Modification Form for Permit BIO-RRI-0029

Permit Holder: David Hess

Approved Personnel
(Please stroke out any personnel to be removed)

Paige Thompson

David Putman

Heather Broughton

Gillian Bell

Debra Robson

Additional Personnel
(Please list additional personnel here)

	Please stroke out any approved Biohazards to be removed below	Write additional Biohazards for approval below. *
Approved Microorganisms		
Approved Cells	[Primary] (Human): Bone marrow, umbilical cord blood. (Mouse): Bone marrow. [Established]) (Human): Fibroblasts HS792 (C)M, skin fibroblast HS707 (B). Ep. (Rodent): MDA-MB-231	Beta-TC-6 mouse beta cell line
Approved Use of Human Source Material	Human blood (whole) or other body fluid, Unpreserved human organ or tissues: human bone marrow.	
Approved GMO	[Plasmid] - pGIPZ	
Approved use of Animals	(mice): NOD/SCID, NoD/SCID K-2R null, NoD/SCID/MPSVI ← Capital "O"	
Approved Toxin(s)		

* *PLEASE ATTACH A MATERIAL SAFETY DATA SHEET OR EQUIVALENT FOR NEW BIOHAZARDS.*
** *PLEASE ATTACH A BRIEF DESCRIPTION OF THE WORK THAT EXPLAINS THE BIOHAZARDS USED AND HOW THEY WILL BE USED.*

As the principal investigator, I have ensured that all of the personnel named on the form have been trained. 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 of Permit Holder: David Hess

Classification: 2

Date of Last Biohazardous Agents Registry Form: Nov 24, 2009

Date of Last Modification (if applicable): David Hess

BioSafety Officer(s):

Chair, Biohazards Subcommittee:

Beta-TC-6 cell line will be used for *in vitro* analysis: characterization of cell surface markers and behaviour in cell culture as a control compared to bone marrow and cord blood derived cell lines.

Cell Biology

ATCC® Number:	**CRL-11506™** Order this Item	Price:	**$349.00**
Designations:	Beta-TC-6		
Depositors:	CytoTherapeutics, Inc.		
Biosafety Level:	2 [Cells contain SV40 viral DNA Sequences]		
Shipped:	frozen		
Medium & Serum:	See Propagation		
Growth Properties:	adherent		
Organism:	Mus musculus, transgenic for SV40 large T antigen (mouse, transgenic for SV40 large T antigen)		
Morphology:	epithelial 		
Source:	**Organ:** pancreas **Disease:** insulinoma **Cell Type:** beta cell;		
Cellular Products:	insulin, glucagon and somatostatin		
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.		
Comments:	The cell line was derived from a pancreatic tumor (insulinoma) arising in a transgenic mouse. The mouse carried the pseudogene construct composed of the SV40 early region controlled by the rat insulin II gene promotor. The cells contain abundant insulin and small amounts of glucagon and somatostatin. They secrete insulin in response to glucose. [46884]		
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formulated Dulbecco's Modified Eagle's medium, Catalog No. 30-2002. To make the complete growth medium, add the following components to the base medium: heat-inactivated fetal bovine serum to a final concentration of 15%. **Atmosphere:** air, 95%; carbon dioxide (CO2), 5% **Temperature:** 37.0°C		

Related Links
NCBI Entrez Search
Cell Micrograph
Make a Deposit
Frequently Asked Questions
Material Transfer Agreement
Technical Support
Related Cell Culture Products

Subculturing:

Protocol:

1. Remove and discard culture medium.
2. Briefly rinse the cell layer with 0.25% (w/v) Trypsin-0.53 mM EDTA solution to remove all traces of serum that contains trypsin inhibitor.
3. Add 2.0 to 3.0 ml of Trypsin-EDTA solution to flask and observe cells under an inverted microscope until cell layer is dispersed (usually within 5 to 15 minutes). Note: To avoid clumping do not agitate the cells by hitting or shaking the flask while waiting for the cells to detach. Cells that are difficult to detach may be placed at 37°C to facilitate dispersal.
4. Add 6.0 to 8.0 ml of complete growth medium and aspirate cells by gently pipetting.
5. Add appropriate aliquots of the cell suspension to new culture vessels.
6. Incubate cultures at 37°C.

Preservation:

Subcultivation Ratio: A subcultivation ratio of 1:3 to 1:4 is recommended

Freeze medium: Complete growth medium supplemented with 5% (v/v) DMSO

Storage temperature: liquid nitrogen vapor phase

Related Products:

Recommended medium (without the additional supplements or serum described under ATCC Medium):ATCC 30-2002

References:

46126: Laurance ME, et al. Glucose responsive insulin secreting beta-cell lines and method for producing same. US Patent 5,773,255 dated Jun 30 1998

46884: Poitout V, et al. Morphological and functional characterization of beta TC-6 cells--an insulin-secreting cell line derived from transgenic mice. Diabetes 44: 306-313, 1995. PubMed: 7533732

46885: Poitout V, et al. Insulin-secreting cell lines: classification, characteristics and potential applications. Diabetes Metab. 22: 7-14, 1996. PubMed: 8697299

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Ron Noseworthy

From: David Hess [dhess@robarts.ca]
Sent: January 12, 2010 1:52 PM
To: Ron Noseworthy
Subject: Re: Biohazard Modification

Absolutely Ron, these cell lines will not be infected with retrovirus or lentivirus vectors.

Dave Hess

>Hi Dr. Hess,
>
>Can you confirm that the cells on your most recent modification:
>HS707(B) and Beta-TC-6 will not be infected with Retro or lentivral
>vectors?
>
>Thanks
>
>Ron
>Ron Noseworthy MCIC CRSP
>Manager, Occupational Health and Safety Robarts Research Institute UWO,
>Schulich School of Medicine and Dentistry 100 Perth Drive, P.O. Box
>5015 London, Ontario N6A 5K8
>Phone: 519-663-5777 ext. 24125
>Fax: 519-931-5267
>

--
David A. Hess PhD

Assistant Professor, Department of Physiology and Pharmacology University of Western Ontario Scientist, Vascular Biology Group Krembil Centre for Stem Cell Biology Robarts Research Institute PO Box 5015, 100 Perth Drive, Room E4-19 London, Ontario, Canada, N6A 5K8
Office: 519-663-5777 ext. 24152
Lab: 519-663-5777 ext. 24415
Fax: 519-663-3789
email: dhess@robarts.ca

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	David Hess
SIGNATURE	David Hess
DEPARTMENT	Robarts Research Institute/Physiology & Pharmacology
ADDRESS	100 Perth Dr., London, Ont., N6A 5K8
PHONE NUMBER	519-663-5777 x 24152
EMERGENCY PHONE NUMBER(S)	519-645-2703
EMAIL	dhess@robarts.ca

Location of experimental work to be carried out: Building(s) Robarts Room(s) 4250, 4244A Robarts Experimental Surgical

*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: CIHR, Canadian Heart and Stroke Foundation
GRANT TITLE(S): MOP# 86702 "Formation of a regenerative niche for the recovery of beta cell function"; MOP# 86759 "~~Molecular~~ Cellular constituents and paracrine factors that mediate functional vascular regenerato

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.

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

Heather Broughton - Technician
Debbie Robson - Technician
Gillian Bell - Graduate Student
David Eatman - Graduate Student
Paige Thompson - Undergrad Student

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

1.1 Does your work involve the use of biological agents? O YES ✓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? O YES O NO
If YES, please give the name of the species. _____
What is the origin of the microorganism(s)? _____
Please describe the risk (if any) of escape and how this will be mitigated:

_____
_____
_____

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
	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
	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? ✓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	✓Yes O No	Human bone Marrow Human umbilical cord blood	Not applicable
Rodent	✓Yes O No	Mouse bone Marrow.	2006-126-12 2006-122-12
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	✓ Yes O No	Human Fibroblasts HS 72(C).M Human Skin Fibroblast HS 707(B).Lep Human Breast Cancer MDA-MB-231	- ATCC - ATCC - ATCC
Rodent	O Yes ✓ No		
Non-human primate	O Yes ✓ No		
Other (specify)	O Yes ✓ 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~~ ~~O~~ 2 O 3

3.0 Use of Human Source Materials

3.1 Does your work involve the use of human source materials? ✓ YES O 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	UCH - St. Joe's Birthing Center ~~BM - University Hosp.~~	~~O~~ Yes O No O Unknown	Not Applicable	O 1 ✓ 2 O 3
Human Blood (fraction) or other Body Fluid		O Yes ✓ No O Unknown		O 1 O 2 O 3
Human Organs or Tissues (unpreserved)	Human Bone Marrow University Hospital	~~O~~ Yes ✓ No O Unknown	Not Applicable	O 1 ✓ 2 O 3
Human Organs or Tissues (preserved)		Not Applicable		Not Applicable

4.0 Genetically Modified Organisms and Cell lines

4.1 Will genetic modifications be made to the microorganisms, biological agents, or cells described in Sections 1.0 and 2.0? ✓ YES O NO If no, please proceed to Section 5.0

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

Bacteria Used for Cloning *	Plasmid(s) *	Source of Plasmid	Gene Transfected	Describe the change that results
None - purified DNA only	pGIPZ	Open Biosystems	- shRNA Nodal - shRNA Control	- exp. inhibition of Nodal expression = tumor cell growth and angiogen - control - no change

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

4.3 Will genetic modification(s) involving viral vectors be made? O YES, complete table below ☑ 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 _____ O NO
- HTLV 1 or 2 or genes from any Level 1 or Level 2 pathogens O YES, specify _____ O NO
- SV 40 Large T antigen O YES O NO
- E1A oncogene O YES O NO
- Known oncogenes O YES, please specify _____ O NO
- Other human or animal pathogen and or their toxins O YES, please specify _____ O NO

4.5 Will virus be replication defective? O YES O NO

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

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

5.0 Human Gene Therapy Trials

5.1 Will human clinical trials be conducted involving a biological agent? O YES ☑ 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 O 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: _____ O NO O PENDING

6.0 Animal Experiments

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

6.2 Name of animal species to be used NOD/SCID, NOD/SCID IL-2Rγnull, NOD/SCID/MPSVII

6.3 AUS protocol # 2006-126-12 and 2006-

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

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

_____

_____

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

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

8.0 Biological Toxins

8.1 Will toxins of biological origin be used? O YES ⊘ 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 ⊘ 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 ✓ 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 ✓ 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

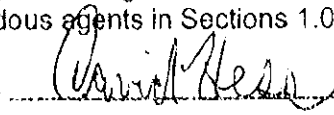
11.4 Has the import permit been sent to OHS? O YES, please provide permit # _____ O NO

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 

*** 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 ✓ 2 O 3

13.2 Has the facility been certified by OHS for this level of containment?
✓ YES, permit # if on-campus Bio-RA1-0029
O NO, please certify
O NOT REQUIRED for Level 1 containment

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 David Head Date: November 12, 2009

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.

14.3 Please outline what will be done if there is an exposure to the biohazards listed, such as a needlestick injury:

15.0 Approvals

UWO Biohazard Subcommittee: SIGNATURE: G M Keller
Date: 24 Nov. 2009

Safety Officer for Institution where experiments will take place: SIGNATURE: Ronald Nostadt
Date: November 23, 2009

Safety Officer for University of Western Ontario (if different from above): SIGNATURE: JHanley
Date: NOV 23/09

Approval Number: Bio-RA1-0029 Expiry Date (3 years from Approval): NOV 23, 2012

Special Conditions of Approval:

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

-------- Original Message --------
Subject: Fw: Fwd: Re: pGIPZ plasmid
Date: Mon, 23 Nov 2009 08:29:41 -0500
From: Ron Noseworthy <rnoseworthy@robarts.ca>
To:jstanle2@uwo.ca

Hi Jennifer

Here the response from Dr. Hess regarding the plasmid.

Ron

----- Original Message -----
From: David Hess <dhess@robarts.ca>
To: Ron Noseworthy
Sent: Sun Nov 22 10:48:51 2009
Subject: Fwd: Re: pGIPZ plasmid

Hi Ron,

Please find below Lynne Postovit's response to our inquiry aboout the pZGIP plasmid system she uses in her lab for the Nodal shRNA knockdown.

Please let me know if this is sufficient for the Biohazzard Committee.

Thanks

David

>Date: Fri, 20 Nov 2009 16:28:59 -0500
>From: "Lynne Postovit" <Lynne.Postovit@schulich.uwo.ca>
>To: "David Hess" <dhess@robarts.ca>
>Subject: Re: pGIPZ plasmid
>
>Hey Dave:
>
>We did not use a lentiviral transduction. We simply use the
>plasmid. The cells were transfected via traditional methods with
>arrestin.
>
>Thanks!
>
>Lynne

>
>Lynne-Marie Postovit, PhD
>Assistant Professor
>438 Medical Science Building
>Dept. of Anatomy & Cell Biology
>The Schulich School of Medicine
>University of Western Ontario
>London, Ontario
>Canada N6A 5C1
>Phone: (519) 661-2111 x 80524
>Fax: (519) 661-3936
>
>
>>>> David Hess <dhess@robarts.ca> 11/20/2009 2:54 PM >>>
>Hi Lynne,
>
>Our Biohazzard renewal was reviewed today by the committee and I have
>been asked to provide more information on the pGIPZ vector that you
>use to transfect the shRNA int6o the MDA-231 cells.
>
>They are concerned that this is a lentiviral transduction vector
>which would push our biohazzard level to the intrepid level 2+. I
>told our biohazzard representative that this is not a lentiviral
>transduction and just the pGIPZ plasmid is used. However he needs
>this in writing.
>
>Can you send me a short email explaining how you use the pGIPZ vector
>with these cells and state clearly that you in no way use a full
>lentiviral transduction?
>
>I will forward this email to Ron and we will be all cleared.
>
>Thanks
>
>Dave
>
>PS. Me and my grad student Dave are going to the grad club now. It
>would be great if you could join us! See you there!
>--
>David A. Hess PhD
>
>Assistant Professor, Department of Physiology and Pharmacology
>University of Western Ontario
>Scientist, Vascular Biology Group

Formation of a regenerative niche for the endogenous recovery of beta-cell function.

Background. Due to an extreme shortage donor islet tissue available for transplantation via the Edmonton protocol, alternate strategies to support the expansion of insulin-secreting beta-cells are continually sought. However, in the context of regenerative therapies for diabetes the contributions of transplanted stem cells are not limited to direct replacement of damaged cells. We have previously established that transplanted bone marrow cells recruit to damaged islets, induce proliferation in recipient beta-cells, and enhance insulin secretion and glycemic control via the regeneration of endogenous beta-cell function. *However, the essential cellular players and paracrine growth factors that form a regenerative niche for endogenous beta-cell recovery remains largely unidentified.*

Bone marrow (BM) and umbilical cord blood (UCB) contain several primitive cell types that demonstrate regenerative potential after transplantation. However, reliable purification of these rare regenerative progenitors has proven inefficient. We have established unique stem cell isolation procedures using high aldehyde dehydrogenase (ALDH) activity in combination with primitive cell surface markers to select highly-purified hematopoietic, endothelial, and hematopoietic progenitor cells from human BM. On the basis of ALDH-activity we have identified highly-purified human cells that reduce hyperglycemia after transplantation into novel immune-deficient murine recipients. Investigation of the following specific aims will identify human cell lineages that form a "regenerative niche" in the murine pancreas, and will identify conserved paracrine-signaling molecules that mediate the endogenous recovery of beta-cell function.

Specific Aims. (1) To establish human hematopoietic, endothelial, and mesenchymal progenitor cell expansion *in vitro*. ALDH-purified cells from human BM and UCB will establish mesenchymal, endothelial, and hematopoietic expansion cultures and progenitor differentiation will be characterized.
(2) To identify paracrine factors secreted by human ALDH^{hi} mesenchymal, endothelial, or hematopoietic progenitors that augment beta-cell proliferation and insulin production *in vitro*. Putative regenerative progenitor subtypes will be compared for the production of developmental, endocrine, and inflammatory mediators. Co-culture of progenitors with isolated murine islets will document paracrine induction of beta-cell proliferation or insulin production *in vitro*.
(3) To determine which human progenitor lineage(s) are recruited to the pancreas and to identify paracrine factors that mediate the recovery of beta-cell function *in vivo*. We will transplant ALDH-purified progenitor cells, or lineage-restricted expanded progeny (*Aim 1*) to assess the ability of distinct human progenitor cells to induce beta-cell regeneration. Donor cell recruitment to peri-islet regions, endogenous beta-cell proliferation and insulin production, and recovery from hyperglycemia will be assessed in streptozotocin-treated NOD/SCID IL-2Rγ null or NOD/SCID/MPSVII mice, novel models for the sensitive detection of transplanted human cells *in situ*. Engrafted cells will be reacquired by FACS and compared for the production of developmental, endocrine, and inflammatory mediators that impact the regeneration of beta-cell function *in vivo*.
(4) To modulate the regenerative niche and augment recovery of beta-cell function. Human mesenchymal progenitor cells will be engineered by retroviral transduction or siRNA technologies to over- or under-express key mediators of beta cell regeneration (such as GLP-1 or HGF), in order to augment the recovery of beta-cell function after transplantation *in vivo*.

Hypotheses. (1) Transplanted myeloid progeny of hematopoietic CFC will recruit to peri-islet regions and initiate endogenous beta-cell regeneration via paracrine mechanisms. **(2)** Peri-islet secretion of developmental and endocrine-acting cytokines will induce beta-cell proliferation, increase insulin

production, and accelerate the recovery from hyperglycemia. **(3)** Co-delivery of supportive mesenchymal-stromal cells will reduce local inflammation and enhance survival of regenerating islets.

Relevance. We will identify the cellular constituents and paracrine pathways that support endogenous beta-cell regeneration. These studies will provide pre-clinical justification for the development of novel cellular therapies to regenerate functional beta cell mass during the treatment of diabetes.

Cellular progenitors and molecular mediators of functional vascular regeneration.

Rationale

Rapid revascularization of diseased or ischemic organs is critical to all regenerative processes, allowing the delivery of circulating cells that formulate a regenerative niche. We have previously established that transplanted human bone marrow (BM) stem cells induce functional revascularization in immune deficient mice with critical limb ischemia (Capoccia et al, (2009) *Blood*). Transplanted purified progenitor cells with hematopoietic and mesenchymal phenotypes engrafted in ischemic regions, and induced mouse capillary formation and recovery of perfusion. This concept termed *stem cell-mediated vascular regeneration* has emerged as a central process during tissue repair after injury.

Background

Human BM and umbilical cord blood represent easily procured sources of progenitor cells from hematopoietic, endothelial, and mesenchymal stromal lineages that potentially modulate angiogenesis. Using high aldehyde dehydrogenase (ALDH) activity, an enzyme involved in the protection of cells from oxidative insult, we have identified a novel population of mixed-lineage progenitor cells based on a conserved stem cell function. High ALDH-activity isolates hematopoietic progenitor cells that reconstitute human hematopoiesis in immune-deficient mice. High ALDH-expression also enriched for expandable colony forming cells with endothelial and mesenchymal functions, rare regenerative cell types difficult to procure using typical stem cell surface markers. Intravenously transplanted $ALDH^{hi}$ cells exhibit widespread tissue infiltration by non-hematopoietic cells, home efficiently ischemic tissues, and augment the endogenous revascularization of ischemic muscle tissue. Thus, cell selection using high ALDH-activity isolates multiple expandable progenitor lineages that potentially direct vessel formation through conserved paracrine mechanisms. *The specific progenitor lineages recruited to ischemic areas, the molecules secreted by regenerative cells, and the signaling pathways engaged in responding endothelial cells (EC) are currently unknown.*

Hypotheses

(1) Hypoxia-expanded progenitor cells of distinct lineages will secrete pro-angiogenic cytokines that promote vascular EC survival, proliferation, and tubule formation *in vitro*.

(2) Transplanted progenitors cells will recruit to ischemic regions and generate a pro-angiogenic microenvironment to potentiate endogenous revascularization *in vivo*.

(3) Mesenchymal progenitor cells will act as pericytes to organize blood vessel assembly and stabilize perfused neovessels through the local secretion of pro-angiogenic cytokines.

Objectives

(1) To characterize the hematopoietic, endothelial, and mesenchymal progenitor functions of expanded under normoxic versus hypoxic culture.

(2) To characterize molecules secreted by human hematopoietic, endothelial, or mesenchymal progenitor cells that support EC survival, proliferation, and tubule formation in vitro.

(3) To document the engraftment of transplanted cells in the ischemic region, and to characterize the purified progenitor cells blood vessel assembly in vivo.

(4) To characterize the molecular pathways that blood vessel formation in vivo.

Relevance

Using unique *in vitro* co-culture systems and progenitor cell transplantation into novel immune-deficient mice with tissue ischemia, we will identify human cells that augment blood vessel formation, and functionally characterize molecular pathways that co-ordinate endogenous vascular regeneration. We propose that the cellular mechanisms that govern vascular repair in ischemic muscle will be conserved in other tissues such as damaged myocardium after infarct, or neural tissue after stroke. ***Ultimately, this research will contribute to the development of novel drug and/or cellular therapies to treat ischemic tissue dysfunction in patients with diabetes, heart disease, and stroke.***

Product Description

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Cell Biology

ATCC® Number:	**CRL-7522™** Order this Item	**Price:**	**$417.00**
Designations:	Hs 792(C).M		**Related Links ▸**
Biosafety Level:	1		NCBI Entrez Search
Shipped:	frozen		Make a Deposit
Medium & Serum:	See Propagation		Frequently Asked Questions
Growth Properties:	adherent		Material Transfer Agreement
Organism:	*Homo sapiens* (human)		Technical Support
Morphology:	fibroblast		Related Cell Culture Products
Source:	**Tissue:** muscle; connective and soft tissue **Disease:** normal **Cell Type:** 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.		
Cytogenetic Analysis:	modal number = 46; range = 41 to 46		
Age:	29 years		
Gender:	female		
Ethnicity:	Caucasian		
Comments:	Part of the NBL Cell Line Collection. This cell line is neither produced nor fully characterized by ATCC . We do not guarantee that it will maintain a specific morphology, purity, or any other property upon passage. Please see the NBL Repository description.		
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formulated Dulbecco's Modified Eagle's Medium, Catalog No. 30-2002. To make the complete growth medium, add the following components to the base medium: fetal bovine serum to a final concentration of 10%. **Atmosphere:** air, 95%; carbon dioxide (CO2), 5% **Temperature:** 37.0°C		

Subculturing:	**Protocol:** 1. Remove and discard culture medium. 2. Briefly rinse the cell layer with 0.25% (w/v) Trypsin- 0.53 mM EDTA solution to remove all traces of serum that contains trypsin inhibitor. 3. Add 2.0 to 3.0 ml of Trypsin-EDTA solution to flask and observe cells under an inverted microscope until cell layer is dispersed (usually within 5 to 15 minutes). Note: To avoid clumping do not agitate the cells by hitting or shaking the flask while waiting for the cells to detach. Cells that are difficult to detach may be placed at 37°C to facilitate dispersal. 4. Add 6.0 to 8.0 ml of complete growth medium and aspirate cells by gently pipetting. 5. Add appropriate aliquots of the cell suspension to new culture vessels. 6. Incubate cultures at 37°C. **Subcultivation Ratio:** A subcultivation ratio of 1:2 to 1:3 is recommended **Medium Renewal:** Every 2 to 3 days
Preservation:	**Freeze medium:** Complete growth medium supplemented with 5% (v/v) DMSO **Storage temperature:** liquid nitrogen vapor phase
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium):ATCC 30-2002 derived from same individual:ATCC CRL-7520 recommended serum:ATCC 30-2020 derived from same individual:ATCC CRL-7521 derived from same individual:ATCC CRL-7522

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All prices are listed in U.S. dollars and are subject to change without notice. A discount off the current list price will be applied to most cultures for nonprofit institutions in the United States. Cultures that are ordered as test tubes or flasks will carry an additional laboratory fee. Fees for permits, shipping, and handling may apply.

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Preservation:	culture medium 95%; DMSO, 5%
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium):ATCC 30-2002 recommended serum:ATCC 30-2020

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Cell Biology

ATCC® Number:	CRL-7449™ Order this Item
Designations:	Hs 707(B).Ep
Biosafety Level:	1
Shipped:	frozen
Medium & Serum:	See Propagation
Growth Properties:	adherent
Organism:	*Homo sapiens* (human)
Morphology:	fibroblast
Source:	**Organ:** skin **Tissue:** epidermis **Disease:** normal
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.
Cytogenetic Analysis:	modal number = 46; range = 45 to 46
Age:	13 years
Gender:	male
Ethnicity:	Caucasian
Comments:	The line was established from apparently normal skin tissue from a patient who had osteogenic sarcoma. Part of the NBL Cell Line Collection. This cell line is neither produced nor fully characterized by ATCC . We do not guarantee that it will maintain a specific morphology, purity, or any other property upon passage. Please see the NBL Repository description.
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formulated Dulbecco's Modified Eagle's Medium, Catalog No. 30-2002. To make the complete growth medium, add the following components to the base medium: fetal bovine serum to a final concentration of 10%. **Temperature:** 37.0°C
Subculturing:	**Subcultivation Ratio:** A subcultivation ratio of 1:2 to 1:4 is recommended **Medium Renewal:** Every 2 to 3 days Remove medium, and rinse with 0.25% trypsin, 0.03% EDTA solution. Remove the solution and add an additional 1 to 2 ml of trypsin-EDTA solution. Allow the flask to sit at room temperature (or at 37C) until the cells detach. Add fresh culture medium, aspirate and dispense into new culture flasks.

Price: $417.00

Related Links
- NCBI Entrez Search
- Make a Deposit
- Frequently Asked Questions
- Material Transfer Agreement
- Technical Support
- Related Cell Culture Products

Preservation:	culture medium 95%; DMSO, 5%
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium):ATCC 30-2002 recommended serum:ATCC 30-2020

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All prices are listed in U.S. dollars and are subject to change without notice. A discount off the current list price will be applied to most cultures for nonprofit institutions in the United States. Cultures that are ordered as test tubes or flasks will carry an additional laboratory fee. Fees for permits, shipping, and handling may apply.

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Product Description

Before submitting an order you will be asked to read and accept the terms and conditions of ATCC's Material Transfer Agreement or, in certain cases, an MTA specified by the depositing institution.
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Cell Biology

ATCC® Number: HTB-26™ Order this Item

Price: $256.00

Designations: MDA-MB-231

Depositors: R Cailleau

Biosafety Level: 1

Shipped: frozen

Medium & Serum: See Propagation

Growth Properties: adherent

Organism: *Homo sapiens* (human)

Morphology: epithelial

Source:
Organ: mammary gland; breast
Disease: adenocarcinoma
Derived from metastatic site: pleural effusion
Cell Type: epithelial

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.

Applications: transfection host (Nucleofection technology from Lonza
Roche FuGENE® Transfection Reagents)

Receptors: epidermal growth factor (EGF), expressed
transforming growth factor alpha (TGF alpha), expressed

Tumorigenic: Yes

DNA Profile (STR):
Amelogenin: X
CSF1PO: 12,13
D13S317: 13
D16S539: 12
D5S818: 12
D7S820: 8,9
THO1: 7,9.3
TPOX: 8,9
vWA: 15,18

Cytogenetic Analysis: The cell line is aneuploid female (modal number = 64, range = 52 to 68), with chromosome counts in the near-triploid range. Normal chromosomes N8 and N15 were absent. Eleven stable rearranged marker chromosomes are noted as well as unassignable chromosomes in addition to the majority of autosomes that are trisomic. Many of the marker chromosomes are identical to those shown in the karyotype reported by K.L. Satya-Prakash, et al.

Related Links ▸
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Cell Micrograph
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Frequently Asked Questions
Material Transfer Agreement
Technical Support
Related Cell Culture Products

Isoenzymes:	AK-1, 1 ES-D, 1 G6PD, B GLO-I, 2 Me-2, 1-2 PGM1, 1-2 PGM3, 1
Age:	51 years adult
Gender:	female
Ethnicity:	Caucasian
Comments:	The cells express the WNT7B oncogene [PubMed: 8168088].
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formulated Leibovitz's L-15 Medium, Catalog No. 30-2008. To make the complete growth medium, add the following components to the base medium: fetal bovine serum to a final concentration of 10%. **Atmosphere:** air, 100% **Temperature:** 37.0°C
Subculturing:	**Protocol:** 1. Remove and discard culture medium. 2. Briefly rinse the cell layer with 0.25% (w/v) Trypsin- 0.53 mM EDTA solution to remove all traces of serum that contains trypsin inhibitor. 3. Add 2.0 to 3.0 ml of Trypsin-EDTA solution to flask and observe cells under an inverted microscope until cell layer is dispersed (usually within 5 to 15 minutes). Note: To avoid clumping do not agitate the cells by hitting or shaking the flask while waiting for the cells to detach. Cells that are difficult to detach may be placed at 37°C to facilitate dispersal. 4. Add 6.0 to 8.0 ml of complete growth medium and aspirate cells by gently pipetting. 5. Add appropriate aliquots of the cell suspension to new culture vessels. 6. Incubate cultures at 37°C without CO2. **Subcultivation Ratio:** A subcultivation ratio of 1:2 to 1:4 is recommended **Medium Renewal:** 2 to 3 times per week
Preservation:	**Freeze medium:** Complete growth medium supplemented with 5% (v/v) DMSO **Storage temperature:** liquid nitrogen vapor phase
Related Products:	purified DNA:ATCC 45518 purified DNA:ATCC 45519 purified DNA:ATCC HTB-26D purified RNA:ATCC HTB-26R recommended serum:ATCC 30-2020 Recommended medium (without the additional supplements or serum described under ATCC Medium):ATCC 30-2008

References:

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ASSURANCES & APPROVALS: (TO BE COMPLETED BY GRADUATE STUDENT)

All research proposals involving human and/or animal subjects, biohazardous or radioactive materials must be approved by a Western ethics, animal-care, or biohazards/radioactive review committee.

Indicate with an X on the chart below the current status of the approvals required for this proposal.

If approval has already been granted, an electronic copy of the approval notice must accompany this application.

		STATUS					
HUMAN SUBJECTS ETHICS APPROVAL	No human subjects	Approval granted	X	Pending		To be sought	
		Authorization #: 12934					
ANIMAL SUBJECTS APPROVAL	No animal subjects	Approval granted	X	Pending		To be sought	
		Authorization #: 2006-126-12					
BIOHAZARDOUS MATERIALS CLEARANCE	No biohazardous materials	Approval Granted	X	Pending		To be sought	
		Authorization #: BIO-RRI-0029 Pending renewal					
RADIOACTIVE MATERIALS CLEARANCE	No radioactive materials	Approval granted	X	Pending		To be sought	
		Authorization #: 2352-RRI-208					

Western

Date: 09 30 2008

Dear Dr. Hess

An ANIMAL NUMBER ADJUSTMENT to your Animal Use Protocol #2006-126-12 entitled **Characterization of the Angiogenic Potential of Aldehyde Dehydrogenase Expressing Stem Cells from Human Bone Marrow** has been approved.

These animal numbers are approved from 09 12 2008 until the protocol full expiry date 12 31 2010

SPECIES	STRAIN &/or OTHER SPECIES DETAIL	AGE or WEIGHT	SEX	ANIMAL NUMBER
Mouse	NOD SCID B2Mnull, bred at RBF	used at 6-12 weeks	M F	750
Mouse	NOD SCID VPS VII, bred at RBF	used at 6-12 weeks	M F	425
Mouse	NOD SCID bred at RBF	used at 6-12 weeks	Female	250
Mouse	NOD SCID IL2Rgamma null bred at RBF	used at 6-12 weeks	Female	250

c.c Approval Letter - D Hess, K Lovac, M Pickering

The University *of* Western Ontario
Animal Use Subcommittee / University Council on Animal Care
Health Sciences Centre, London, Ontario, CANADA, N6A 5C1
TEL 519-661-2111 ext 86330 FL 519-661-2028 www.uwo.ca/animal

Western

Biosafety Approval Number: BIO-RRI-0029

Expiry Date: October 23, 2009

July 22, 2008

Dear Dr. Hess:

Please note your biosafety approval number listed above. This number is very useful to you as a researcher working with biohazards. It is a requirement for your research grants, purchasing of biohazardous materials and Level 2 inspections.

Research Grants:

- This number is required information for any research grants involving biohazards. Please provide this number to Research Services when requested.

Purchasing Materials:

- This number must be included on purchase orders for Level 1 or Level 2 biohazards. When you order biohazardous material, use the on-line purchase ordering system (www.uwo.ca/finance/people/). In the "Comments to Purchasing" tab, include your name as the Researcher and your biosafety approval number.

Annual Inspections:

- If you have a Level 2 laboratory on campus, you are inspected every year. This is your permit number to allow you to work with Level 2 biohazards.

To maintain your Biosafety Approval, you need to:

- Ensure that you update your Biohazardous Agents Registry Form at least every three years, or when there are changes to the biohazards you are working with.
- Ensure that the people working in your laboratory are trained in Biosafety.
- Ensure that your laboratory follows the University of Western Ontario Biosafety Guidelines and Procedures Manual for Containment Level 1 & 2 Laboratories.
- For more information, please see: www.uwo.ca/humanresources/biosafety.

Please let me know if you have questions or comments.

Regards,

Jennifer Stanley
Biosafety Coordinator for Western
Stevenson Lawson Building Room 295G
Phone: 519-661-2111 X81135
Fax: 519-661-3420

Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Western

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. D.A. Hess

Review Number: 12934 **Revision Number:** 1

Review Date: February 28, 2008 **Review Level:** Expedited

Protocol Title: Transplantation of human stem cells for the induction of angiogenesis and the regeneration of beta-cell function

Department and Institution: Vascular Biology, Robarts Research Institute

Sponsor: JUVENILE DIABETES RESEARCH FOUNDATION

Ethics Approval Date: February 28, 2008 **Expiry Date:** October 31, 2009

Documents Reviewed and Approved: revised study end date

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald

Ethics Officer to Contact for Further Information

☐ Janice Sutherland (jsutherl@uwo.ca)	☑ Jennifer McEwen (jmcewen4@uwo.ca)	☐ Grace Kelly (grace.kelly@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

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LHRI