association for Neuroscience; Society for Neuroscience.

Summary of Research Interests

Anticancer drug discovery; cancer prevention; cancer cell metabolism and signaling; nanotoxicology; nanopore transport of biomolecules; regulation and compartmentation of brain intermediary metabolism; functional roles of glutathione and other antioxidants; hypoxia and brain metabolism and adaptation; neurotoxicity and metabolism of metals, ammonia, and fatty acids; temporal lobe epilepsy: mechanisms that lead to elevation of extracellular brain

glutamate.

B. Selected Peer-Reviewed Publications (Selected from **173** publications)

Most relevant to the current application

1. Puli S, Lai JCK & Bhushan A (2006) Inhibition of Matrix Degrading Enzymes and Invasion in Human Glioblastoma (U87MG) Cells by Isoflavones. J. Neuro-Oncol. 79(2):135-142. [PMID: 16598420]
2. Puli S, Lai JCK, Edgley KL, Daniels CK, & Bhushan A (2006) Signaling Pathways mediating Manganese-Induced Neurotoxicity in Human Glioblastoma Cells (U87) Neurochem. Res. 31: 1211-1218. [PMID: 17043766]
3. Johnson TL, Lai MB, Lai JCK & Bhushan A (2008) Inhibition of Cell Proliferation and MAP Kinase and Akt Pathways in Oral Squamous Cell Carcinoma by Genistein and Biochanin A. Evidence-Based Complementary and Alternative Medicine (published on line February 29, 2008; eCAM, doi:10.1093/ecam/nen011).
4. Sehdev V, Lai JCK & Bhushan A (2009) Biochanin A modulates cell viability, invasion and growth promoting signaling pathways in HER-2-positive breast cancer cells, J. Oncol. (in press).
5. Bhardwaj V, Rizvi N, Lai MB, Lai JCK & Bhushan A (2010) Glycolytic Enzyme Inhibitors Affect Pancreatic Cancer Survival by Modulating its Signaling and Energetics. Anticancer Res. 30:743-750.

Additional recent publications of importance to the field (in chronological order)

1. Lai JCK, White BK, Buerstatte CR, Haddad GG, Novotny Jr EJ & Behar KL (2003) Chronic Hypoxia in Development Selectively Alters the Activities of Key Enzymes of Glucose Oxidative Metabolism in Brain Regions. Neurochem. Res. 28: 933-940.
2. Malthankar GV, White BK, Bhushan A, Daniels CK, Rodnick KJ & Lai JCK (2004) Differential Lowering by Manganese Treatment of Activities of Glycolytic and Tricarboxylic Acid Cycle Enzymes in Neuroblastoma and Astrocytoma Cells Is Associated with Manganese-Induced Cell Death. Neurochem. Res. 29:709-717.
3. Isaac AO, Kawikova I, Bothwell ALM, Daniels CK & Lai JCK (2006) Manganese Treatment Modulates the Expression of Peroxisomal Proliferator Activated Receptors (PPARs) in Astrocytoma and Neuroblastoma Cells. Neurochem. Res. 31(11):1305-1316. [PMID: 17053972]
4. Dukhande VV, Malthankar-Phatak GH, Hugus JJ, Daniels CK & Lai JCK (2006) Manganese Induced Neurotoxicity is Differentially Enhanced by Glutathione Depletion in Astrocytoma and Neuroblastoma Cells. Neurochem. Res. 31(11):1349-1357. [PMID: 17053969]
5. Isaac AO, Dukhande VV & Lai JCK (2007) Metabolic and Antioxidant System Alterations in an Astrocytoma Cell Line Challenged with Mitochondrial DNA Deletion. Neurochem. Res. 32(11):1906-1918. [PMID: 17562167]

C. Ongoing research support

Idaho State University and a Private Source Contract Grant Bhushan (PI) Lai (Co-PI) 4/1/06-6/30/2011
Use of Chinese Herbal Extracts for Anti-Cancer Drug Discovery: Phase II.
This study determines the anti-cancer drug potentials in Chinese Herbal Extracts.
Role: Co-PI

USAMRMC Project Grant (Contract #W81XWH-07-2-0078, administered by USA MED RESEARCH ACQ ACTIVITY). Naidu S (PI) Lai (Co-PI/Researcher)
Phase I:7/23/2007-4/30/2010; Phase II:5/1/2010-4/30/2012
Smart Prosthetic Hand Technology.
This study determines the feasibility of a new smart prosthetic hand technology and its biocompatibility. Role: Co-PI and Researcher

Biographical Sketch-Vikas Bhardwaj

Address: 1051, SOUTH 4TH AVENUE, APT # 15, POCATELLO 83201, IDAHO, US
Phone 208-852-6309
E-mail bharvika@pharmacy.isu.edu

Education:

1. Currently pursuing **Ph. D in Pharmaceutical Sciences** at Idaho State University, ID, US (Fall 2006-present). Cumulative GPA- 3.86 / 4.00.
2. Completed **Bachelors of Pharmacy** from Faculty of Pharmacy, Jamia (University) Hamdard with 66%, (Fall 2002-Spring 2006) New Delhi, Delhi, INDIA**.** Major – Pharmacy.

Internships:

1. Ashoka Medicine House. (June 2002) Dealt with dispensing and drug storage paradigms.
2. Aimil Pharmaceuticals. (June 2003) Learnt extraction procedure for medicinal agents from herbal drugs, also worked in the quality assurance department.
3. Vasistha Pharmaceuticals Ltd. (June 2004) Learnt formulation of tablet, suspensions and capsules.

Current Research Areas:

1. Anti-metabolite drug resistance in pancreatic cancer.
2. Effect of isoflavones on pancreatic cancer progression.
3. Effect of glycolytic enzyme inhibitors on pancreatic cancer survival and signaling.

Positions:

1. President, 2009-2010, Associated Graduate Students of Pharmacy, Idaho State University.
2. Graduate Research Assistant, 2007-present, Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, Idaho State University.

Membership:

1. Associated Graduate Student of Pharmacy, ISU. 2006- present.
2. Associate member, American Association of Cancer Research (AACR). 2007-present.
3. Student member, Idaho Academy of Sciences. 2010-11.
4. Student member, Sigma XI.

Awards, grants and scholarships:

1) Graduate Research Assistant, ISU. 2007- Present.
2) Associated Students of Idaho State University scholarship 2007.
3) Claudia Senekowitsch Summer Fellowship, 2007.
4) Best oral presentation, IAS 2010, Twin Falls, ID.
5) Graduate Student Research and Scholarship Committee (GSRSC) grant, ISU. 2010-11.

Oral presentations:

1. Effect of biochanin A on pancreatic cancer cell survival and signaling. Annual INBRE summer program, June 2008, Idaho State University, Pocatello, ID.
2. Bhardwaj V, Lai JCK & Bhushan A (2010) Selection and Characterization of a Novel 5-Fluorouracil Resistant Pancreatic Cancer Cells. 52nd Annual Symposium of the Idaho Academy of Sciences, March 11-13, 2010, College of Southern Idaho, Twin Falls, ID, Program/Abstract Volume, p. 16 & Journal of the Idaho Academy of Science 46(1):19-20.

3. Role of epidermal growth factor receptor in 5-fluorouracil resistance in pancreatic cancer cells. Annual INBRE Research Conference, Aug 2-4, 2010, Moscow, ID.

Publications:

1. **Bhardwaj V**, Rizvi N, Lai MB, Lai JCK, Bhushan A. Glycolytic Enzyme Inhibitors Affect Pancreatic Cancer Survival by Modulating its Signaling and Energetics. Anticancer Res. 2010 Mar; 30(3):743-9.
2. Bhushan A, **Bhardwaj V**, Frandsen C & Lai JCK (2010) Bioactive Isoflavones: Implications in Cancer Treatment and Prevention. In Isoflavones: Biosynthesis, Occurrence and Health Effects, Nova Science, Hauppauge, NY (Accepted, Pub. Date: 2010 - 3rd Quarter).
3. **Bhardwaj V**, Daniels CK, Lai JCK & Bhushan A (2010) Selection and Characterization of a Novel 5-Fluorouracil Resistant Pancreatic Cancer Cell Line. Journal of the Idaho Academy of Science 46(1):46-51.
4. **Bhardwaj V**, Daniels CK, Lai JCK & Bhushan A. Biochanin A reduces pancreatic cancer progression and potentiates gemcitabine cytotoxicity (Under review; Journal Pancreas).

Abstracts and presentations:

1. **Bhardwaj V**, Rizvi N, Lai MB, Lai JCK, and Bhushan A. Decrease in survival of pancreatic cancer cells on treatment with 3-bromopyruvate and iodoacetate. Sixth Annual Research Conference of Idaho INBRE, August 6-8, 2007, Moscow, ID.
2. Bhushan A, Johnson T, Sehdev V, **Bhardwaj V**, Lai MB & Lai JCK. Differential Modulation by Biochanin A on Effects of Glycolytic Enzyme Inhibitors in Cancer Cells. 2nd International Symposium on Translational Cancer Research: Natural Products and Cancer, December 9-12, 2007, Lonavala (Mumbai), India.
3. **Bhardwaj V**, Rizvi N, Lai MB, Lai JCK, and Bhushan A. Crosstalk between cellular signaling and energetics: a proposed new target for cancer chemotherapy. Idaho Academy of Sciences, 50th Annual Meeting, March 27-29, 2008. Nampa, Idaho
4. **Bhardwaj V**, Rizvi N, Lai MB, Lai JCK, and Bhushan A. Iodoacetate and 3-bromopyruvate modulate cell signaling to decrease the pancreatic cancer cell survival. American Association of Cancer Research Annual Meeting, April 2008, San Diego, CA.
5. **Bhardwaj V**, Lai JCK, and Bhushan A. Effect of Biochanin A on pancreatic cancer cell survival and signaling. Seventh Annual Research Conference of Idaho INBRE, August 2008, Boise, ID.
6. **Bhardwaj V**, Lai JCK, and Bhushan A; " Biochanin A potentiates the cytotoxic effect of 5-fluorouracil on pancreatic cancer cells" American Association of Cancer Research Annual Meeting, April 2009, Denver, CO.
7. **Bhardwaj V**, Lai JCK, and Bhushan A; Biochanin A potentiates the cytotoxic effect of 5-fluorouracil on pancreatic cancer cells. Graduate Student Symposium for Research and Creative Excellence, April 2009, Idaho State University, Pocatello, ID.
8. **Bhardwaj V**, Lai JCK, and Bhushan A; Biochanin A potentiates the cytotoxic effect of 5-fluorouracil on pancreatic cancer cells. Eighth Annual Research Conference of Idaho INBRE, August 2009, Pocatello, ID.
9. **Bhardwaj V**, Lai JCK, and Bhushan A. “Characterization of a novel 5-fluorouracil resistant pancreatic cancer cell line and effect of biochanin A on it.” Graduate Student Symposium for Research and Creative Excellence, April 2010, Idaho State University, Pocatello, ID.
10. **Bhardwaj V**, Lai JCK, and Bhushan A. Alterations of molecular mechanisms in newly selected 5-fluorouracil resistant pancreatic cancer cell line and the effect of biochanin A thereon. American Association of Cancer Research Annual Meeting, April 2010, Washington DC.

1. Provide documentation of other sector resource commitments.

SUMMARY PROPOSAL BUDGET

Name of Institution: Idaho State University

Name of Project Director: Alok Bhushan

A. FACULTY AND STAFF

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
None					
% OF TOTAL BUDGET:				**SUBTOTAL:**	

B. VISITING PROFESSORS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
None					
% OF TOTAL BUDGET:				**SUBTOTAL:**	

C. POST DOCTORAL ASSOCIATES / OTHER PROFESSIONALS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
None					
% OF TOTAL BUDGET:				**SUBTOTAL:**	

D. GRADUATE / UNDERGRADUATE STUDENTS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
Aditi Jain, PhD student (16hrs/week)	$ 17/ hour	5		5	$ 16,253
% OF TOTAL BUDGET:				**SUBTOTAL:**	$16,253

E. FRINGE BENEFITS

Rate of Pay (%)	Salary Base	Dollar Amount Requested
8.9%	$16,253	$1447
	SUBTOTAL:	$1447

F. EQUIPMENT: (List each item with a cost in excess of $1000.00.)

Item/Description	Dollar Amount Requested
None	
SUBTOTAL:	

G. TRAVEL:

Dates of Travel (from/to)	No. of Persons	Total Days	Transportation	Lodging	Per Diem	Dollar Amount Requested
					SUBTOTAL:	

H. Participant Support Costs:

	Dollar Amount Requested
1. Stipends	
2. Travel (other than listed in section G)	
3. Subsistence	
4. Other	
SUBTOTAL:	

I. Other Direct Costs:	Dollar Amount Requested
1. Materials and Supplies	$ 13,500
2. Publication Costs/Page Charges	
3. Consultant Services (Include Travel Expenses)	
4. Computer Services	
5. Subcontracts	
6. Other (specify nature & breakdown if over $1000) Synthesis of ABBB1	$ 6, 300
Animal studies (180 mice @ $ 30/ animal. Housing @ $ 0.4 per diem for 14 weeks)	$ 12,500
SUBTOTAL:	$32,300
J. Total Costs: (Add subtotals, sections A through I) **TOTAL:**	$50,000
K. Amount Requested: **TOTAL:**	$50,000
Project Director's Signature: 	Date: 12/3/10

Budget Justification:

1. Expenditures:

Synthesis:
10 grams of minimum amount of ABBB1 will be needed for the studies. Funds have been requested to purchase chemicals and solvents. $6,300 have been requested.

Supplies $13,500
Tissue culture supplies-$3000, electrophoresis supplies and Ras activity-$2,000, antibodies-$2000, Media and Fetal Bovine serum-$3000, General lab supplies-$2000, Drugs for studies(gemcitabine and 5-fluorouracil)-$1,500.

Total expenditure $13,500

Animal studies $12,500
180 mice @ $ 30/ animal. Housing @ $ 0.4 per diem for 14 weeks

2. Personnel Salaries:
Graduate student will be involved in carrying out the experiments. Student will be paid for 956 hours. The student will devote 16 hours per week on this project.
at $17/ hour. $16,253 has been requested

Fringe benefits: 8.9% fringe has been requested.
$1447.00
Total: $17,700