MMPC
National Mouse Metabolic Phenotyping Center

60 years NIDDK 1950 2010 NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
60 Years of Advancing Research to Improve Health
Research supported by NIDDK

National Mouse Metabolic Phenotyping Center at UMass Medical School

Jason K. Kim, Ph.D.

MMPC National Steering Committee Meeting

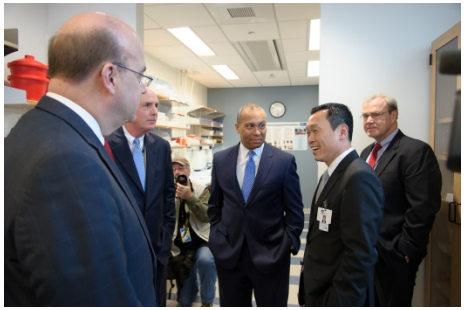
University of California, Davis

November 7, 2013

UMass MMPC

Administrative Core:	**Jason Kim, Ph.D.**
Animal Core:	**Jerald Silverman, D.V.M.**
Metabolism Core:	**Jason Kim, Ph.D., Dae Young Jung, Ph.D.**
Analytical Core:	**David Harlan, M.D., Randall Friedline, Ph.D.**

Albert Sherman Center



- ✓ **On Jan. 30th, a ribbon-cutting ceremony for the opening of the $400 million, 512,000-sq-ft Albert Sherman Center took place attended by Gov. Deval Patrick.**
- ✓ **The UMass MMPC is located at the 9th floor (lab space) and 2nd floor animal facility.**

Albert Sherman Center Inaugural Scientific Symposium

The University of Massachusetts Medical School

Presents the

Albert Sherman Center Inaugural Scientific Symposium

Thursday, October 10, 2013

1:00 PM - Welcome by Chancellor Michael Collins and Dean Terence Flotte

Joseph L. Goldstein, M.D.

Chairman, Department of Molecular Genetics at the University of Texas Southwestern Medical Center

1:15 p.m. - *"Scap: Anatomy of a Sterol Sensor. Part 1"*

Michael S. Brown, M.D.

Professor of Molecular Genetics and Director of the Jonsson Center for Molecular Genetics at the University of Texas Southwestern Medical Center

2:10 p.m. - *"Scap: Anatomy of a Sterol Sensor. Part 2"*

Carolyn M. Clancy, M.D.

Assistant Deputy Undersecretary for Health, Quality Safety and Value for Veterans Administration

3:35 p.m. - *"From Knowledge to Impact: Better Care and Health"*

Robert S. Langer Sc.D.

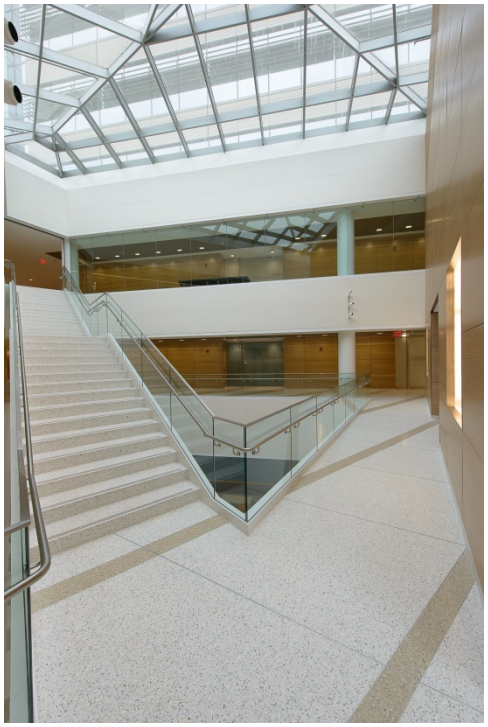
Institute Professor at Massachusetts Institute of Technology

4:20 p.m. - *"Controlled Drug Delivery and Tissue Engineering for Angiogenesis Inhibitors"*

5:15 PM - Reception in the Foyer and CUBE

Albert Sherman Center Auditorium

University of Massachusetts Medical School
55 Lake Avenue North
Worcester, MA



UMass MMPC – Administrative Core

Center Director:	**Jason Kim, Ph.D.**
Associate Director:	**Roger Davis, Ph.D.**
Administrator:	**Elana Hastings, M.S.**
Biostatistics:	**Bruce Barton, Ph.D.**
External Advisor:	**Michael Czech, Ph.D.**

UMass MMPC – Administrative Core

UMPC Metabolism Core
55 Lake Avenue North
Worcester, MA 01655

Invoice - Academic

Date	Invoice #
3/12/2013	PM13-8

Order Identifier
5687

Remit Check Payments to:
UMass Medical School
55 Lake Avenue North
Worcester, MA 01655
Attn: Bursar's Office

Visa or Mastercard Also Accepted
Call 508-856-2248

Bill To
Harvard/Joslin Mary-Elizabeth Patti

FEIN# 04-316 7352

Terms	Purchase Order
Due on receipt	

Description	Project	Quantity	Rate	Amount
Academic Metabolic Cages		24	200.00	4,800.00
Academic Hyperinsulinemic-euglycemic clamp		40	380.00	15,200.00
Academic 1H-MRS for body composition		48	0.00	0.00

Please Send A Copy of This Invoice to the Bursar's Office with Check Payment

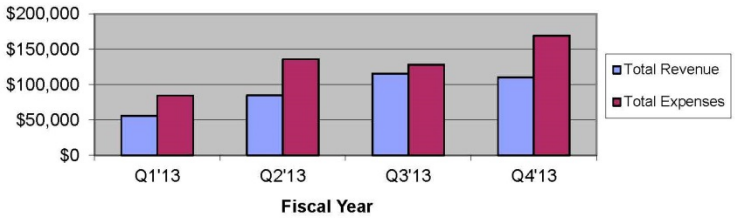
Note to Bursar - Speed Chart 114788

FOR INVOICE QUESTIONS CONTACT ELANA HASTINGS

Total $20,000.00

Phone #	Fax #	E-mail	Web Site
508-856-6840	508-856-6881	Dennis.Rosencrance@umassmed.edu	http://www.umassmed.edu/umpc/index.aspx

Mouse Phenotyping Consolidation
Fund 51126



Beginning Fund Balance *0*

	FY'12 YE	Q1'13	Q2'13	Q3'13	Q4'13	FY'13 YTD
Revenue	**148,560**	18,650	16,710	29,985	37,076	**102,421**
U-24 Grant	**215,481**	37,354	68,090	85,600	73,412	**264,455**
Total Revenue	**364,041**	56,004	84,800	115,585	110,488	**366,876**
Expenses	**387,404**	47,258	67,888	42,806	95,871	**253,823**
U-24 Grant	**215,481**	37,354	68,090	85,600	73,412	**264,455**
Total Expenses	**602,885**	84,612	135,978	128,406	169,283	**518,278**
Net Balance	**(238,844)**	(28,608)	(51,178)	(12,821)	(58,795)	**(151,402)**
Molecular Med	**238,845**	28,257	48,196	15,093	59,856	**151,402**
					Ending Fund Balance	*0*

Outstanding Revenue:

* Animal Core U-24 $32,204 Expenses included in Totals

Personnel	**Core**	**U24 Grant**
Jason Kim		9%
Azuma, Yoshihiro		
Benoit, Vivian		75%
Hastings, Elana	50%	50%
Hu, Xiaodi	50%	50%
Jung, Dae Young		100%
Patel, Payal		25%
Freidline, Randall		25%
Wang, Hsun-Fan	100%	
Total FTE	**2.0**	**3.3**

University of Massachusetts Medical School

QUARTERLY REPORT OF RESEARCH CORE ADMINISTRATION

Fiscal Year 2013
April 1, 2013—June 30, 2013

OFFICE OF RESEARCH

- ✓ **Overseen by Office of Vice Provost for Research and Dean's Office**
- ✓ **40 core facilities on campus**
- ✓ **$16.4M revenue in FY13**
- ✓ **$20M expense in FY13**
- ✓ **$3.2M subsidy from UMMS**
- ✓ **Research Core Open House in Fall and Spring**
- ✓ **Bioinformatics Core, Deep Sequencing Core, Morphology Core, Tissue & Enzyme Reagent Supply Core, Vectore Core, Advanced MRI Center, Humanized Mouse Core, Mutagenesis Core**

UMass MMPC – Administrative Core

Hyperinsulinemic-euglycemic clamp

Version: 1
Edited by: Jason Kim

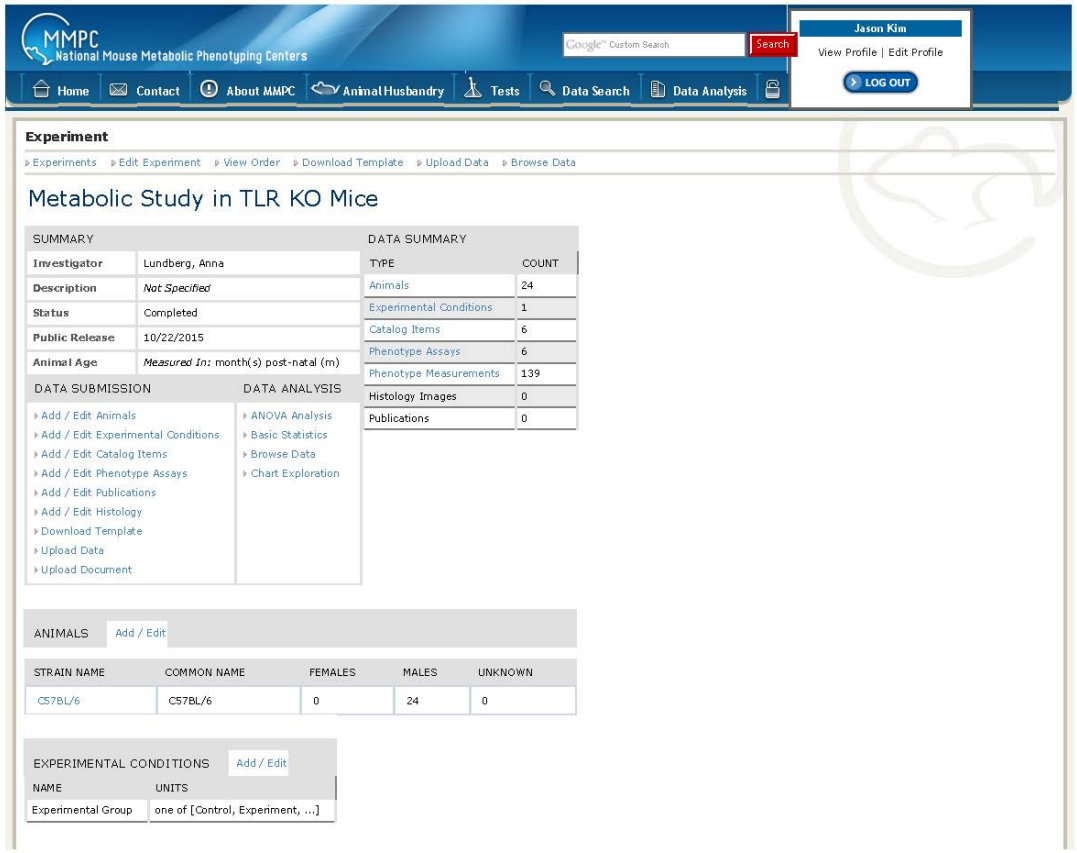
(note that the following list should be linked to the appropriate location.)

Summary: *(This area will include a brief description of what the protocol is used for and why someone would need to use it.)*

Hyperinsulinemic-euglycemic clamp is the gold-standard method to assess insulin sensitivity. The hyperinsulinemic-euglycemic clamp is widely used in clinics and laboratories to measure insulin action on glucose utilization in humans and animals for clinical and basic science research. Incorporation of radioactive-labeled glucose during hyperinsulinemic-euglycemic clamps makes it possible to measure glucose metabolism in individual organs in awake mice. Impaired insulin sensitivity (insulin resistance) is a major characteristic of obesity and an early requisite event in the development of type 2 diabetes.

Reagents and Materials: *(This should be a comprehensive list of stock solutions and material. The reagent list for the stock solutions is included in the reagent preparation area that is included at the end of this SOP.)*

Reagent/Material	Vendor	Stock Number
HelixMark Standard Silicone Tubing	Helix Medical, Inc.	0.012" ID / 0.025" OD
[3-^{3}H] D-glucose	Perkin Elmer	NET331C005MC
2-[1-^{14}C] Deoxy-D-glucose	Perkin Elmer	NEC495001MC
0.9 % Sodium Chloride, Injection, USP	B.Braun Medical Inc	NDC0264-4001-55
Pentobarbital	Oak Pharmaceuticals, Inc.	NDC76478-501-50
Microdialysis pumps	CMA/Microdialysis	CMA402
Analox GM7 Micro-stat Rapid Multi-assay Analyser	Analox Instruments Ltd.	GM7
Insulin	Novolin	Regular human insulin, U-100
20 % Dextrose, injection, USP	Hospira	NDC0409-7935-19
0.9 % Sodium Chloride, Injection, USP	B.Braun Medical Inc	NDC0264-4001-55
1 ml tuberculin syringes	BD	REF 309659



UMass MMPC Internal Users (Year 2)

User	Department	Service Core
Mike Czech	Molecular Medicine	Metabolism/Analytical
Roger Davis	Molecular Medicine	Metabolism/Analytical
Michael Schwartz	Medicine – Neurology	Metabolism
Michael Green	Gene Function & Expression	Metabolism
Laura Alonso	Medicine – Diabetes	Metabolism
Neil Aronin	Medicine – Endocrinology	Analytical
John Keaney	Cardiology	Analytical
Michelle Kelliher	Medicine	Analytical
Guangping Gao	Medicine – Gene Therapy	Analytical
Kate Fitzgerald	Medicine	Analytical
Douglas Golenbock	Medicine – Infectious D.	Analytical
Chris Mueller	Medicine	Analytical
Lisa Selin	Medicine - Pathology	Analytical

UMass MMPC External Users (Year 2)

User	Department	Service Core
Gokhan Hotamisligil	Harvard Public Health	Metabolism/Analytical
Mary-Elizabeth Patti	Harvard – Joslin Diabetes Ct.	Metabolism/Analytical
Alan Saghatelian	Harvard – Chemistry	Metabolism/Analytical
William Aird	Harvard – BIDMC	Metabolism/Analytical
Ta-Yuan Chang	Dartmouth	Metabolism/Analytical
Anna Lundberg	Sweden – Karolinska Inst.	Metabolism/Analytical
Jiandie Lin	University of Michigan	Metabolism/Analytical
Shengkan Jin	Rutgers University	Metabolism/Analytical
Rajeev Malhotra	Harvard – MGH	Metabolism
Ann Marie Schmidt	New York University	Metabolism
Michelle Pardue	Emory University	Analytical
C. Michael Hart	Emory University	Analytical
Ian Rifkin	Boston University	Analytical
Martha Stipanuk	Cornell University	Analytical
Xiao-feng Yang	Temple University	Analytical

UMass MMPC Publications (Year 2)

User	Institution	Publications
Roger Davis	UMass Medical School	*Genes & Dev* 27:2345-2355
Roger Davis	UMass Medical School	*Science* 339:218-222
Roger Davis	UMass Medical School	*Cell Reports* 4:681-688
Jiandie Lin	University of Michigan	*Nature Med* 19:640-645
Susan Gray	UMass Medical School	*PLoS One* 8(10):e77851
Gerald Karsenty	Columbia University	*Cell Metab* 16:588-600
Forest White	MIT	*Integrative Biology* 5:940-963
Amy Lee	Univ. of Southern Calif.	*FASEB J* 27:955-964
Michael Czech	UMass Medical School	*Am J Physiol* 304:E951-E963
Barbara Miller	Penn State University	*Am J Physiol* 304:C548-C560
Hayla Sluss	UMass Medical School	*Endo Research* 38:139-150
Guangping Gao	UMass Medical School	*Nature Methods* 9:403-409
Joel Richter	UMass Medical School	*PLoS Genetics* 8:e1002457
Fawaz Haj	UC Davis	*Endocrinology* 153:3158-3169
Angela Valverde	Spain – CSIC/UAM	*Aging Cell* 11:284-296
Sonia Najjar	University of Toledo	*Diabetologia* 55:763-772

UMass MMPC Supporting Grants Submitted by NIH-funded Investigators (Year 2)

Investigator	Institution	Funding Agency
Mary-Elizabeth Patti	Harvard Medical School	NIH
Masako Shimada	Harvard Medical School	NIH
Keertik Fulzele	Harvard Medical School	NIH
Nick Stylopoulos	Harvard Medical School	NIH
Miklos Peterfy	UCLA	NIH
Shankar Subramaniam	UC San Diego	NIH
Ira Goldberg	Columbia University	NIH
Changcheng Zhou	University of Kentucky	NIH
Jiandie Lin	University of Michigan	NIH
Andrea Zsombok	Tulane University	NIH & Am. Diabetes Assoc.
Jongsook Kim Kemper	Univ. of Illinois at Urbana-C.	NIH
Abraham Kovoor	Univ. of Rhode Island	NIH
Yong-Xu Wang	UMass Medical School	NIH
David Weaver	UMass Medical School	NIH
Usha Acharya	UMass Medical School	NIH

UMass MMPC – Animal Core

Director: Jerald Silverman, D.V.M.

Coordinator: Valerie Romer

- ✓ Provide stable, biocontainment housing, husbandry, and health care for mice using MMPC-dedicated animal house room
- ✓ Process and monitor quarantine procedure of external mice
- ✓ Receipt and evaluate animal health report for mouse shipping
- ✓ Transport and transfer of internal mice
- ✓ Assess the microbiological profile of each cohort

✓ **The UMass MMPC Animal Core, housing, and procedure facility are located at the 2nd floor of Albert Sherman Center.**

UMass MMPC – Metabolism Core

Director:	**Jason Kim, Ph.D.**
Co-Director:	**Dae Young Jung, Ph.D.**
Staff:	**Xiaodi Hu, M.S.**
	Hsun-Fan Wang, M.S.
	Jong Hun Kim, Ph.D.
	Payal Patel, Ph.D.

Dae Young Jung, Ph.D.
Instructor of Molecular Medicine

Metabolism Core is highlighted by hyperinsulinemic-euglycemic clamps to measure insulin sensitivity and glucose metabolism, hyperglycemic clamps to assess β-cell function, ^{1}H-MRS to determine body composition, and metabolic cages to examine food intake, energy expenditure, and physical activity.

UMass MMPC – Metabolism Core

11. Technical data

11.1. O_2 Sensor

Measuring response [2]	
Zero drift	< 0.5%/month of smallest possible span
Measured-value drift	< 0.5%/month of respective span
Repeatability	< 1% of respective span
Linearity deviation	< 0.1% of respective span
Dead time (purging time of gas path in analyzer at 1l/min)	Ca. 0.5 - 2.5s depending on version
Time for internal signal processing	< 1s

[2] Maximum accuracy achieved after 2h.

11.2. CO_2 Sensor

Measuring response [2]	
Zero drift	< ± 1% of measuring range/week
Span drift	< ± 1% of measuring range/week
Repeatability	≤ 1% of respective measuring range
Linearity deviation	< 0.5% of full-scale value
Dead time(purging time of gas path in analyzer at 1l/min)	Ca. 0.5 to 5s depending on version
Time for internal signal processing	< 1s

[2] Maximum accuracy achieved after 2h.

UMass MMPC Metabolism Core (Year 2)

Service	Internal	External	Total
Body composition (^{1}H-MRS)	**3,152**	**642**	**3,794**
Metabolic cages	**609**	**320**	**929**
Jugular vein surgery	**813**	**237**	**1,050**
Hyperinsulinemic-euglycemic clamp	**671**	**212**	**883**
Hyperglycemic clamp	**15**	**25**	**40**
Basal glucose metabolism	**40**	**0**	**40**
Basal lipid metabolism	**28**	**0**	**28**
GTT/ITT	**58**	**0**	**58**
Osmotic pump implantation	**50**	**0**	**50**
Acute lipid infusion	**21**	**0**	**21**
Total Number of Animals	**8,143 (↓ 21%)**	**1,758 (↑ 20%)**	**9,901 (↓16%)**
Total Number of Animals in Year 1	10,366	1,459	11,825

UMass MMPC – Analytical Core

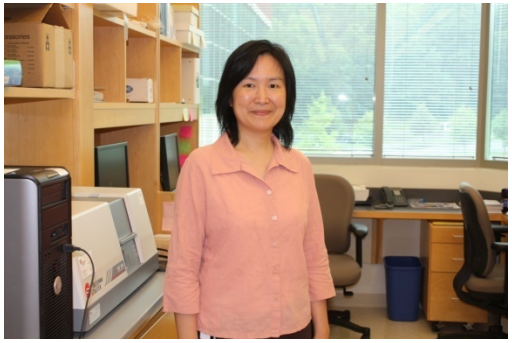
Director:	**David Harlan, M.D.**
Co-Director:	**Randall Friedline, Ph.D.**
Co-Director:	**Bruce Barton, Ph.D.**
Staff:	**Xiaodi Hu, M.S.**
	Hsun-Fan Wang, M.S.

David M. Harlan, M.D.
Director of the Diabetes Center
Director, UMass DERC

Analytical Core utilizes high-throughput instruments to measure hormones, metabolites, and cytokines in serum/tissue samples obtained from mice. The Core also has a leading expertise in islet biology for histological and molecular analysis of islet cells.

UMass MMPC – Analytical Core

Randall Friedline, Ph.D.
Instructor of Molecular Medicine
Co-Director, Analytical Core



Xiaodi Hu, M.S.
Lab Manager

Luminex and Cobas Clinical Chemistry Analyzer

UMass MMPC Analytical Core (Year 2)

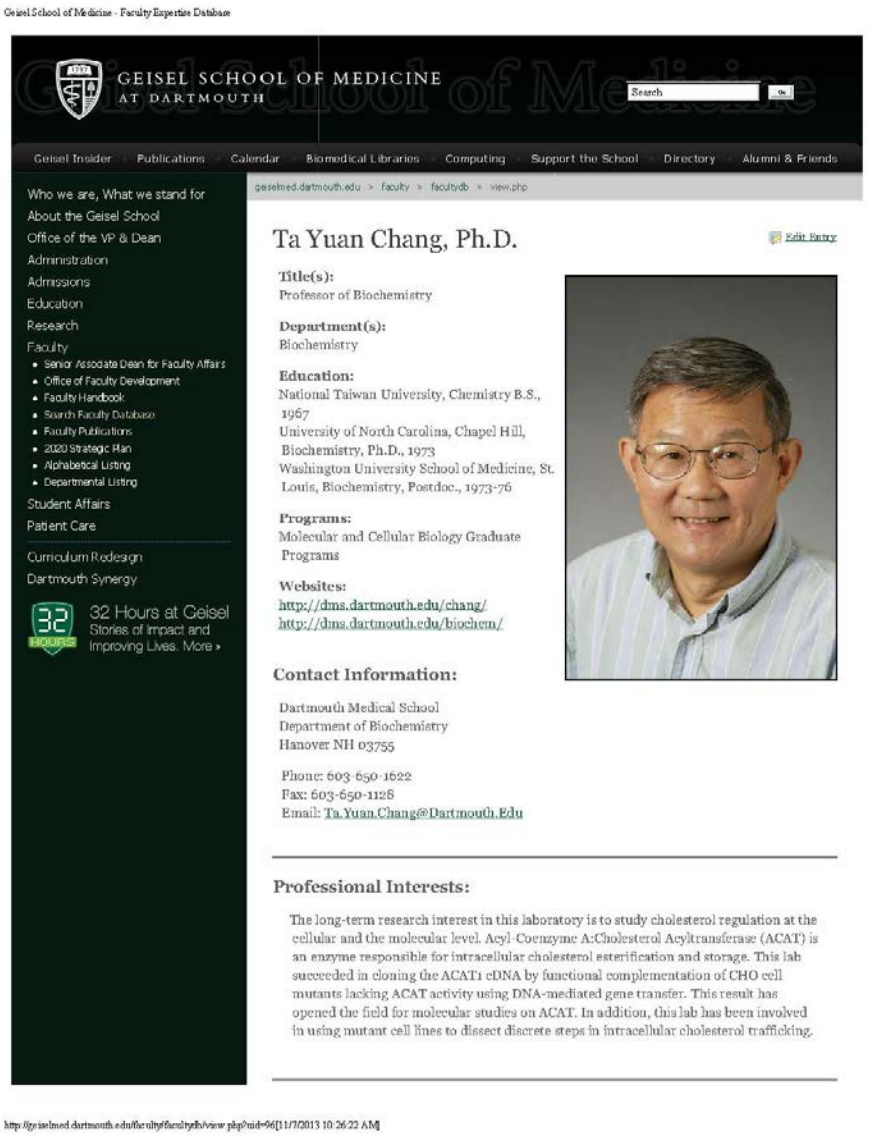
Service	Internal	External	Total
Cytokine panels	**6,939**	**296**	**7,235**
Hormones (insulin, c-peptide, glucagon,corticosterone, FGF21,CRP)	**765**	**218**	**983**
Adipokines (leptin, adiponectin, resistin)	**269**	**555**	**824**
Cholesterol (total, HDL, LDL)	**299**	**134**	**433**
Liver panel (total protein, ALT, AST)	**44**	**25**	**69**
Creatine kinase, urea/BUN, uric acid	**0**	**99**	**99**
Lipid panel (TG, lipase, FFA, b-OHB)	**179**	**146**	**325**
Metabolites (glucose, lactate)	**0**	**110**	**110**
Total Number of Samples	**8,495 (↑ 5%)**	**1,583 (↑ 360%)**	**10,078 (↑ 18%)**
Total Number of Samples in Year 1	8,100	445	8,545

UMass MMPC Revenue in Year 2

	Q1	Q2	Q3	Q4	Year 2
Metabolism Core	**$38,264**	**$3,360**	**$78,338**	**$35,811**	**$155,773 (↓ 10%)**
Analytical Core	**$5,265**	**$9,903**	**$15,584**	**$20,198**	**$50,950 (↑ 55%)**
UMass MMPC	**$43,529 (↓ 25%)**	**$13,263 (↓ 78%)**	**$93,922 (↑ 311%)**	**$56,009 (↓ 4%)**	**$206,723 (↑ 1%)**

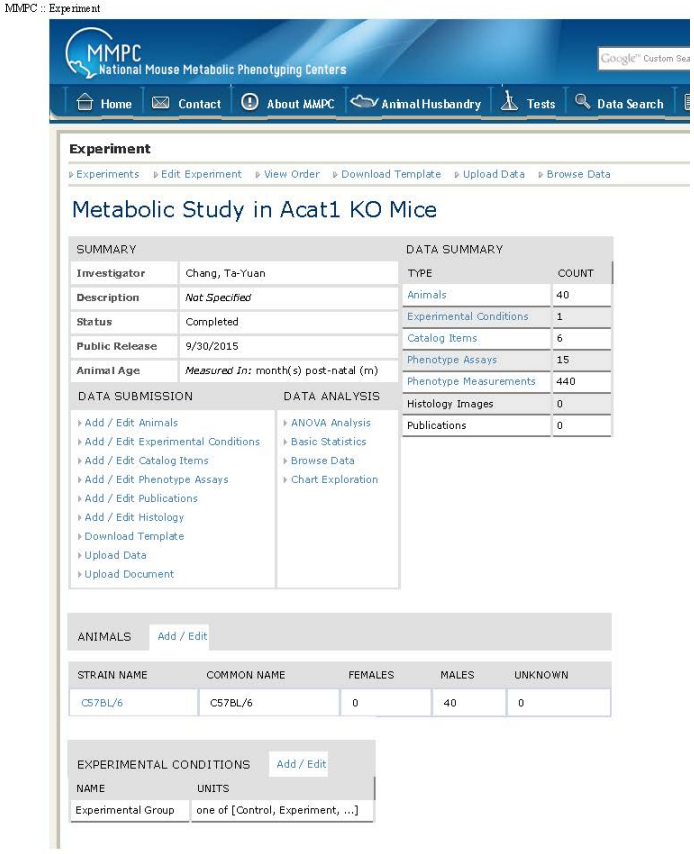
	Q1	Q2	Q3	Q4	Year 1
Metabolism Core	$47,640	$53,690	$23,340	$48,344	$173,013
Analytical Core	$10,251	$5,400	$6,888	$10,274	$32,813
UMass MMPC	$57,891	$59,090	$30,228	$58,618	$205,826

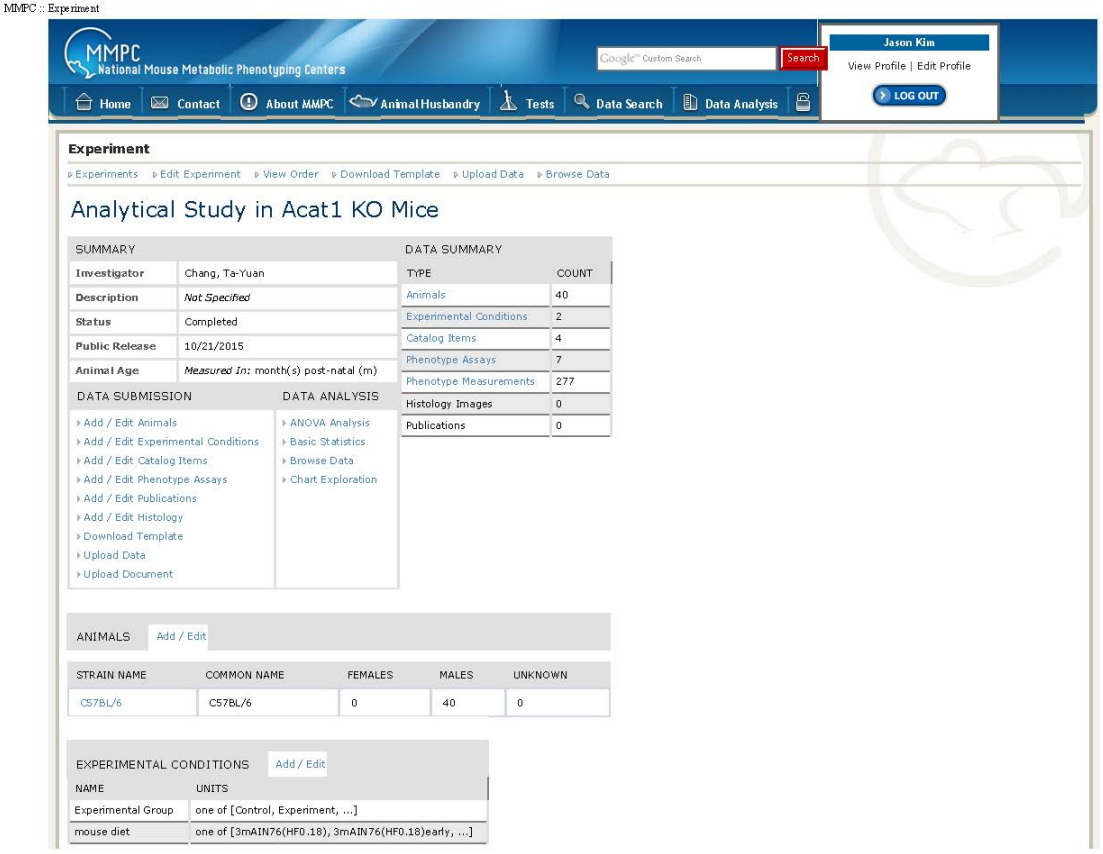
Human Stories in Year 2



- ✓ **Dr. Ta Yuan Chang is a Professor of Biochemistry at Dartmouth.**
- ✓ **Dec. 4th, 2012: Requested to collaborate on metabolic / analytical studies in KO mice.**
- ✓ **Jan. 25th, 2013: MTA approved.**
- ✓ **Feb. 4th, 2013: Mouse health report approved.**
- ✓ **Feb. 15th, 2013: Dartmouth HFD arrived.**
- ✓ **Feb. 19th, 2013: Dartmouth mice arrived.**
- ✓ **Apr. 4th, 2013: Metabolic & analytical studies began.**
- ✓ **Apr 22nd, 2013: 1st batch data were completed.**

Human Stories in Year 2





Human Stories in Year 2

Myeloid acyl-CoA:cholesterol acyltransferase 1 as a new target for obesity

Li-Hao Huang[1], Paul Sohn[1], Elaina M. Melton[1], DaeYoung Jung[2], Maximillian A. Rogers[1], Hiroyuki Sano[1], Tian Ma[3], Steven N. Fiering[4], HyeKyung Ha[2], Randall H. Friedline[2], Jason K. Kim[2], Catherine C.Y. Chang[1,5], and Ta-Yuan Chang[1,5]

Department of [1]Biochemistry, [3]Pharmacology and Toxicology, [4]Immunology and Microbiology, Geisel School of Medicine at Dartmouth, Hanover, NH 03755, USA
[2]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA.
[5]Corresponding authors.

Contact
T.Y.C.: ta.yuan.chang@dartmouth.edu, Tel. 603-650-1622, Fax 603-650-1128

All authors declare no conflicts of interests.

- ✓ Apr 26th, 2013: Teleconference meeting took place to discuss data.
- ✓ Jun 5th, 2013: 2nd batch study began
- ✓ Jun 28th, 2013: 2nd batch data were completed.
- ✓ Aug 5th, 2013: 3rd batch data were completed.
- ✓ Aug 12th, 2013: Dr. Chang requests another study involving KO mice on different genetic background.
- ✓ Oct 5th, 2013: Collaborative manuscript was submitted and currently in review.
- ✓ Oct 7th, 2013: 2nd study began.
- ✓ Oct 25th, 2013: 2nd study data were completed.

Human Stories in Year 2

Center for Vascular Biology Research: Christopher Carman, Ph.D.

William C. Aird, M.D.
Director, Center for Vascular Biology Research
Beth Israel Deaconess Medical Center
Harvard Medical School

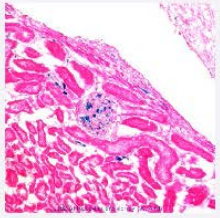
330 Brookline Avenue, RN-237
Boston, MA 02215

Office: 617-667-1033
Fax: 617-667-1035
Email:
waird@bidmc.harvard.edu

EDUCATION/TRAINING/APPOINTMENTS:

Dr. Aird completed medical school and internal residency training in Toronto, Canada. After completing a fellowship in hematology at the Brigham and Women's Hospital, Harvard Medical School and a postdoctoral fellowship in the Department of Biology at Massachusetts Institute of Technology, Dr. Aird established an independent research program at the Beth Israel Deaconess Medical Center in 1996. He is currently Director of the Center for Vascular Biology Research and Chief, Division of Molecular and Vascular Medicine at BIDMC, and Professor of Medicine at Harvard Medical School.

RESEARCH INTERESTS: Endothelial Cell Phenotypes in Health & Disease



Basic Research - Phenotypic heterogeneity of the endothelium plays a critical role not only in subserving the wide needs of underlying tissues and but also in mediating focal vascular pathology. As much as our appreciation of endothelial cell heterogeneity has evolved over the last two decades, our fundamental understanding of the molecular basis of vascular diversity remains poorly developed. My lab is focused on understanding the proximate and evolutionary mechanisms underlying endothelial cell heterogeneity. To that end, we have focused on three related areas.

Mechanisms underlying vascular bed-specific gene expression. We have developed novel tools for dissecting mechanisms of vascular bed-specific gene regulation, including a plug-in-socket approach for targeting a single copy transgene to a defined locus of the mouse genome by homologous recombination. Our studies have revealed a model of modular gene regulation in which the expression of a single gene within the vascular tree is governed by a constellation of vascular bed-specific signaling pathways that begin in the extracellular milieu and end at distinct regions of the promoter. The ultimate goal of this work is to develop a foundation for selectively targeting subsets of endothelial cells in the intact vasculature.

Spatial and temporal regulation of endothelial cell signal transduction. Using a combination of in vitro and in vivo assays, including sepsis models, we have demonstrated that different activation agonists (e.g., vascular endothelial growth factor, thrombin, tumor necrosis factor, and endotoxin) trigger overlapping yet distinct downstream signaling pathways, and that the net effect of a given agonist depends on the history of signal input (i.e., the set point of the cell). The goal of these studies is to understand how we can selectively alter the extracellular microenvironment and/or intracellular signaling to achieve site-specific modulation of endothelial phenotypes.

Evolutionary origins of endothelial heterogeneity. This pursuit is inspired by our belief that every biological trait requires both proximate and evolutionary explanations, and that the phylogeny of the endothelium holds important clues about its core properties and design constraints (i.e., vulnerability to disease). We have shown that the endothelium in hagfish, the oldest extant vertebrate, is heterogeneous in both structure and function. We are presently using molecular tools to explore the phylogenetic history of several functions of the

http://cvbr.bwh.harvard.edu/researchers/aird.html[11/7/2013 10:49:41 AM]

- ✓ **Dr. Bill Aird is the Director of Center for Vascular Biology Research at BIDMC-Harvard Medical School.**
- ✓ **Mar 1st, 2013: Requests a fee-for-service study to study KO/Tg mice.**
- ✓ **May 16th, 2013: MTA approved.**
- ✓ **Jun 5th, 2013: Health report approved.**
- ✓ **Jul 22nd, 2013: Metabolic study began.**
- ✓ **Aug 5th, 2013: Study data were completed.**
- ✓ **Oct 8th, 2013: Data discussion meeting with Dr. Aird and his lab staff took place at UMass MMPC.**
- ✓ **Oct 10th, 2013: A 2nd study is requested and currently in progress.**

Challenges in Year 2

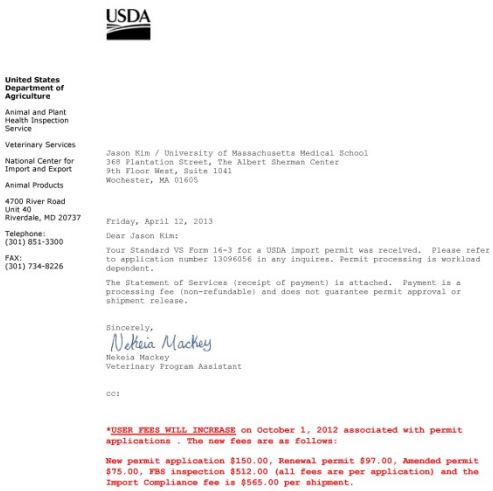
Jan. 25, 2013: Service request from Dr. Anna Lundberg (Karolinska Institute) for hyperglycemic clamps in HFD-fed mice

Mar. 7, 2013: MTA received and approved.

Mar. 18, 2013: Health report approved.

Mar. 26, 2013: Shipment of HFD from Sweden faces an issue due to the diet containing ingredients from animal source requiring FDA & USDA approval

Apr. 12, 2013: USDA permit was submitted to receive Sweden HFD.



USDA

United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

National Center for Import and Export

Animal Products

4700 River Road
Unit 40
Riverdale, MD 20737

Telephone:
(301) 851-3300

FAX:
(301) 734-8226

Jason Kim / University of Massachusetts Medical School
368 Plantation Street, The Albert Sherman Center
9th Floor West, Suite 1041
Wochester, MA 01605

Friday, April 12, 2013

Dear Jason Kim:

Your Standard VS Form 16-3 for a USDA import permit was received. Please refer to application number 13096056 in any inquires. Permit processing is workload dependent.

The Statement of Services (receipt of payment) is attached. Payment is a processing fee (non-refundable) and does not guarantee permit approval or shipment release.

Sincerely,

Nekeia Mackey

Nekeia Mackey
Veterinary Program Assistant

cc:

*USER FEES WILL INCREASE on October 1, 2012 associated with permit applications . The new fees are as follows:

New permit application $150.00, Renewal permit $97.00, Amended permit $75.00, FBS inspection $512.00 (all fees are per application) and the Import Compliance fee is $565.00 per shipment.

Challenges in Year 2

Jan. 25, 2013:	**Service request from Dr. Anna Lundberg (Karolinska Institute) for hyperglycemic clamps in HFD-fed mice**
Mar. 7, 2013:	**MTA received and approved.**
Mar. 18, 2013:	**Health report approved.**
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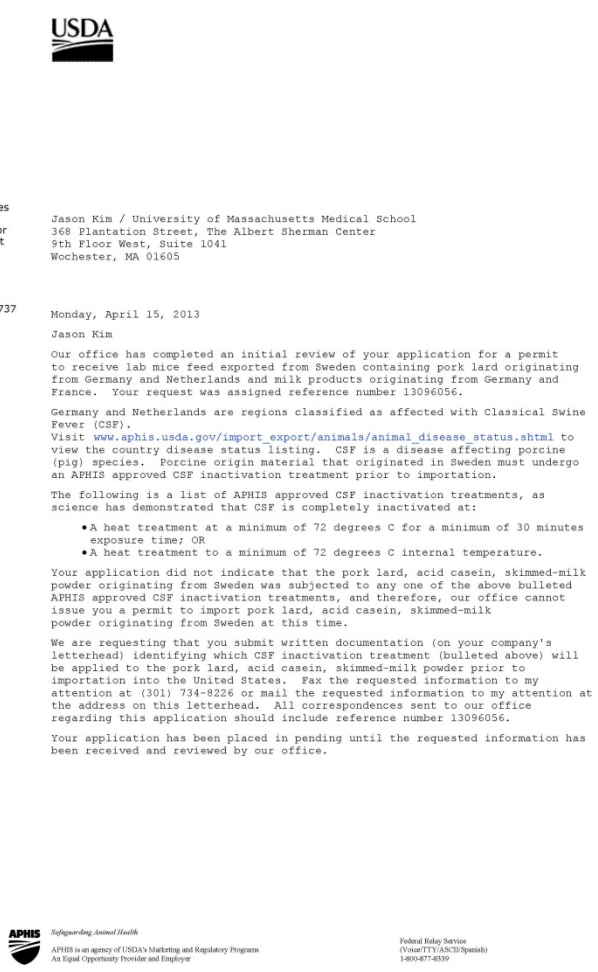
Challenges in Year 2



USDA

United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

National Center for Import and Export

Animal Products

4700 River Road
Unit 40
Riverdale, MD 20737

Telephone:
(301) 851-3300

FAX:
(301) 734-8226

Jason Kim / University of Massachusetts Medical School
368 Plantation Street, The Albert Sherman Center
9th Floor West, Suite 1041
Wochester, MA 01605

Monday, April 15, 2013

Jason Kim

Our office has completed an initial review of your application for a permit to receive lab mice feed exported from Sweden containing pork lard originating from Germany and Netherlands and milk products originating from Germany and France. Your request was assigned reference number 13096056.

Germany and Netherlands are regions classified as affected with Classical Swine Fever (CSF).
Visit www.aphis.usda.gov/import_export/animals/animal_disease_status.shtml to view the country disease status listing. CSF is a disease affecting porcine (pig) species. Porcine origin material that originated in Sweden must undergo an APHIS approved CSF inactivation treatment prior to importation.

The following is a list of APHIS approved CSF inactivation treatments, as science has demonstrated that CSF is completely inactivated at:

- A heat treatment at a minimum of 72 degrees C for a minimum of 30 minutes exposure time; OR
- A heat treatment to a minimum of 72 degrees C internal temperature.

Your application did not indicate that the pork lard, acid casein, skimmed-milk powder originating from Sweden was subjected to any one of the above bulleted APHIS approved CSF inactivation treatments, and therefore, our office cannot issue you a permit to import pork lard, acid casein, skimmed-milk powder originating from Sweden at this time.

We are requesting that you submit written documentation (on your company's letterhead) identifying which CSF inactivation treatment (bulleted above) will be applied to the pork lard, acid casein, skimmed-milk powder prior to importation into the United States. Fax the requested information to my attention at (301) 734-8226 or mail the requested information to my attention at the address on this letterhead. All correspondences sent to our office regarding this application should include reference number 13096056.

Your application has been placed in pending until the requested information has been received and reviewed by our office.

APHIS *Safeguarding Animal Health*

APHIS is an agency of USDA's Marketing and Regulatory Programs
An Equal Opportunity Provider and Employer

Federal Relay Service
(Voice/TTY/ASCII/Spanish)
1-800-877-8339

"Our office has completed an initial review of your application for a permit to receive lab mice feed exported from Sweden containing pork lard originating from Germany and Netherlands and milk products originating from Germany and France."

"Germany and Netherlands are regions classified as affected with Classical Swine Fever"

"We are requesting that you submit written documentation identifying a heat treatment at 72°C or above for a minimum of 30 min be applied to park lard, acid casein, skimmed-milk powder prior to importation into the US."

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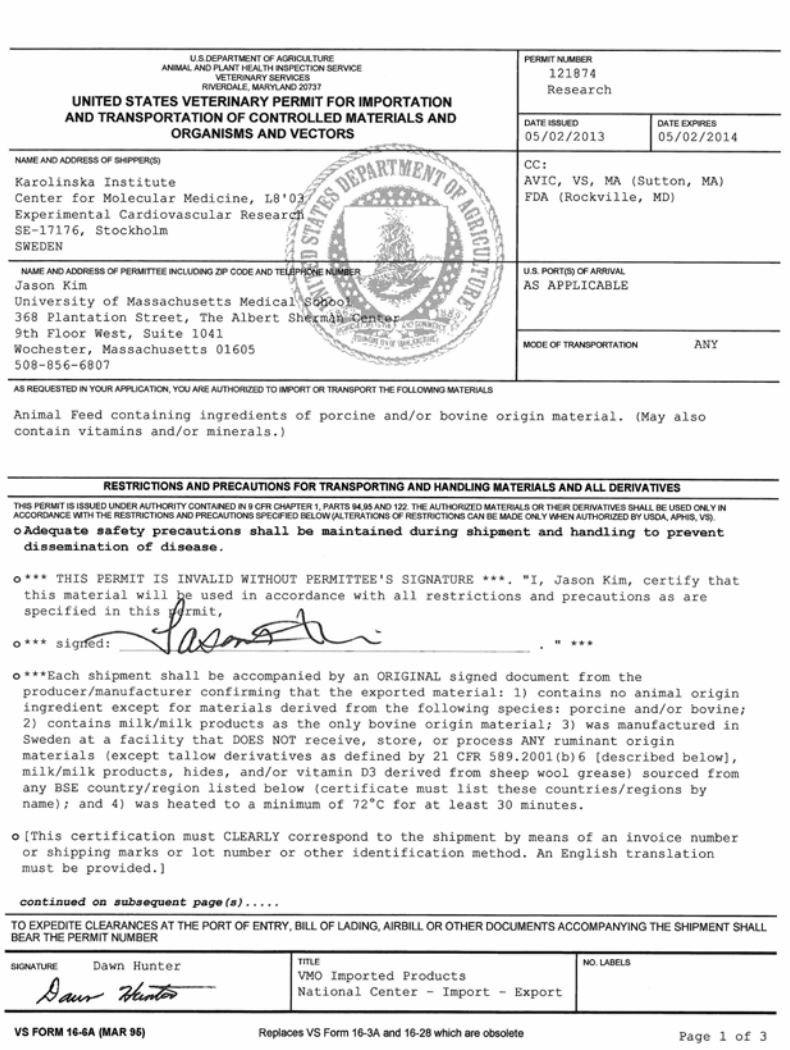

U.S.DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
VETERINARY SERVICES
RIVERDALE, MARYLAND 20737

UNITED STATES VETERINARY PERMIT FOR IMPORTATION AND TRANSPORTATION OF CONTROLLED MATERIALS AND ORGANISMS AND VECTORS

PERMIT NUMBER: 121874 Research
DATE ISSUED: 05/02/2013
DATE EXPIRES: 05/02/2014

NAME AND ADDRESS OF SHIPPER(S)
Karolinska Institute
Center for Molecular Medicine, L8'03
Experimental Cardiovascular Research
SE-17176, Stockholm
SWEDEN

CC:
AVIC, VS, MA (Sutton, MA)
FDA (Rockville, MD)

NAME AND ADDRESS OF PERMITTEE INCLUDING ZIP CODE AND TELEPHONE NUMBER
Jason Kim
University of Massachusetts Medical School
368 Plantation Street, The Albert Sherman Center
9th Floor West, Suite 1041
Wochester, Massachusetts 01605
508-856-6807

U.S. PORT(S) OF ARRIVAL: AS APPLICABLE

MODE OF TRANSPORTATION: ANY

AS REQUESTED IN YOUR APPLICATION, YOU ARE AUTHORIZED TO IMPORT OR TRANSPORT THE FOLLOWING MATERIALS

Animal Feed containing ingredients of porcine and/or bovine origin material. (May also contain vitamins and/or minerals.)

RESTRICTIONS AND PRECAUTIONS FOR TRANSPORTING AND HANDLING MATERIALS AND ALL DERIVATIVES

THIS PERMIT IS ISSUED UNDER AUTHORITY CONTAINED IN 9 CFR CHAPTER 1, PARTS 94,95 AND 122. THE AUTHORIZED MATERIALS OR THEIR DERIVATIVES SHALL BE USED ONLY IN ACCORDANCE WITH THE RESTRICTIONS AND PRECAUTIONS SPECIFIED BELOW (ALTERATIONS OF RESTRICTIONS CAN BE MADE ONLY WHEN AUTHORIZED BY USDA, APHIS, VS).

- **Adequate safety precautions shall be maintained during shipment and handling to prevent dissemination of disease.**
- *** THIS PERMIT IS INVALID WITHOUT PERMITTEE'S SIGNATURE ***. "I, Jason Kim, certify that this material will be used in accordance with all restrictions and precautions as are specified in this permit,
- *** signed: _____ . " ***
- ***Each shipment shall be accompanied by an ORIGINAL signed document from the producer/manufacturer confirming that the exported material: 1) contains no animal origin ingredient except for materials derived from the following species: porcine and/or bovine; 2) contains milk/milk products as the only bovine origin material; 3) was manufactured in Sweden at a facility that DOES NOT receive, store, or process ANY ruminant origin materials (except tallow derivatives as defined by 21 CFR 589.2001(b)6 [described below], milk/milk products, hides, and/or vitamin D3 derived from sheep wool grease) sourced from any BSE country/region listed below (certificate must list these countries/regions by name); and 4) was heated to a minimum of 72°C for at least 30 minutes.
- [This certification must CLEARLY correspond to the shipment by means of an invoice number or shipping marks or lot number or other identification method. An English translation must be provided.]

continued on subsequent page(s).....

TO EXPEDITE CLEARANCES AT THE PORT OF ENTRY, BILL OF LADING, AIRBILL OR OTHER DOCUMENTS ACCOMPANYING THE SHIPMENT SHALL BEAR THE PERMIT NUMBER

SIGNATURE: Dawn Hunter — Dawn Hunter
TITLE: VMO Imported Products, National Center - Import - Export
NO. LABELS:

VS FORM 16-6A (MAR 95) Replaces VS Form 16-3A and 16-28 which are obsolete Page 1 of 3

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Kim, Jason

From: Flanagan, Peter
Sent: Thursday, May 30, 2013 10:11 AM
To: Kim, Jason
Cc: Romer, Valerie
Subject: It's never good to hear from me.....

Hi Jason –

Val just got some bad news from the facility in Sweden. They have detected MPV in the room where the mice that you want are housed. Are you available sometime today for me to drop by to discuss what options, if any exist?

Let me know what time works best for you and I will come visit you and your group.

(you'll recognize me because I will be wearing my football helmet despite the hot weather.)

Peter
X6-4197

"Val just got some bad news from the facility in Sweden. They have detected MPV in the room where the mice are housed."

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May 7, 2013:	New health report was submitted and MPV was found.
June 6, 2013:	Animal Core approved surgery & hyperglycemic clamps to be performed at satellite UMMS campus in Shrewsbury.
June 14, 2013:	Sweden HFD arrived.
June 21, 2013:	Mice from Karolinska Institute arrived.
July 5~18 2013:	Hyperglycemic clamps were performed, and samples were processed by Analytical Core.
Aug. 5, 2013:	Study was completed and data were sent to Dr. Lundberg.

The End