THE UNIVERSITY OF WESTERN ONTARIO
BIOHAZARDOUS AGENTS REGISTRY FORM
Approved Biohazards Subcommittee: September 25, 2009
Biosafety Website: www.uwo.ca/humanresources/biosafety/

This form must be completed by each Principal Investigator holding a grant administered by the University of Western Ontario or in charge of a laboratory/facility where the use of Level 1, 2 or 3 biohazardous agents is described in the laboratory or animal work proposed. The form must also be completed if any work is proposed involving animals carrying zoonotic agents infectious to humans or involving plants, fungi, or insects that require Public Health Agency of Canada (PHAC) or Canadian Food Inspection Agency (CFIA) permits.

This form must be updated at least every 3 years or when there are changes to the biohazards being used.

Containment Levels will be established in accordance with Laboratory Biosafety Guidelines, 3rd edition, 2004, Public Health Agency of Canada (PHAC) or Containment Standards for Veterinary Facilities, 1st edition 1996, Canadian Food Inspection Agency (CFIA).

Completed forms are to be returned to Occupational Health and Safety, (OHS), (Support Services Building, Room 4190) for distribution to the Biohazard Subcommittee. For questions regarding this form, please contact the Biosafety Officer at extension 81135 or biosafety@uwo.ca. If there are changes to the information on this form (excluding grant title and funding agencies), contact Occupational Health and Safety for a modification form. See website: www.uwo.ca/humanresources/biosafety

PRINCIPAL INVESTIGATOR	Dr. Jim W Xuan
SIGNATURE	
DEPARTMENT	Surgery
ADDRESS	Rm.2222, HSB. 375 South St Campus, LHSC,
PHONE NUMBER	Ext 76682 or 75346
EMERGENCY PHONE NUMBER(S)	519 649 4007
EMAIL	Jim.xuan@lhsc.on.ca

Location of experimental work to be carried out: Building(s) __HSB_____ Room(s)_222_ ✓ Level 2 certified July 16, 2008

*For work being performed at Institutions affiliated with the University of Western Ontario, the Safety Officer for the Institution where experiments will take place must sign the form prior to its being sent to the University of Western Ontario Biosafety Officer (See Section 12.0, Approvals).

FUNDING AGENCY/AGENCIES: Ontario Institute of Cancer Research, Research grant (OICR)
GRANT TITLE(S): Molecular diagnosis and therapy of prostate cancer by UTMD (ultrasound targeted microbubbles destruction) technology in genetically engineered mouse models

PLEASE ATTACH A BRIEF DESCRIPTION OF YOUR WORK THAT EXPLAINS THE BIOHAZARDS USED AND HOW THEY WILL BE USED. PROJECTS SUBMITTED WITHOUT A SUMMARY WILL NOT BE REVIEWED. A GRANT SUMMARY PAGE MAYBE ADEQUATE IF IT PROVIDES SUFFICIENT DETAIL ABOUT EACH BIOHAZARD USED.

Detection and treatment of cancer at the earliest stages of carcinogenesis is critical to improved treatment and prevention strategies. Identifying activity of cancer inducing genes (oncogenes) activity early in carcinogenesis is a key strategy and we have characterized a "hit-and-run" effect of an oncogene (SV40Tag) in a genetically engineered mouse (GEM) prostate cancer (CaP)models, in which this oncogene is active in the tumor-initiation stage (tumorigenesis), but not in later stages of CaP development and progression. We have used GeneChip (a tiny block containing probes for testing more than 30 thousand genes on biologic samples) by a differential screening approach (subtract and comparison procedures) to identify other genes correlated with tumorigenesis. One such gene, TRIM59, a novel computer predicted gene, has been selected for detailed study

in our laboratory for its significant correlation with the "hit-and-run" effect of an oncogene activated early in tumorigenesis

We have found TRIM59 gene over-activation (up-regulation) and modification (phosphorylation) correlates with tumorigenesis in our GEM-CaP mouse model of prostate cancer. These findings are based on two kinds of experiments: interfering RNA technology (RNAi) eliminates (knockdown) TRIM59 function by blocking the gene through binding with short fragments of RNA. Secondly, when TRIM59 is modified to over-function in our GEM-CaP model, TRIM59 is able to induce cancer development like other oncogenes. In both tests of up- and down-regulation of TRIM59 gene function, GeneChip analyses have demonstrated that TRIM59 is an early signal originating from within a known oncogene pathway (Ras gene pathway, activated in up to 30% of human cancers) for tumorigenesis. We also found TRIM59 serves as an early molecular signal, as TRIM59 signals precedes the subsequent development of detectable tumors in our animal models. We have found that TRIM59 also appears to be an important molecular marker in kidney cancer patients as TRIM59 is over activated in the kidney cancers as compared with normal kidney tissues. In addition, our collaborators at the Vancouver Prostate Research Center, in evaluating 88 men with prostate cancer, confirmed over-activation of TRIM59 protein in men with early prostate cancer but not men with late stage prostate cancer, in keeping with our findings that TRIM59 over activation is an early event in tumorigenesis.

Summary of ongoing research projects: we will extend our investigations of TRIM59 an early molecular marker of tumorigenesis in kidney cancer and prostate cancer patients and explore the significance of TRIM59 in other malignancies by utilization of TMA (Tissue MicroArray) bank in Department of Pathology. (2) We will test TRIM59 shRNA in cultured prostate cancer cells utilization of targeted microbubbles to facilitate efficient transfer in to cells for therapy. We will study several Ras associated genes, including TRIM59 determine significance of TRIM59 as a novel proto-oncogene in the important Ras signaling pathway. Our finding of this novel gene in the Ras pathway, TRIM59, provides us with a unique opportunity for the development of a novel marker for molecular detection of early cancer development and possibly therapeutic strategies for prevention and treatment.

We do not, from the past till now, use SV40 virus or SV40Tag oncogene in any cell lines. We only used SV40Tag DNA in cloning procedure in *E.coli* in 2001. We have used SV40 Tag in genetically engineered mouse prostate cancer models since 2001. We have got animal protocols approval since 2001, (e.g.# 2008-098, #2004-74-09 etc) in this regard. In any cases from the past till now, there have been no use of SV40 virus or SV40Tag in cell culture studies (PC3, NIH3T3) in our lab. SV40 Tag is a gene, part of SV40 virus, However, it does not produce any SV40 virus at all.

Names of all personnel working under Principal Investigators supervision in this location:

Vida Khatamianfar

Rucha Khandekar

1.0 Microorganisms

1.1 Does your work involve the use of biological agents? x YES O NO
(including but not limited to bacteria and other microorganisms, viruses, prions, parasites or pathogens of plant or animal origin)? If no, please proceed to Section 2.0

Do you use microorganisms that require a permit from the CFIA? x YES O NO
If YES, please give the name of the species. _____
What is the origin of the microorganism(s)? __E.coli, DH5α_____
Please describe the risk (if any) of escape and how this will be mitigated: _____
All used plates, cultured cells will be autoclaved.

Please attach the CFIA permit.
Please describe any CFIA permit conditions:

1.2 Please complete the table below:

Name of Biological agent(s)*	Is it known to be a human pathogen? YES/NO	Is it known to be an animal pathogen? YES/NO	Is it known to be a zoonotic agent? YES/NO	Maximum quantity to be cultured at one time? (in Litres)	Source/ Supplier	PHAC or CFIA Containment Level
E.coli, DH5α	O Yes x No	O Yes x No	O Yes x No	1 litter		x 1 x 2 O 3
	O Yes O No	O Yes O No	O Yes O No			O 1 O 2 O 3
	O Yes O No	O Yes O No	O Yes O No			O 1 O 2 O 3
	O Yes O No	O Yes O No	O Yes O No			O 1 O 2 O 3

*Please attach a Material Safety Data Sheet or equivalent from the supplier.

2.0 Cell Culture

2.1 Does your work involve the use of cell cultures? x YES O NO
If no, please proceed to Section 3.0

2.2 Please indicate the type of primary cells (i.e. derived from fresh tissue) that will be grown in culture:

Cell Type	Is this cell type used in your work?	Source of Primary Cell Culture Tissue	AUS Protocol Number
Human	x Yes O No	N/A	Not applicable
Rodent	x Yes O No	N/A	
Non-human primate	O Yes O No		
Other (specify)	O Yes O No		

*** DESCRIPTION MUST BE ATTACHED TO THIS FORM OR PROJECT WILL NOT BE REVIEWED***

2.3 Please indicate the type of established cells that will be grown in culture in:

Cell Type	Is this cell type used in your work?	Specific cell line(s)*	Supplier / Source
Human	x Yes O No	PC3, DU145, LNCaP	ATCC
Rodent	x Yes O No	NIH 3T3	ATCC
Non-human primate	O Yes x No		
Other (specify)	O Yes x No		

*Please attach a Material Safety Data Sheet or equivalent from the supplier. (For more information, see www.atcc.org)

2.4 For above named cell types(s) indicate PHAC or CFIA containment level required O 1 x2 O 3

3.0 Use of Human Source Materials

3.1 Does your work involve the use of human source materials? O YES x NO
If no, please proceed to Section 4.0

3.2 Indicate in the table below the Human Source Material to be used.

Human Source Material	**Source/Supplier /Company Name**	**Is Human Source Material Infected With An Infectious Agent? YES/NO**	**Name of Infectious Agent (If applicable)**	**PHAC or CFIA Containment Level (Select one)**
Human Blood (whole) or other Body Fluid		O Yes x No O Unknown		O 1 O 2 O 3
Human Blood (fraction) or other Body Fluid		O Yes x No O Unknown		O 1 O 2 O 3
Human Organs or Tissues (unpreserved)		O Yes x No O Unknown		O 1 O 2 O 3
Human Organs or Tissues (preserved)		Not Applicable		Not Applicable

4.0 Genetically Modified Organisms and Cell lines
Mouse prostate cancer models established since 2001
4.1 Will genetic modifications be made to the microorganisms, biological agents, or cells described in Sections 1.0 and 2.0? O YES x NO If no, please proceed to Section 5.0

4.2 Will genetic modification(s) involving plasmids be done? x YES, complete table below O NO

Bacteria Used for Cloning *	Plasmid(s) *	Source of Plasmid	Gene Transfected	Describe the change that results
E,coli	*PBluescript derived*			*N/A.*

* Please attach a Material Data Sheet or equivalent if available.

*** DESCRIPTION MUST BE ATTACHED TO THIS FORM OR PROJECT WILL NOT BE REVIEWED***

4.3 Will genetic modification(s) involving viral vectors be made? O YES, complete table below x NO

Virus Used for Vector Construction	Vector(s) *	Source of Vector	Gene(s) Transduced	Describe the change that results

* Please attach a Material Safety Data Sheet or equivalent.

4.4 Will genetic sequences from the following be involved?

- HIV O YES, please specify _____ x NO
- HTLV 1 or 2 or genes from any Level 1 or Level 2 pathogens O YES, specify _____ x NO
- SV 40 Large T antigen x YES O NO
- E1A oncogene O YES x NO
- Known oncogenes O YES, please specify _SV40Tag_____ O NO
- Other human or animal pathogen and or their toxins O YES, please specify _____ x NO

4.5 Will virus be replication defective? N/A O YES O NO

4.6 Will virus be infectious to humans or animals? N/A O YES O NO

4.7 Will this be expected to increase the containment level required? N/A O YES O NO

5.0 Human Gene Therapy Trials

5.1 Will human clinical trials be conducted involving a biological agent? O YES x NO
(including but not limited to microorganisms, viruses, prions, parasites or pathogens of plant or animal origin)
If no, please proceed to Section 6.0

5.2 If YES, please specify which biological agent will be used: _____
Please attach a full description of the biological agent.

5.2 Will the biological agent be able to replicate in the host? O YES x NO

5.3 How will the biological agent be administered? _____

5.4 Please give the Health Care Facility where the clinical trial will be conducted:_____

5.5 Has human ethics approval been obtained? O YES, number: _____ x NO O PENDING

6.0 Animal Experiments

6.1 Will live animals be used? x YES O NO If no, please proceed to section 7.0

6.2 Name of animal species to be used___C57BL6 mouse_____

6.3 AUS protocol # ____2008-98_____

6.4 Will any of the agents listed in section 4.0 be used in live animals O YES, specify: _____ x NO

6.5 Will the agent(s) be shed by the animal: O YES x NO, please justify:

_____

_____

*** DESCRIPTION MUST BE ATTACHED TO THIS FORM OR PROJECT WILL NOT BE REVIEWED***

7.0 Use of Animal species with Zoonotic Hazards

7.1 Will any of the following animals or their organs, tissues, lavages or other body fluids including blood be used?

- Pound source dogs O YES x NO
- Pound source cats O YES x NO
- Cattle, sheep or goats O YES xNO
- Non-human primates O YES, please specify species _____ x NO
- Wild caught animals O YES, please specify species & colony # _____ x NO
- Birds O YES x NO
- Others (wild or domestic) O YES, please specify _____Rabbit antiserum_____ ___NO

8.0 Biological Toxins

8.1 Will toxins of biological origin be used? O YES x NO If no, please proceed to Section 9.0

8.2 If YES, please name the toxin(s)_____
Please attach information, such as a Material Safety Data Sheet, for the toxin(s) used.

8.3 What is the LD_{50} (specify species) of the toxin_____

8.4 How much of the toxin is handled at one time*? _____

8.5 How much of the toxin is stored*? _____

8.6 Will any biological toxins be used in live animals? O YES, Please provide detais:_____ O NO

*For information on biosecurity requirements, please see:
http://www.uwo.ca/humanresources/docandform/docs/healthandsafety/biosafety/Biosecurity_Requirements.pdf

9.0 Insects Requiring CFIA Permits

9.1 Do you use insects that require a permit from the CFIA? O YES x NO
If no, please proceed to Section 10.0

9.2 If YES, please give the name of the species. _____

9.3 What is the origin of the insect? _____

9.4 What is the life stage of the insect? _____

9.5 What is your intention? O Initiate and maintain colony, give location: _____
O "One-time" use, give location: _____

9.6 Please describe the risk (if any) of escape and how this will be mitigated:
_____

9.7 Please attach the CFIA permit.

9.8 Please describe any CFIA permit conditions:
_____
_____

*** DESCRIPTION MUST BE ATTACHED TO THIS FORM OR PROJECT WILL NOT BE REVIEWED***

10.0 Plants Requiring CFIA Permits

10.1 Do you use plants that require a permit from the CFIA? O YES x NO
If no, please proceed to Section 11.0

10.2 If YES, please give the name of the species. _____

10.3 What is the origin of the plant? _____

10.4 What is the form of the plant (seed, seedling, plant, tree...)? _____

10.5 What is your intention? O Grow and maintain a crop O "One-time" use

10.6 Do you do any modifications to the plant? O YES O NO
If yes, please describe: _____
_____

10.7 Please describe the risk (if any) of loss of the material from the lab and how this will be mitigated:
_____
_____
_____

10.8 Is the CFIA permit attached? O YES O NO
If NO, please forward the permit to he Biosafety Officer when available.

10.9 Please describe any CFIA permit conditions:
_____
_____
_____

11.0 Import Requirements

11.1 Will any of the above agents be imported? O YES, please give country of origin_____
If no, please proceed to Section 12.0 x NO

11.2 Has an Import Permit been obtained from HC for human pathogens? O YES O NO

11.3 Has an import permit been obtained from CFIA for animal or plant pathogens? O YES O NO

11.4 Has the import permit been sent to OHS? O YES, please provide permit # _____ O NO

12.0 Training Requirements for Personnel Named on Form

All personnel named on the above form who will be using any of the above named agents are required to attend the following training courses given by OHS:

- Biosafety
- Laboratory and Environmental/Waste Management Safety
- WHMIS (Western or equivalent)
- Employee Health and Safety Orientation

As the Principal Investigator, I have ensured that all of the personnel named on the form who will be using any of the biohazardous agents in Sections 1.0 to 9.0 have been trained.

SIGNATURE _____Dr. Jim W Xuan_____

*** DESCRIPTION MUST BE ATTACHED TO THIS FORM OR PROJECT WILL NOT BE REVIEWED***

13.0 Containment Levels

11.1 For the work described in sections 1.0 to 9.0, please indicate the highest HC or CFIA Containment Level required. O 1 x 2 O 3

13.2 Has the facility been certified by OHS for this level of containment?
x YES, permit # if on-campus_____
O NO, please certify
O NOT REQUIRED for Level 1 containment

Level 2 certified on June 14, 2008 by Mike Ryden.

14.0 Procedures to be Followed

14.1 As the Principal Investigator, I will ensure that this project will follow the Western Biosafety Guidelines and Procedures Manual for Containment Level 1 & 2 Laboratories (and the Level 3 Facilities Manual for Level 3 projects). I will ensure that UWO faculty, staff and students working in my laboratory have an up-to-date Hazard Communication Form, found at http://www.wph.uwo.ca/

SIGNATURE _____ **Date:**_____

14.2 Please describe additional risk reduction measures will be taken beyond containment level 1, 2, or 3 measures, that are unique to this agent.
We will follow all stadandard procedures for those routinely used chemicals (toxic, flammable): phenol, Ethedium bromide (EB), chroform, zylene, ethanol, methanol. Beta-mercaptoethanol...
We do not have any irregular release on those chemicals, so everything will keep good order. All lab people have take UWO courses already.

14.3 Please outline what will be done if there is an exposure to the biohazards listed, such as a needlestick injury:
First is to avoid from happening (we never have this experience in our lab), i.e. to remind lab people be careful.
In case accident, cleaning all released materials, stop bleeding, washing, may go to staff health....

15.0 Approvals

UWO Biohazard Subcommittee: SIGNATURE: _____
Date:_____

Safety Officer for Institution where experiments will take place: SIGNATURE: Mike Ryden
Date: January 11, 2010

Safety Officer for University of Western Ontario (if different from above): SIGNATURE:_____
Date:_____

Approval Number: _____ Expiry Date (3 years from Approval): _____

Special Conditions of Approval:

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			PHOTO
Source:	**Organ:** embryo **Cell type:** fibroblast; fibroblast		
Permits/Forms:	In addition to the MTA mentioned above, other ATCC and/or regulatory permits may be required for the transfer of this ATCC material. Anyone purchasing ATCC material is ultimately responsible for obtaining the permits. Please click here for information regarding the specific requirements for shipment to your location.		

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Biosafety Level:	1	**Shipped:**	frozen
Medium & Serum:	See Propagation	**Growth Properties:**	adherent(The cells form clusters in soft agar and can be adapted to suspension growth)
Organism:	*Homo sapiens* (human)	**Morphology:**	epithelial

P1010

Source:
Organ: prostate
Disease: adenocarcinoma
Tumor stage: grade IV
Derived from metastatic site: bone

Permits/Forms: In addition to the MTA mentioned above, other ATCC and/or regulatory permits may be required for the transfer of this ATCC material. Anyone purchasing ATCC material is ultimately responsible for obtaining the permits. Please click here for information regarding the specific requirements for shipment to your location.

12/10/2007 2:48 PM

Ontario Institute of Cancer Research, Research grant (07NOV-52), "Molecular diagnosis and therapy of prostate cancer by UTMD (ultrasound targeted microbubbles destruction) technology in genetically engineered mouse models" PI Jim W Xuan, Co-applicants: Madeleine Moussa, Siu-Pok Yee, Glenn S. Bauman, Aaron Fenster

Lay Summary

Describe in non-scientific terms the research to be carried out, materials and technologies to be employed and how the research will contribute to OICRs mandate. Note that OICR and the Ontario Government may use this description in whole or in part for news releases or promotional material.

Specific *in vivo* delivery of drugs is a key goal for all therapies. We propose the first application of UTMD (Ultrasound Targeted Microbubbles Destruction) technology for prostate tissue targeting, molecular diagnosis and therapy in our two genetically engineered mouse prostate cancer models.

Many human diseases, including cancer, are the consequence of multiple factors and multiple consecutive procedures, therapy targeted only on one factor/gene will be less effective than targeting simultaneously to multiple factors. For this purpose, we propose an improved **Compound MBs enhanced UTMD (CME-UTMD)** strategy, which will enable us to include multiple therapeutic agents in to each targeted microbubble for *in vivo* delivery simultaneously. Both preventional and interventional therapy targeting to several well studied genes in our laboratory will be performed and monitored by micro- and molecular imaging in our citywide multidisciplinary team.

Scientific Summary

Provide a detailed scientific summary of the proposed research including the rationale for the approach, the milestones and aims and how the research may lead to better cancer treatments. Note that OICR and the Ontario Government may use this description in whole or in part for news releases or promotional material.

CaP (prostate cancer) is the most common cancer in adult men in North America. Since there is no naturally occurring CaP in rodents, both basic and preclinical studies employ genetically engineered (GE) mouse with autochthonous CaP. Currently, the most widely used GEM-CaP models all utilize the SV40 Tag oncogene, which demonstrates the complete process of tumorigenesis, tumor progression and metastasis and thereby more accurately recapitulate the biology of human CaP. We have established two PSP94 gene-directed TransGenic (TGMAP, Gene Therapy2002) and Knock In (KI) Mouse Adenocarcinoma Prostate (MAP) (Oncogene 05) models. The knock in model (KIMAP) represents the first application of knock-out mouse technology to generate GEM-CaP.

Specific *in vivo* delivery of drugs or treatments to tumor tissues is always the key issue for all therapies, including chemotherapy, radiotherapy, surgery, and gene therapy. Currently there is no effective way for tissue specific delivery of chemicals (including RNAi technology) *in vivo*, we propose **the first application of UTMD (Ultrasound Targeted Microbubbles Destruction) technology** for precise prostate tissue targeted delivery of therapeutic agents *in vivo* in animal models. Microbubbles (MBs) are small bubbles constructed of a lipid shell and fill with a biologically inert gas as a contrast agent for imaging. MBs as contrast materials require a small dosage and show excellent detection sensitivity. UTMD takes advantage of the physical properties of MBs to enable *in vivo* tissue-specific focal release of entrapped materials in the sonification zone, such as oligopeptides, plasmid DNA, siRNA and recombinant viruses, together with the imaging contrast materials, this will result in a technological innovation from the conditional knockout (Cre-LoxP system) in that, the process may take a few seconds to days instead of years.

For molecular diagnosis and prognosis, we propose to use Flk1 (VEGFR2) and CD31 for conjugating of targeted microbubbles for molecular targeted imaging of prostate cancer in both of our TGMAP and KIMAP mice. The application to KIMAP will more closely mimic clinical CaP situation. We have obtained published results as pilot studies in these two genes (Can Res 2005, 2007).

For molecular therapy, we must consider that all human diseases are caused by multiple factors and multiple consecutive procedures, targeted therapy only on one factor/gene will less effective than targeting simultaneously to multiple factors. For this purpose, we propose an improved **Compound MBs enhanced UTMD (CME-UTMD)** strategy, which will enable us to include multiple therapeutic agents into each targeted microbubble for *in vivo* delivery. Both preventional and interventional therapy targeting to several well studied genes in our laboratory will be performed and monitored by micro- and molecular imaging in our citywide multidisciplinary team.

Our citywide multi-disciplinary research team consists of molecular biologists, oncologists, urologists, imaging specialists, biophysicists, and pathologists. We have the expertise in micro- and molecular imaging (Can Res 05, 07) and UTMD technology (manuscript in submission) in our GEM-CaP mice. The current proposals will be continuing our current UTMD molecular imaging work with the targeted MBs in our CaP models. Since MBs have been approved by US FDA as type IV contrast agent, we are confident that by developing UTMD technology to interfere SV40Tag oncogene induced tumorigenesis *in vivo* in our GEM-CaP models, will enable us to develop new strategies for therapies on new tumorigenesis targets in pre- clinical studies of CaP, which would potentially lead to clinical trials.